PONTIFICIAE ACADEMIAE SCIENTIARVM SCRIPTA VARIA
78

STUDY WEEK

ON:

THE PRINCIPLES OF DESIGN AND OPERATION OF THE BRAIN

October 19-24, 1988

EDITED BY

JOHN C. ECCLES and OTTO CREUTZFELDT

PONTIFICIA
ACADEMIA
SCIENTIARVM

EX AEDIBVS ACADEMICIS IN CIVITATE VATICANA

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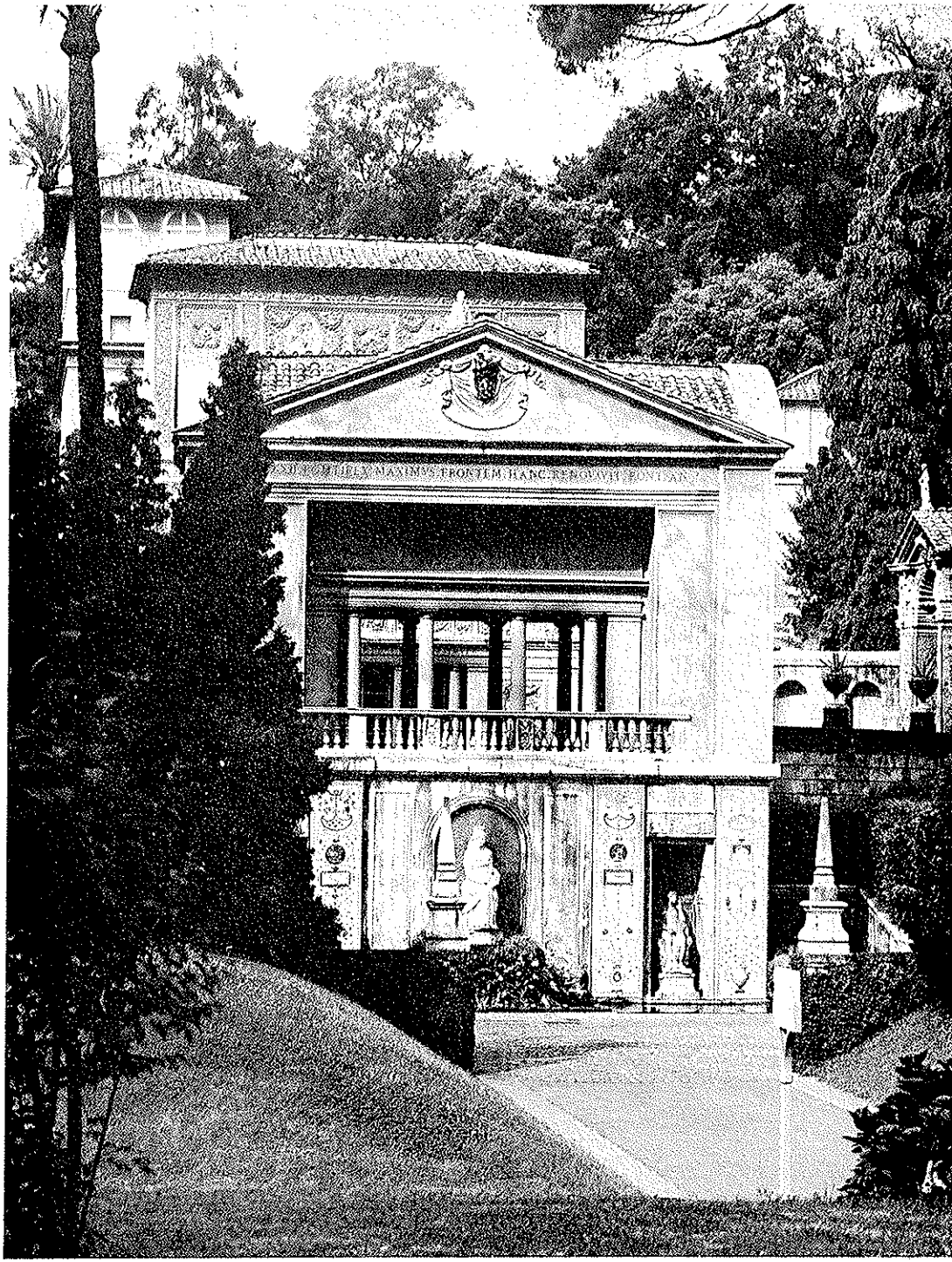

Casina Pio IV in the Vatican gardens
Seat of the Pontifical Academy of Sciences

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The opinions expressed with absolute freedom during the presentation of the papers and in the subsequent discussions by the participants in the Study Week, although published by the Academy, represent only the points of view of the participants and not those of the Academy.

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John C. Eccles and Otto Creutzfeldt

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FOREWORD

It is a pleasure and an honour to introduce this volume containing the papers and the discussions of the Study Week, "The Principles of Design and Operation of the Brain". This symposium, which was so capably organized by Sir John Eccles, gave renewed proof of the importance the Pontifical Academy of Sciences attaches to the rapidly evolving field of brain research.

In the course of the symposium, mention was often made of the meeting held in this Academy in 1964, Brain and Conscious Experience, *which was also organized by Professor Eccles. The published proceedings of that meeting constitute a milestone in the literature of the field* (1). *Since then, the Pontifical Academy of Sciences has continued to encourage research and the exchange of views in several sectors of neuroscience, organizing meetings such as*: Study Week on Nerve Cells, Transmitters and Behaviour, Study Week on Pattern Recognition Mechanisms *and* Working Group on Developmental Neurobiology of Mammals (2). *Presentations of related topics can also be found in the papers presented at two Working Groups convened by the Academy,* Mental Deficiency *and* The Artificial Prolongation of Life and the Determination of the Exact Moment of Death (3).

The papers and discussions of the present volume make available an unusually large spectrum of research, starting from the evolution of the hominid brain, and extending to the processes and higher functions involved in language and cognition, and to the concept of mind itself.

(1) Pontificiae Academiae Scientiarum Scripta Varia 30, Vatican City, 1965.
(2) Scripta Varia 45, 1980; Scripta Varia 54, 1985; Scripta Varia 59, 1987.
(3) Scripta Varia 47, 1981; Scripta Varia 60, 1986.

The high quality of these proceedings is due to the authors, first and foremost, but also to Sir John Eccles and Professor Otto Creutzfeldt, who shared the many responsibilities involved in preparing this extensive material for publication.

CARLOS CHAGAS

President of the Pontifical Academy of Sciences
1972-1988

PREFACE

These proceedings are the result of a request that Professor Carlos Chagas, President of the Pontifical Academy of Sciences, made early in 1987. He expressed the wish for a symposium that would be broadly based, and not simply an assemblage of reports of the latest experimental discoveries. Thus the comprehensive title, *Principles of Design and Operation of the Brain* was chosen, and Professor Mario Wiesendanger kindly assisted in the organization of the conference, which was to be specially related to the human brain, with support by studies on the brains of higher primates.

Molecular neurobiology has been dominant in the field of the neurosciences for some time. The undoubtedly great success of genetics, molecular biology and immunology have concentrated attention on the molecular phenomena of the brain. Another recent trend has been the attempts at computer simulation of the brain, in which efforts are made to apply approximations of the brain's neuronal networks to artificial intelligence and robotics.

As a consequence there has been a relative neglect of what is often called the systems approach to the neurosciences. Hence there is the possibility that these molecular and simulation fields of neuroscience may be deflecting attention from the ultimate problems of the neurosciences, namely the nature and meaning of the cerebral performance as experienced in learning and memory and in consciousness in all of its inexhaustible range of perceptions, of thinking, of planning, of criticizing, of imagining, of creating.

It was decided that the conference should start with origins both phylogenetic and ontogenetic, for which P. V. Tobias and P. Rakic were chosen. In the systems approach there has to be study of the immense problems of the neuronal communication systems of the brain, which can be so effectively investigated by the sophisticated tracing and labelling systems. The communications by E. Jones and J. Szentágothai report and evaluate these studies on the neuronal complexities of the cerebral cortex.

An important section of the conference was on the cerebral responses to sensory inputs, with special concentration on the important visual inputs to the primate cortex. G. Baumgartner, W. Singer, S. Zeki and V. Mountcastle presented diverse studies in this field.

It is of particular importance to develop techniques for studying the activity of the human brain in diverse series of mental tasks. Such human investigations can be accomplished by non-invasive techniques, using radio-tracers injected into the vascular system. As yet the records are relatively crude with spatial grains of several millimeters and time scales of seconds, but there is the inestimable advantage of cooperation by the human subject. Moreover, these techniques can be used in the study of human brain disorders. P. Roland and D. Ingvar describe such investigations and critically evaluate them.

By carefully controlled averaging techniques it has been possible to study the electric potentials generated by the human brain, as has been reported by B. Libet and L. Deecke. Other sophisticated studies of the cerebral activities concerned in movements and skills are reported by H. Freund, M. Jeannerod, M. Wiesendanger, V. Brooks and M. Ito, often with important clinical overtones. Necessarily in these studies of movements there have been parallel studies of the brains of non-human primates where invasive techniques can be employed in studying the responses of individual nerve cells. Moreover this microrecording can be done ethically on single neurons of the human brain. Advantage is taken of the exposure of the brain for the surgical excision of damaged areas or of tumors. It is a very exacting technique, but it has a great future as can be realized in the study by O. Creutzfeldt of neurons marginal to the speech areas.

The summit of the conference was on the higher functions of the human brain as particularly illustrated by memory, language, cognition and consciousness. Study of clinical lesions as well as of surgical lesions gave very interesting material for discussion. The reports of P. Andersen, P. Goldman-Rakic, P. McGeer, D. Ingvar, P. Roland, K. Poeck, J. Levy, O. Creutzfeldt and J. Eccles belong to this extensive category.

The wide-ranging vivacious discussions gave opportunities for further developing the concepts expressed in the papers, and for the display of critical rationalism. Unfortunately due to limitations of space there had to be extensive editing, but we hope without serious omissions.

JOHN C. ECCLES

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ADDRESS OF THE PRESIDENT OF THE PONTIFICAL ACADEMY OF SCIENCES TO THE PARTICIPANTS IN THE STUDY WEEK

It is a pleasure to welcome you here in the name of the Pontifical Academy of Sciences. I wish first of all to thank Professor Eccles for the work he has done in organizing this meeting — a meeting which is assured of success by the quality of the participants he has assembled. I had the privilege of being here during the very excellent Study Week which Professor Eccles organized in 1964, Brain and Conscious Experience, *and I am pleased to see that some of the participants in that meeting are here today.*

For many of you, however, this is your first contact with the Pontifical Academy of Sciences. This Academy traces its origins to the year 1603 when Federico Cesi, a Roman count, brought together a group of young scientific researchers who decided to call themselves the Academy of the Lynxes (or Lincei, in Italian). Cesi and his companions believed that the lynx could see much farther than any other animal, and that the "naturalists" as scientists were then called, were able to see farther than the common man.

After many difficulties, and some periods of dormancy, this Academy was renewed in 1847 by Pope Pius IX under the name, Pontificia Accademia dei Nuovi Lincei. Finally, Pius XI reconstituted the Academy in 1936 by means of his motu proprio *"De multis solaciis", bringing into being the Pontifical Academy of Sciences, the one in which you will soon present and discuss your scientific work.*

The rules established by Pius XI are still in force. The aim of the Academy is to promote science, and also to serve as the scientific senate of the Vatican. Its eighty members are chosen without racial or religious discrimination.

The Academy works on two levels. First, there are the Plenary Sessions which take place every two years, and to which all Pontifical

Academicians are invited. At each Plenary Session the deliberations concentrate on a chosen theme. The 1988 theme is The Responsibility of Science. *Second, we also convene Study Weeks and Working Groups. To these meetings we invite scientists who are not Members of the Academy, as well as those Pontifical Academicians who are specialized in the relevant fields. Significant meetings have been devoted to areas as diverse as remote sensing, the environment, mental deficiency, leprosy, the evolution of primates, and astrophysical cosmology.*

The Academy has also been instrumental in bringing together many segments of the scientific community in order to take a strong stand against nuclear war. Moreover, at the request of the present Pope, the Academy has recently participated in a reconsideration of various aspects of Galileo's work and his trial. Galileo was, in fact, an early member of the Academy. He was so proud of his membership that all his books and documents are signed Galileo Galilei Linceano.

To sum up, the work of the Academy is geared towards the examination of important problems in science, problems of global significance, problems of interest to developing countries, and problems related to bioethics.

I am indeed happy that you are here for this meeting, and that the Academy, which has always had a keen interest in furthering work in neurobiology, and which has hosted a number of meetings in this field, will be the scene of your presentations and exchanges. As is our policy, we encourage complete freedom of discussion, and we wish you a stimulating and scientifically rewarding Study Week.

INTRODUCTORY TALK TO THE STUDY WEEK PARTICIPANTS

JOHN C. ECCLES

Professor Carlos Chagas, President of the Pontifical Academy of Sciences, I join you in welcoming all participants and observers at the Study Week devoted to The Principles of Design and Operation of the Brain.

Last year you invited me to organize this Study Week with the wise advice that it should be devoted to general considerations in which we should attempt to develop and discuss hypotheses or scientific ideas on the basis of existing scientific knowledge. Professor Wiesendanger has kindly joined me in the task of organization.

As you have already mentioned, over twenty-four years ago I organized a rather similar Study Week here, from September 28 to October 3, 1964. It was attended by many great neuroscientists, and it proved to be most successful — scientifically, and also culturally and socially, as can be seen from the published record, Brain and Conscious Experience, *which is known to all neuroscientists.*

I am most happy that six of the participants in that Study Week are present in 1988. Through the good arrangements of the Director, Dr. Dardozzi, we are meeting in the same long, frescoed room as in 1964. I think we have one of the loveliest venues for a Study Week, both inside this room, and outside in the Vatican gardens. The setting is replete with beautiful distractions. I believe that the quality of scientific conferences is very much dependent on the beauty of the environment and the excellence of the more mundane facilities. Under such conditions one thinks more imaginatively and discusses with more wisdom and understanding.

We are a band of adventurers dedicated to the study of the brain, unquestionably the most wonderful structure in existence and, speaking dualistically, our most intimate companion. This is what binds us together — our dedication to this wonderful study.

SCIENTIFIC PAPERS

SOME CRITICAL STEPS IN THE EVOLUTION OF THE HOMINID BRAIN

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Much has been learned from the endocranial cavities of past forms of life, including higher primates, some of which were most probably ancestral to extant humankind. The close fit of the brain and its coverings within the calvaria in all modern Primates is the basis upon which one is enabled to make inferences as to the size and the form of the brain, when one possesses an empty calvaria or a cast of the interior of a cranium. In fossils, a natural endocranial cast may form by soft matrix filling the endocranial cavity after burial, the filling then becoming consolidated by lime or other minerals. In the absence of such a natural endocranial cast, it is possible to make an artificial endocast of plaster or plastic materials. The principle is the same with both kinds of endocast (Tobias, 1971).

From studies of empty calvariae and of endocranial casts of Pliocene and Pleistocene crania of higher Primates, especially hominoids, light has been thrown on some aspects of brain development. These aspects include size, form and, by inference, function, in the early stages following the emergence of the hominid family and in those successive stages leading to modern *Homo sapiens*.

Currently available data and inferences are reviewed here, and some new thoughts are offered on the emergence of spoken language during hominization.

1. *Absolute Brain Size*

The Hominoidea are a taxonomic superfamily, whose living representatives are *Homo sapiens* of the family *Hominidae*; and the apes of Africa and Asia, classified by G.G. Simpson (1945) as members of another family, the *Pongidae*.

When we compare the living great apes (gorilla, chimpanzee and orang-utan) with living man, one of the most obtrusive differences is that modern *H. sapiens* has a mean brain size approximately three times the mean values for the great apes.

There are many technical difficulties related to the determination of the volume and the weight of a brain (the author has listed the main problems elsewhere, Tobias 1970, 1971). Not the least of these problems is the relative paucity of adequate samples of such measurements on actual brains (Pearl, 1905; Appel and Appel, 1942; Bailey and von Bonin, 1951). Partly for this reason, many scholars have relied on the endocranial capacity in comparative studies of "brain size" (Todd, 1923; Brandes, 1927; Zuckerman, 1928; Mettler, 1955; Blinkov and Gleser, 1968; Tobias, 1971). Owing to the availability of enormous samples of dried crania, of both modern pongids and modern man, large and statistically valid samples of endocranial capacities have become available. Moreover, in fossilized remains, it is often possible to determine the endocranial capacity of a specimen: thus comparative data have been amassed for the endocranial capacities of extinct and extant hominoids. As with the volumetric and gravimetric data on the brains themselves, the mean endocranial capacity values show that modern *H. sapiens* has a value three times that of the extant great apes.

2. *Some Questions Related to the Absolute Brain Size of Hominoids*

(i) Is the difference in brain-size "real", or is it simply the consequence of differing body sizes, among modern men and modern apes?

A number of different techniques have been proposed to determine the degree of encephalization, when body size is taken into account. Cuvier first introduced the concept of relative brain weight, that is the weight of the brain expressed as a fraction of the weight of the body. More recent techniques for the study of relative brain size include Hemmer's Constant of Cephalization (CC) (Hemmer, 1967, 1971) and Jerison's Encephalization Quotient (EQ) (Jerison, 1970, 1973). Lashley (1949) had suggested that the total amount of brain material, expressed

as a fraction of total body size, "seems to represent the amount of brain tissue in excess of that required for transmitting impulses to and from the integrative centers". Based on this concept, Jerison (1963) proposed a formula for the calculation of the "extra neurones": by this index, Jerison attempted to estimate *Nc*, the number of neurones in *EQ* (the part of the central nervous system associated with improved adaptive capacities), if one knew the total brain size and the total body size for a number of species in a major systematic group.

All of these and other methods for the assessment of relative brain size in extant species, including the hominoids, confirm that modern *H. sapiens* is appreciably advanced over the apes, not only in absolute brain size, but also in relative brain size — i.e., when the size of the body is taken into consideration. This pre-eminence of man is often spoken of as a higher *degree of encephalization* of modern *H. sapiens.*

(ii) Does the occurrence of a greater relative brain size in man connote advantages which might have been favoured by Natural Selection? If so, what manner of advantage did the larger brain size confer?

On Lashley's and Jerison's approach, we should be tempted to think of "improved adaptive capacities" as the key to the advantage conferred by increased encephalization. It is doubtful whether this alone provides a satisfactory answer. "Improved adaptive capacities" might be paraphrased as increased adaptability. Long ago Mather (1943) showed that adaptability and adaptedness are inversely proportional to one another. If progressively increasing adaptability was conferred by progressively increasing encephalization, it would follow that the most highly encephalized members of an evolutionary lineage were least adapted. It is doubtful whether this inference would stand up to close scrutiny, since strongly encephalized members of several lineages (e.g., Cetaceans, some New World monkeys, *Tupaia* and certain rodents) would appear to be highly adapted in their respective eco-niches.

Or, did the increased encephalization provide a means for rising above the constraints suggested by Mather's paradox? Was the relative enlargement of the hominid brain a mechanism by which enhanced adaptability might be furnished, without the sacrifice of adaptation, that is, of adaptedness?

What other advantages would progressive encephalization have conferred? Many suggestions have been made in regard to encephalization (e.g., duration of memory, sustained hunting proclivities, etc.), and most

of these relate to the particular degree of encephalization manifested by the hominid lineage. They do not necessarily seek a common denominator between the advantages conferred by hominid encephalization and those associated with encephalization in other evolutionary lineages.

(iii) A third set of questions related to the absolute brain size would see the mean values in living hominoids as the end-result of phylogenetic processes. How long have the hominids had an absolute and relative brain size in excess of those that characterised their fellow-hominoids, the apes? If, as all evidence seems to indicate, the hominids and some at least of the pongids shared a common ancestry, when did the phenomenon of inordinate encephalization first manifest itself among these early ancestral hominoids? What light does our study of the fossil record throw on the evolution of hominid encephalization? Closely related to this question — how did the inception of marked encephalization relate to other aspects of the inception of the family of the Hominidae? Since much evidence shows that upright posture and bipedal locomotion were important early features in the emergence of the hominids, we may ask which came first — uprightness or encephalization? Or was there some kind of interrelatedness between these two major phenomena, some sort of positive feedback system?

Moreover, how was encephalization related, temporally and causally (if at all), to such other components of hominid emergence as the reduction of the canine teeth and other dental and gnathic changes, the conversion of the pelvis to an organ of bipedalism without sacrifice of its obstetrical role, the hominidisation of the foot and toes and of the forelimb?

Yet again, since we dare not speak of brain evolution without at the same time considering the functional correlates, what evidence do we have of "fossilized behaviour" in the record of the rocks? How does the appearance of tools in the fossil record relate to the stage of encephalization?

3. *Endocranial Capacities in the Earliest Fossil Hominids*

Paleo-anthropologists, however much they may disagree on details, are agreed that the earliest fossil specimens which may be ascribed to the family Hominidae are those South and East African specimens to which the generic name *Australopithecus* has been given. This genus has been known since R.A. Dart first named it and presented the first known

specimen in 1925. Subsequent discoveries from 5 sites in southern Africa and from a number of localities in Tanzania, Kenya and Ethiopia have revealed that several different species of *Australopithecus* lived in Africa between 4 and 1 million years ago. They differed in respect of many cranial and dental features: yet all showed signs of upright bipedalism and reduced canines; on such criteria, all were manifestly members of the family of man, the hominids.

However, in one crucial respect, the australopithecines were like the pongids — in their absolute brain-size. Some fossil hominid crania had natural endocasts contained within them; others were empty, thus permitting the investigator to make artificial endocasts. From either source of material, it is clear that the australopithecines had brains volumetrically no larger than those of modern great apes. If encephalization of absolute brain size were a mark of the evolution of the hominids, here were a group of hominids that had not yet begun that long process. It was this very smallness of absolute brain-size that was primarily responsible for a 25-year-long disputation about whether *Australopithecus* could be allowed a place on the hominid lineage, or even within the hominid family.

While *Australopithecus* — in all of its recognised species — had not started to show the marked increase of absolute brain size, which is the mark of the hominid family, body size estimates have been made from limb-bones and vertebrae of *Australopithecus*. These have permitted investigators to make estimates of relative brain size in these early hominids. Although such body size estimates vary greatly at this stage, there is a tendency for the relative brain size of various australopithecine species to be slightly but definitely in advance of corresponding values for the chimpanzee, according to recent estimates by McHenry (1982) and by Tobias (1988).

4. *The Emergence of Homo habilis*

With the emergence of the genus *Homo*, about 2.3 million years (Myr) ago, one finds the beginnings of the dramatic enlargement in absolute and relative brain-size. In absolute terms, the mean endocranial capacity in the earliest species of *Homo*, *H. habilis*, is 45.1% greater than the mean for *A. africanus*, while the latest estimate of the mean for *H. erectus* is some 46.4% greater again than the sample mean for *H. habilis*.

It may be noted here that it is with the emergence of *H. habilis* that we find the *consistent* association of stone tools with the hominid remains. This correlation led a few years ago to the inference that some causal connection seems to have existed between the accelerated increase in brain-size shown by *H. habilis* and the capacity for stone cultural activities. We shall revert to this theme later.

There is now agreement that *H. habilis* was appreciably more encephalized than the australopithecines and indeed that its emergence marked the beginning of the phase of aggrandisement of the hominid brain (Pilbeam and Gould, 1974; McHenry, 1982; Hofman, 1983; Tobias, 1987).

5. *Regional Enlargement or Overall Enlargement?*

It is a nice question to enquire whether the 45% increase in absolute brain-size shown by *H. habilis* was a generalised increase, affecting all parts of the brain equally, or whether some parts were favoured over other parts. In raising this question, one must immediately admit that the study of fossil endocasts is beset with limitations. The study is restricted to external features, that is, only such features whose imprint could have been impressed upon the endocranium. Especially valuable in this respect are the surface features of the cerebral hemispheres. However, these must perforce exclude such surfaces as the superior surface of the temporal lobes and the medial face of the two cerebral hemispheres. Needless to say all internal structural features remain mute when one addresses an endocast.

When one compares the outline tracings or encephalometric readings of endocasts of *A. africanus* and *H. habilis*, one finds that, in length and in height, the latter is only very slightly greater (on average) than the former. It is, however, in the breadth of the endocasts that *H. habilis* far exceeds *A. africanus*. The increase is appreciable in the region of the frontal lobes, but considerable in the region of the parietal lobes (Holloway, 1981). It is clear that *H. habilis* had gained the greatest part of its volumetric increase by transverse expansion, especially of the parietal lobes (Tobias, 1987).

During the course of these studies, the author made the interesting observation that marked asymmetry characterises the impressions of the superior parietal lobules. In several endocasts of *H. habilis*, the impression of the left superior parietal lobule is appreciably more protuberant

and elevated than that of the right lobule (Tobias, 1986, 1987). Such an asymmetry has been confirmed by the author on a small number of modern *H. sapiens* brains and endocasts so far examined for this feature. It is, to the author's knowledge, a "new" asymmetry, not so far included in the catalogue of cerebral asymmetries (Le May and Culebras, 1972; Le May, 1976, 1977, 1984; Holloway and de la Coste-Lareymondie, 1982). Its functional significance remains to be addressed.

6. *Motor Speech Areas*

A number of years ago, G.W.H. Schepers (1946) drew attention to the fact that *A. africanus* endocasts differed from those of apes in showing a strong prominence in the posterior third of the inferior frontal convolution — Broca's area. While this is not a feature of pongid endocasts or brains, it is well shown — as the author has confirmed — on the endocasts of *A. africanus*. It is present also in the endocasts of *H. habilis*, *H. erectus* and early *H. sapiens*.

Some 9 or 10 years ago, the author first detected a marked fullness or bulbosity in the region of the inferior parietal lobule of *H. habilis*. In the modern human brain, this region, comprising the supramarginal and angular gyri, is considered part of *Wernicke's area*, which is the second motor speech area of the cerebrum. That part of the brain or endocast of an ape is not protuberant or bulbous (Bailey *et al.*, 1950; Critchley, 1953; Geschwind, 1965). When the author examined the endocasts of *A. africanus*, he found that they resembled those of pongids in lacking a regional fullness of the inferior parietal lobule. In other words, there is no surface expression of Wernicke's area in apes or australopithecines; it is however present in *H. habilis* as in *H. sapiens*. (The superior motor speech area lies in the Supplementary Motor Area, Ms II, which is on the *medial* surface of the cerebral hemisphere and is thus not detectable on an endocast.)

Meantime, Dean Falk (1983) has drawn attention to the fact that, as well as in respect of Broca's area, the sulcal pattern of the frontal lobe of the brain differs appreciably between modern man and modern apes. In her study of the endocasts, she finds that the frontal lobe impression of *A. africanus* closely resembles that of the apes, whereas that of *H. habilis* is nearly identical with that of modern *H. sapiens* (cf. Holloway, 1978). Thus, on both the sulcal pattern and the Broca and Wernicke protrusions, the brain represented by the endocast of *H. habilis* closely

resembles that of modern man. It should be mentioned that the geological, palaeontological and radio-isotopic evidence shows that *H. habilis* was present in East and South Africa from about 2.3 to about 1.6 Myr before the present — that is from the later aeons of the Pliocene to the early part of the Pleistocene.

The exciting representation of these Motor Speech Areas on the endocasts of *H. habilis* led me to propose in 1980 that *H. habilis* possessed the neurological basis of spoken language (Tobias, 1980, 1981, 1983b). When this evidence was considered along with the evidence of a complex and diversified stone tool culture (which Mary Leakey, 1971, and Glyn Isaac, had revealed) I was moved to put forward the hypothesis that *H. habilis* was a speaking primate (Tobias, 1983a). Although some have doubted whether even so recent a relative as Neandertal Man could speak properly (Lieberman and Crelin, 1971), my proposal would take the frontier of spoken language back from 40,000 years ago to some 2 million years ago! It is possible that the range of habiline speech sounds might not have been as great as it is in the varieties of modern human languages; the linguistic complexities need not have been as intricate as they are in today's languages. Nevertheless, it seemed to me that it was no coincidence that the dramatic enlargement of the brain, and the appearance of the motor speech centres, nearly coincided in the phylogenetic history of mankind; nor was it to be seen as accidental that these two neurological phenomena seemed to coincide with the behavioural evidence that *H. habilis* was dependent on implemental activities as its predominant strategy of survival.

This was the position up until some three years ago. I was led to see in the emergence of *H. habilis* an evolutionary transcendence (cf. Dobzhansky, 1967) from what I had called the *animal hominids* (*Australopithecus*) to a new level of organization, that of the *human hominids* (*Homo* species).

7. *Did* A. Africanus *Possess the Propensity for Spoken Language?*

A. africanus is best known from Sterkfontein (dated to 2.8-2.3 Myr) and from Makapansgat (3.0 Myr), both in the Transvaal, South Africa. It has already been mentioned that its endocasts show a fullness or bulbosity in the anterior motor speech area (Broca's area), which represents an extension of the primary somatomotor cortex into the inferior frontal gyrus. It coincides with Brodmann area 44 and part of area 45.

There is no surface evidence for the existence in *A. africanus* of the posterior motor speech area (the second motor speech area of Wernicke). This area corresponds to the inferior parietal lobule and areas 39 and 40, and an extensive part of the temporal lobe, especially the superior temporal gyrus, the planum temporale and adjacent areas. Closely related are Brodmann areas 22 and 37, which are considered by some to be respectively auditory and visuo/auditory areas associated with speech and language.

It is true that much remains to be learned of the connections of the three motor speech areas. Moreover, it is probably a gross oversimplification to suggest that only three areas of the cerebral cortex have to do with all of the intricacies of language, including its speaking, listening, reading and writing aspects. The most that may be claimed, for our present purposes, is that two of the three motor speech areas obtrude themselves on to the outer surface of the cerebrum in such a way that the presence or absence of well-developed elevations in the areas in question may be detected on endocasts: Broca's area alone in *A. africanus*, and Broca's and Wernicke's areas in *H. habilis* and all later forms of man.

The question arises: could a hominid which possessed only a bulbous Broca area have used spoken language? Behavioural evidence might provide indirect indications bearing on this question. For a long time, we have been unsure of the behavioural characteristics of *Australopithecus*. Dart's (1957) claim that *A. africanus* wielded a bone, tooth and horn industry ("Osteodontokeratic culture") has been largely overturned by the researches of Brain (1981).

Recent researches in Ethiopia by Corvinus (1976), Harris (1983), and Roche and Tiercelin (1977, 1980) have revealed signs of stone tools as early as 2.6, 2.7 and even 2.8 Myr before the present! This is possibly as much as 500,000 years before the earliest known appearance of *H. habilis*. It is the time of *A. africanus* in the Transvaal, and of late *A. afarensis* in Ethiopia (perhaps the East African equivalent of *A. africanus*). This important new archaeological evidence raises the possibility that some populations of advanced *A. africanus* might have been responsible for the earliest stone tool-making activities.

There is independent, parallel evidence — adduced by Skelton, McHenry and Drawhorn (1986), and reinforced by Tobias (1988) — that late-surviving members of *A. africanus* underwent a number of morphological changes, to produce what McHenry and his colleagues have called a "derived *A. africanus*". These advances in morphology presaged the

splitting of the hominid lineage into the late, specialized, robust australopithecines and the derivative *Homo habilis* line.

It is tempting to suggest that the postulated derived *A. africanus* was the manufacturer of the early tools reported by Corvinus, Roche and Harris. Indeed there is scarcely any other competitor for this honour.

If *A. africanus* was the first stone tool-maker, and if *A. africanus* had a manifest Broca's area on its endocast, is it conceivable that *A. africanus* (in its derived manifestation) could first have been capable of spoken language — even before *H. habilis* came to be dependent on language for survival?

This raises the neurologically interesting and challenging question — whether *A. africanus* could have spoken with a bulbous Broca's area but no protuberant Wernicke's area. What mode of language could this have been?

It raises anew the view, long cherished by some investigators, that signing might have preceded speaking.

8. *Signing or Speaking?*

Various modes of language expression have been considered in relation to hominid evolution:

(1) For well over a century eminent scholars have advanced and supported the view that the first hominid language was primarily *gestural*, carried on with hand and arm signals rather than vocal sounds. Hewes (1973) has amassed much evidence in support of this hypothesis, including much new evidence that was not available to the earlier upholders of this theory. The new data have emanated from studies on communication among chimpanzees and other primates (e.g., Gardner and Gardner, 1969, 1971, 1978; Premack, 1970a, b, 1971, 1976; Menzel, 1973).

(2) A second concept, supporting the view that spoken language was preceded by non-spoken communication, was that of Livingstone (1973) who laid stress on those laryngeal vocalizations, which he called singing. However, several investigators have suggested that the interesting parallels between the biology of bird song and human speech represent analogies rather than homologies and are therefore irrelevant to the evolution of human speech (Marler, 1970; Steklis and Raleigh, 1973). Nevertheless, Livingstone has argued cogently that anthropoid apes are capable of producing the laryngeal vocalizations of speech which he calls *singing* and

Westcott (1973) calls *humming*, and that from this evidence early hominids might be inferred to have developed a complex system of calls based primarily on pitch differences.

(3) A third view builds human speech directly from a primate call system. The blending hypothesis of Hockett and Ascher (1964) provides one possible route by which this might have been achieved. On their hypothesis a call system, such as that of the gibbon, began to open by the blending of various calls. Westcott (1973), whilst agreeing that the blending of calls is an important language-generating mechanism, does not accept that it is the only such mechanism: he would add the imitation of nature and iconic representation as two other processes productive of linguistic materials.

Attractive as the signing hypothesis of Hewes (1973) has proved, a number of recent investigators have emphasized the idea of vocal continuity between hominids and other Old World primates (Falk, 1978, 1980; Holloway, 1969; Steklis, 1981; Ragir, 1985), and have stressed the probable early origin of human vocal language (Tobias, 1980, 1981, 1983a, b).

Steklis (1981) has re-evaluated the evidence favouring respectively the gestural and "vocal continuity" models of human language origins. He draws attention to a number of similarities in communicative abilities and their neural bases between humans and other Old World primates: (1) some non-human primates employ at least incipient symbolic/propositional calls and gestures; (2) learning can modify calls and gestures; (3) neural specializations (including lateralization and neocortical control) are present in non-human primates that are similar to those governing vocal and other praxic movements in humans. Insofar as these similarities arose through common ancestry and therefore represent homologies, this evidence suggests that the earliest hominids already possessed significantly developed "anlagen", at both the behavioural and neural levels, to make possible the evolutionary development of a primordial speech system. Gestural language, Steklis concludes, need not have preceded vocal language and probably never played more than a secondary role in hominid propositional communication.

9. A. africanus *a Facultative Speaker,* H. habilis *an Obligate Speaker*

So I come to the view that *A. africanus* could well have been the first hominoid to be capable of spoken language. This property would have

facilitated the transmission of his lithicultural advances to the offspring. It was a propensity, we must suppose, which was incipient, perhaps *facultative*: and it was there before the great cladogenetic splitting of the hominid lineage into *H. habilis* and the robust australopithecines. It preceded and anticipated that splitting, rather than — as I used to think — followed the splitting. The development of early stone culture and the cultural transmission of this faculty by rudimentary language, on this analysis, provided the setting for the splitting of a lineage. Both derivative stocks should have inherited the propensity for cultural and linguistic behaviour: but in the robust lineage, it remained facultative, incipient, not the essential basis of survival.

In the other derivative, *H. habilis*, cultural and linguistic behaviour became *obligate*, providing the very basis of the survival strategy. This was the first culture-bound and language-dependent primate. That duality marked the beginnings of humanity as we comprehend it today.

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DISCUSSION

For most demanding reasons, Professor Tobias was unable to attend the Study Week. His paper which is published here arrived at the meeting just after the scheduled time of presentation. In order to maintain the planned sequence of the conference, Professor Eccles, who is very familiar with the work of Professor Tobias, and who was provided with slides and other material by Professor Tobias, gave a substitute presentation.

The discussion which is printed below refers, therefore, to that presentation.

CREUTZFELDT

I have a question concerning the time scale. I should like to know whether the volume increase is really linear down through time, or are there kinks in the volume development which could be attributed to some environmental or genetic factor? Is there really a linear increase of the brain volume over the millions of years?

ECCLES

The brain volumes are averages of large numbers. If you look at the individual fossils and put the dates on, you see all kinds of jumps on the line. For example, ER1470 is dated at about 2 million years ago and yet it's got a brain of about 780 ccs. At that time the average size was down in the 600s. The point is that there was a wide range of variations, partly due to sex.

CREUTZFELDT

I wonder to what extent one can conclude from brain shape and brain size whether there was language or not. If I look at a brain of a modern Homo sapiens sapiens and just look at the right hemisphere, then I would have difficulties in concluding whether it has language or not.

The second point I'd like to make is that it's not just the brain which develops. The anatomy of the whole body develops in order to provide the apparatus for performing new functions. Lenninger, in his book on language, made a very good case that speech was not possible without the peripheral

anatomy we have as Homo sapiens sapiens. It's not just the larynx, it is the whole face structure, the bones and muscles. I wonder whether Homo habilis could have speech of the sort we have, simply for phonetic reasons.

I think one should realize that the evolution of the body and its apparatus go parallel with brain development, and it's not just the brain that becomes bigger. There is a very interesting connection between body development and brain development. The brain is a control system which must be fit to deal with the body and its apparatus. What is essential in mammalian development is not just the change in brain structure but the differentiation of the periphery in developing new apparatuses for perceiving and handling of the environment. The brain increases in size accordingly and adapts itself to the new situation due to its inherent plasticity. We tend to look at brain sizes in isolation, but I think we have to realize that Homo habilis and erectus are much smaller, they have a much poorer anatomy and may have a much poorer differentiation of face and larynx.

ECCLES

Tobias in 1983 discussed the question. John Limber (1980) reviewed the acquisition of language by children despite extreme disability of the vocal apparatus. Children have such an extreme propensity for speech that they will learn to speak without a larynx or a tongue, or with a severely damaged pharynx. They make tremendous efforts to overcome all the deficiencies. Lieberman maintained the alternative position, namely, that in hominid evolution speech came very late, delayed even to Neanderthalians, because of the deficiencies in larynx and pharynx. However, this position is now untenable against the alternative view that it was brain evolutionary development that made speech possible. The important question is: how did the brain grow so rapidly in hominid evolution? It must have been because of the tremendous advantage of a developed language in natural selection. There is no other explanation.

CREUTZFELDT

Just to make it clear: I don't want to say that it's not the brain that produces language. I only wonder where the evolutionary pressure comes from. You might as well say that the body makes its own brain as you can say that the brain makes the body. What is first in evolution? This is not a trivial question. It's not that the brain becomes a bit larger on an existing body — that is what's generally thought. This is not so, and all that we know about

comparative anatomy and evolution is that brain size, the size and differentiation of sensory surfaces, of muscle differentiation, etc., are closely related to each other. The brain-to-body weight factor may be higher in humans as compared to lower animals, but in new world monkeys it is higher than in humans. The brain to body weight indexes are linear if one introduces a certain transformation. Therefore, one should realize that the whole human being evolved with all its features, not just the brain.

MOUNTCASTLE

Can I make a comment? I think this is an interesting and difficult problem that Dr. Creutzfeldt raises. There are some counter examples. For example, the monkey hand differs from the human hands only in the absence of the opponent. The short muscles controlling the fingers are identical and yet the monkey has not the capacity for individual manipulation of the four digits that the human has. This is a case, I think, in which the peripheral apparatus is available but the nervous control is not.

RAKIC

I just want to make a point that the peripheral system is there to execute those decisions that occur in the brain. Evolutionary pressure would not fully develop an organ for execution and see whether the brain adapts to that execution, but it would be the opposite, to have a purpose and then the organ would develop.

ECCLES

I would just question the words "evolutionary pressure". What we do know is natural selection. There are phenotypes that are genetically controlled and some succeed because of the adaptability of their language and movement and so on, and some don't. There is no pressure. Natural selection is the basis of evolution.

DEECKE

The emphasis on speech as a first event to take stock of may be wrong, or may not be the only event to take into account. Look at the toolmaking abilities, look at the relation to extra-personal space, as directed by the right

hemisphere. I think toolmaking and action on the external world in a consistent manner are very important considerations which have an anatomical basis mainly in the right hemisphere.

ECCLES

Tobias links the tool with language and he thinks that when you are training toolmaking by the young you naturally would talk and use gestures and signs. The growth of the brain to Homo habilis and from then on is the greatest miracle of all evolution and I think that the development of language was responsible.

GOLDMAN-RAKIC

Language needs to develop in the sense that it must be an adaptation to the need to process multiple channels of information. I would think that we shouldn't totally ignore the sensory periphery as an entrée to the brain to give it the information which has to be processed through language.

ECCLES

The sensory information of Pongids today is as good as ours, so we have to recognize that evolution of the sensory systems preceded a spoken language.

LIBET

For communication, language is essential. Perhaps the emphasis ought to be on communication and language because man is successful as a social animal, and language would be essential.

JONES

I am prepared to believe that Homo habilis was capable of speech. I am even prepared to believe that Australopithecines were capable of speech, but I find it very hard to accept that on the basis of any of the data that have been presented so far. In other words, we have seen a great increase in cranial capacity which more or less translates into a great increase in brain volume. It is not sufficient, in my opinion, simply to say that this increase in brain size necessarily translates into a capacity for speech, logical thought, conceptual thought, the recognition of language as symbolic of thought. These are questions which I don't think we can answer.

First of all, is there hemispheric specialization? Is there area specialization? And try as we might to identify a Broca area or a Wernicke area on these endocasts, I really think we are pushing that a bit far.

So I don't know that language necessarily can be derived from data that we currently have. We need to know things that are lost.

ECCLES

Already the Australopithecines had all of the peripheral performances with movements, skills with walking, as in the footprints. They had already the beginning undoubtedly of a wooden tool culture, which of course is lost to us. They were on the way to hominization, yet they had only a small brain increase. We must make the most of the records we have, and be generous to the story as it has been put up by Tobias: "Language is not necessarily important for its own sake, at least in the beginning, but for what is made possible. Speech became a vehicle for concepts, tribal law, a sense of the past and the future and not just the immediate present, for standards of behaviour, laws, morals, customs, for knowledge, belief, art. Speech was an indispensable prerequisite for the development of all of these things that from a behavioural point of view have made man man".

This was written by Tobias in 1987, and as I am trying to stand in for him, I thought we should hear him on these very questions.

WIESENDANGER

If I may come in just briefly here and ask, in his title he has "some critical steps" which indicates a bit what David Ingvar had in mind. It was probably not a continual evolution but occurring in steps.

ECCLES

Yes, that would certainly be the case. (Note: *It was discussed in the delayed paper, now printed above*).

BAUMGARTNER

If you teach chimpanzees to speak by sign, they are quite good. So I think the most important thing, in order to make a differentiation in the sense of the developing and increasing brain, is that cognition improves considerably and speech was just the necessity of this development to communicate.

ECCLES

Chimpanzees don't speak, probably because they don't have the speech areas. With evolution there was an enormous development of the speech areas.

ROLAND

Could I comment on the cytoarchitectonics, because really the key issue in the discussion is whether it's possible by determination of the Broca cap in evolution to infer that the being has language. If one compares, if I am not wrong, with the cytoarchitectonics of chimpanzee brains, not the orangutan brain, I think that Campbell in 1905 showed that there are actually the same cytoarchitectonic fields, 39 and even 44, in the chimpanzee brain and yet the chimpanzee cannot speak. I would like to carry the argument a little bit further. For instance, dolphins have an extremely well-folded brain, and they certainly might also have a language in the sense that they communicate with sound signals, and also they have a well-developed Broca cap. So I think it would be very dangerous to infer from gross anatomy and even cytoarchitectonics that a being has language. I think the issue is certainly very complex. For instance the dolphins might have a very well-developed communication system, a very well-developed language, yet they haven't been able to build a culture because of their gross anatomy.

ECCLES

There are many things to answer there. You have to think that language has different levels. You have language for expression, language for signalling, all animals down to bees have language for signalling, for communication, that's not what we're talking about. We're talking about human language which is in the first place descriptive and secondly argumentative. Using language for these purposes is what came in Hominid evolution.

FREUND

This is a very important point which you just made, because I think the neural and the peripheral apparatus in chimpanzees is there to produce for a broad repertoire of communication. This is shown by those chimpanzees raised in human families which have a vocabulary of up to 300 signs. So I think that the evidence for a human kind of language is the inflection of the basic cranium.

Only those with a low throat really use a human type of language. Primatologists have assigned the first human type of language to have occurred about 80,000 years ago, not earlier, on the inflection of the basic cranium.

ECCLES

My criticism of this Neanderthal origin is that it takes no account of the unprecedented speed of the evolutionary development of the brain. As stated earlier, it could only have been for speech, as Tobias suggests.

RADIAL UNIT HYPOTHESIS OF CEREBRAL CORTICAL EVOLUTION

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There is probably little disagreement among contemporary neurobiologists that distinctly human mental capacities are a reflection of the expansion of the cerebral neocortex (Rakic and Singer, 1988). The present article is concerned with the evolution of this remarkable structure in nonhuman primates. Examination of the cerebral hemispheres in various living primates shows a large range in the size and pattern of cytoarchitectonic maps. For example, since the time that humans and old world monkeys departed from their common ancestor at the beginning of the Miocene period some 23 million years ago (Fleagle, 1988), the cortex of both species has undergone considerable modification. The total surface area of cortex in humans is not only about ten times larger than in monkey, but the relative proportion of various cytoarchitectonic areas is also quite different, with humans having a larger proportion of association cortex (Blinkov and Glezer, 1968). In addition, humans have some new cytoarchitectonic subdivisions, notably the speech area, that monkeys do not possess. How these differences are introduced at the genetic, molecular, and cellular level is a major challenge of neuroscience.

It seems reasonable to start with the assumption that evolutionary novelties in the neocortical cytoarchitectonic map (e.g., overall size, relative proportions of existing areas and introduction of new areas) occur as structural modifications that are introduced as mutations in an individual common ancestor and passed on to descendents. Most evolutionary biologists believe that we have to rely on the study of ontogeny to uncover the cellular and molecular mechanisms that generate major mor-

phological changes on an initial blueprint. There are many examples from evolutionary biology that support the validity of this approach (e.g., Gould, 1977). In the present article I will try to suggest and interpret possible cellular events that could occur during evolution in the framework of the *radial unit hypothesis* (Rakic, 1988). This hypothesis derived from a series of neuroembryological studies starting about two decades ago (Rakic, 1971, 1972). The experimental evidence and documentation for most of the factual statements can be found in the primary references listed in the bibliography and in a recent review (Rakic, 1988).

A study of cortical ontogeny (Rakic, 1988) indicates that the changes in cytoarchitectonic maps could be explained by a *heterochronic process* or modification of timing and proliferation kinetics in the ventricular zone. I will present some arguments that a relatively small alteration of onset, offset and rate of cell proliferation in a particular embryonic zone can explain the difference in size and pattern of the cytoarchitectonic maps between *macacus rhesus* and *homo sapiens*. The formulation which describes the introduction of novelty in evolution by the process of heterochrony is described for various morphological features of the body by Alberch *et al.*, 1979. However, understanding phylogenetic or ontogenetic development of the central nervous system presents its own special problems because of the complex interplay of nerve cells, hormones, and various growth factors which control gene expression (Easter *et al.*, 1985; Purves, 1988; Edelman, 1988). In the cerebral cortex this type of cellular interaction probably plays a more significant role than in any other organ, and has to be taken into consideration.

To make a problem manageable I will focus on the relative size and selected anatomical and biochemical differences between two visual areas (V1 and V2): distinct lamination, separate thalamic input, and characteristic distribution of the mitochondrial enzyme cytochrome oxidase (CO). These anatomical and biochemical features of the two areas are remarkably similar in all old world primates, including macaque and human (Allman, 1989; Burkhalter and Bernardo, 1989; Shkol'nik-Yarros, 1971; VanEssen, 1985). How is a cortex with such diverse anatomical and biochemical characteristics in adjacent areas created in phylogeny? What controls their relative size and appearance?

Early Cellular Events and Formation of Embryonic Zones

To understand the relevance of the radial unit hypothesis for cortical phylogeny it is essential to review early cellular events that occur in the telencephalon during cortical ontogeny. The telencephalic wall in the embryo contains several cellular zones that do not have counterparts in the adult cerebrum (renewed and updated in Rakic, 1982). The lining of the cerebral ventricle during the entire first half of gestation of both the macaque and human consists of proliferative cells that eventually produce all neurons of the neocortex. These precursor cells form the germinal, or *ventricular zone* (Figure 1). The proliferative cells in this zone are in different phases of mitotic cycle and have radial processes that protrude towards the pial surface and form the outer cell-free marginal zone (Figure 1C). These neuronal precursors, intermixed with dividing radial glial cells, are arranged in a pseudostratified manner and are attached to the ventricular surface by their endfeet. I termed a group of precursor cells that form a pseudostratified column separated by a glial cell a *proliferative unit* (Rakic, 1978). Cohorts of cells produced in succession from the same proliferative unit migrate along radial glial fascicles and pass through the *intermediate* and *subplate zones* before entering the developing cortical plate (Figure 1C).

Neurons that arrive at the cortical plate pass by each other and become arranged radially in the form of *ontogenetic columns* (Rakic, 1982). Thus, an ontogenetic column is defined as a cohort of neurons that originate from several progenitors of the same proliferative unit. These columns are easily discernible in the cortical plate during midgestation (e.g., Figure 1 in Rakic, 1988). The radial unit, migrating pathway, and ontogenetic column together form the *radial unit* that extends from the ventricular to pial surface. Therefore, the developing neocortex can be considered as a mosaic composed of a large number of such radial units. A full description of cytological details, including ultrastructural and immunocytochemical documentation for the underlying developmental events can be found in previously published papers (Rakic, 1971, 1972, 1974, 1976, 1978, 1982, 1988; Rakic *et al.*, 1974; Levitt and Rakic, 1980; Levitt, Cooper and Rakic, 1981, 1983; Schmechel and Rakic, 1979a, b).

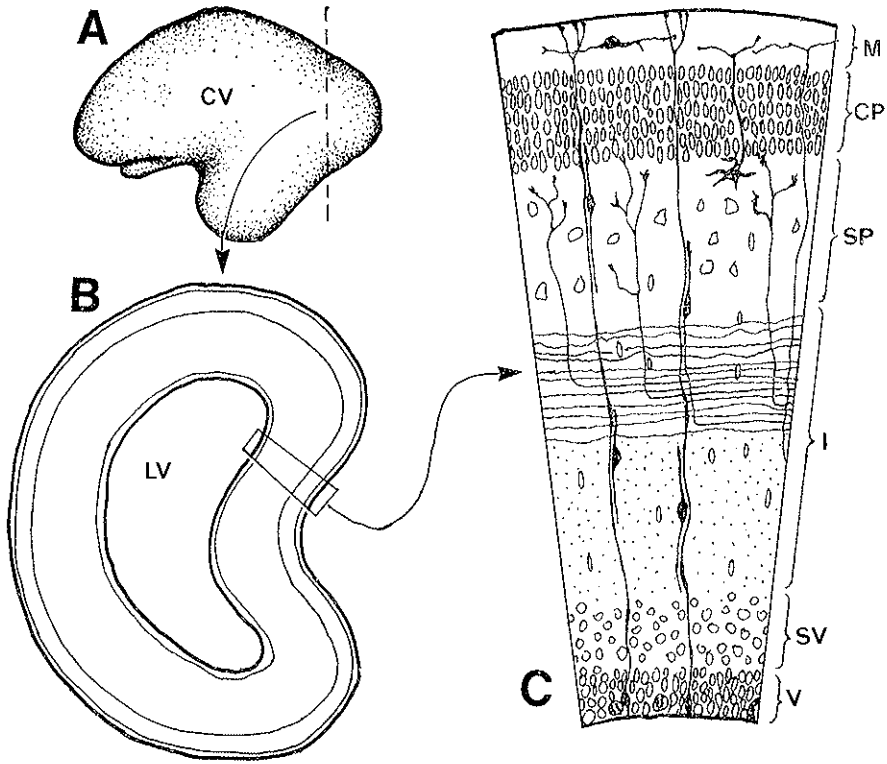

FIG. 1. Cytological organization of the primate cerebral wall during the first half of gestation. A. Cerebral vesicle of 60-65 day old monkey fetuses is still smooth and lacks characteristic convolutions that will emerge in the second half of gestation. B. Coronal section across the occipital lobe at the level indicated by a vertical dashed line in A. The lateral ventricle at this age is still relatively large and only the identification of incipient calcarine fissure marks the position of the prospective visual cortex. C. A block of the tissue dissected from the upper bank of calcarine fissure. At this early stage one can recognize all embryonic layers: ventricular zone (V); subventricular zone (SV); intermediate zone (I); subplate zone (SP); cortical plate (CP); and marginal zone (M). Note the presence of migrating neuron (dark bipolar profiles) moving along radial glial fibers which span the full thickness of the cortex. The early afferents from the brain stem and thalamus invade the cerebral wall and accumulate in the subplate zone, where they make transient synapses before entering the cortical plate. Further explanation in text.

Formation of Radial Units

Before E40 all cells in the ventricular zone of the monkey telencephalon are still dividing. Most divisions during this phase are symmetrical, indicating that each progenitor produces two additional progenitor cells during each mitotic cycle (Rakic, 1988). As a consequence, this mode of proliferation leads to an exponential increase in the number of cells in the ventricular zone: e.g., each extra round of mitosis before E40 doubles the number of progenitor cells (Figure 2A). This increase

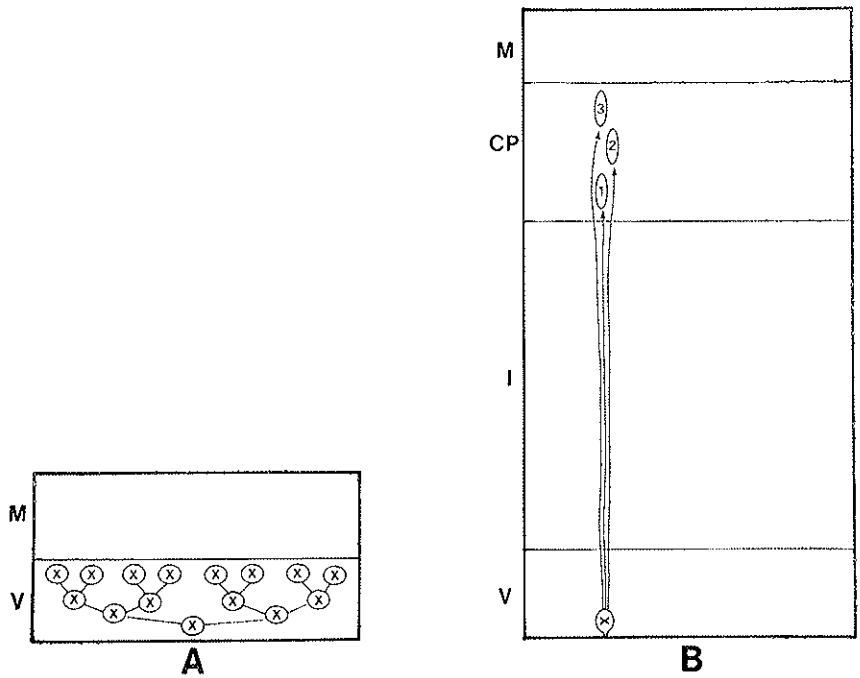

FIG. 2. A. Schematic model of symmetrical cell divisions which predominate before the 40th embryonic day (E40). At this early age the cerebral wall consists of only the ventricular zone (V), where all cells proliferate and the marginal zone (M), where they extend their radial processes. Symmetric division produces two progenitors during each cycle and causes lateral spread. B. Model of asymmetrical division which becomes predominant in the monkey after E40. During each asymmetrical division progenation produces one postmitotic neuron which leaves the ventricular zone and another progenitor which remains within the proliferative zone. Postmitotic neurons migrate across the intermediate zone (I) and become arranged in the cortical plate (CP) in reverse order of their arrival (1, 2, 3). Further explanation in text.

in turn may be responsible for the surface enlargement of the cerebral cortex or, in the case of regional differences in mitotic activity, for enlargement of certain areas.

Around E40 some progenitors begin to produce postmitotic neurons that will never divide again (Rakic, 1974, 1988). The inhibition of DNA synthesis in neurons after this point is so powerful that they can not be induced to reenter the cell cycle even in pathological conditions or malignancy (Rakic, 1985). Many precursor cells, after E40, divide asymmetrically and therefore only one of the two daughter cells becomes permanently postmitotic. It detaches its endfoot from the ventricular surface and migrates towards the pial membrane to become a cortical neuron (Figure 2B). The other daughter remains attached to the ventricular zone by the endfoot and continues to divide giving additional pairs of unequal cells: one postmitotic progenitor and one neuron (Rakic, 1988). This pattern of cell division proceeds during the next 30 to 60 days depending on the cortical area (Rakic, 1974, 1976, 1982).

Initial evidence for the radial organization of the developing cortex comes from the light and electron microscopic analysis of the developing cerebral vesicle. The ventricular zone from early stages shows a pseudostratified organization of cells that are deployed radially. Electron microscopic analysis reveals columns of radially oriented bipolar cells that are directly apposed to the elongated radial glial fibers (Rakic, 1971, 1972). This model is presented schematically (e.g., Rakic, 1971, 1972, 1978; Rakic *et al.*, 1974). The affinity between migrating neurons and the surface of radial glial cells initially implied from electron microscopic observations was also demonstrated in tissue culture analysis (Hatten and Mason, 1986) and several candidate adhesion molecules are currently under study (e.g., Schachner *et al.*, 1985; Edmondson *et al.*, 1988; Edelman, 1983). A series of experiments, in which prelabeled ventricular cells from an embryo are transplanted into the cerebral wall of a neonatal animal, show that donor neurons move along radial pathways and become arranged predominantly in a radial fashion — settling in the cortex according to their origin and laminar position in the donor (McConnell, 1988).

The radial unit organization of the cerebral cortex has been also confirmed by recent experiments using recombinant retroviral vectors to trace cell lineages from the place of their origin to their ultimate destiny. The viral marker gets introduced into a dividing cell's genome and is passed without dilution to all progeny of an infected cell (Sanes, 1988).

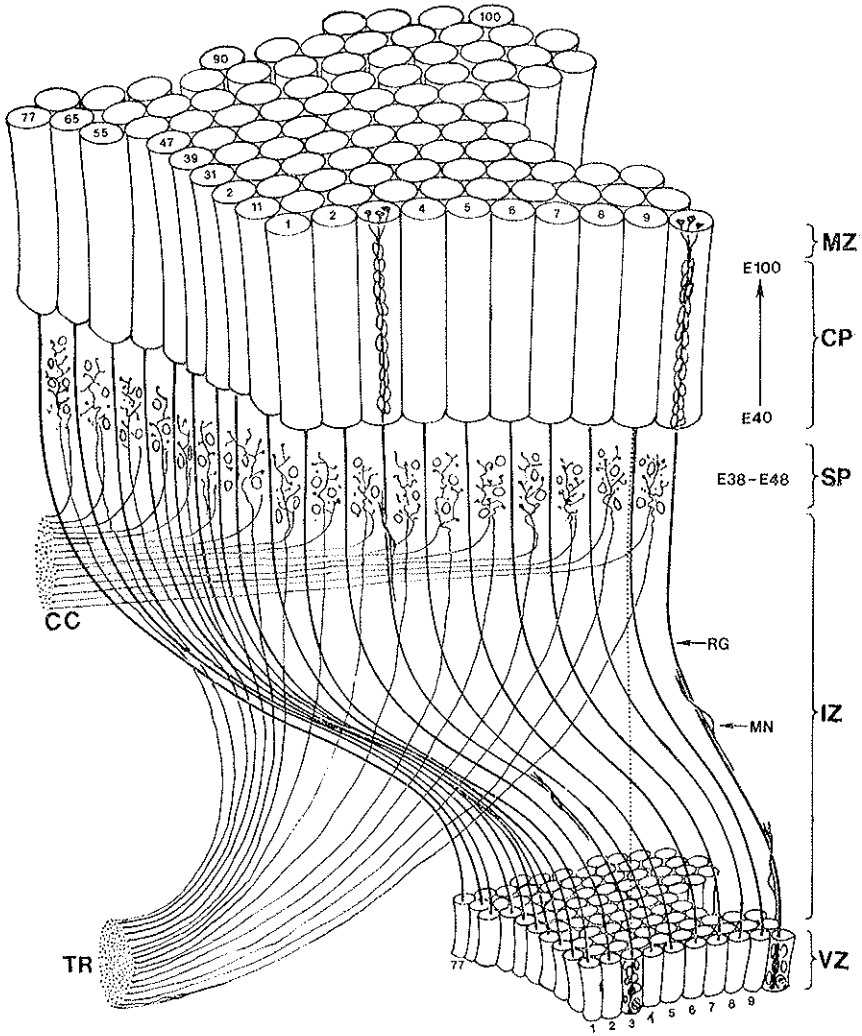

FIG. 3. The relationship between a small patch of the proliferative, ventricular zone (VZ) and its corresponding area within the cortical plate (CP) in the developing cerebrum. Although the cerebral surface in primates expands during prenatal development, resulting in a shift between the VZ and CP, ontogenetic columns (outlined by cylinders) remain attached to the corresponding proliferative units by the grid of radial glial fibers. Cortical neurons produced between embryonic age 40 and 100 by a given proliferative unit migrate in succession along the same radial glial guides (RG) and form a single ontogenic column. Each migrating neuron traverses the intermediate (IZ) and subplate (SP) zones, which contain « waiting » afferents from the thalamic radiation (TR) and callosal and intrahemispheric fasciculi (CC). After entering the cortical plate, each wave of migrating neurons bypasses previously generated neurons and assumes a positoin at the interphase between the CP and marginal zone (MZ). As a result, proliferative units 1-100 produce ontogenetic columns 1-100 in the same relative position to each other. The glial scaffolding prevents a mismatch between proliferative unit 3 and ontogenic column 9 (dashed line). Thus, the specifications of topography and/or modality depend on the spatial distribution of proliferative units, while the phenotype of neurons within each unit depends on its time of origin. (From Rakic, 1988).

Retrovirus injected directly into the embryonic cerebral ventricle at the time of corticogenesis is incorporated into only a few cells and clonally-related cells follow a common migratory pathway and remain radially oriented in the developing cortical plate (Luskin *et al.*, 1988). The labeled clones of neurons form interrupted columns, interspersed with unlabeled neurons that are presumably generated in the same proliferative unit from different progenitors just as could be predicted from the radial unit hypothesis.

Proliferative activity in the ventricular zone that leads to the establishment of the cortex can be divided into two broad phases (Rakic, 1988): the phase of unit formation which proceeds by symmetrical division and occurs mostly before E40 and the phase of ontogenetic column formation which begins around E40 and lasts until the completion of corticogenesis. I suggested that these two phases may be controlled by different regulatory genes — the first one controlling the size and duplication of cytoarchitectonic areas, the second controlling the formation and differentiation of neuronal phenotypes within each ontogenetic column (Rakic, 1988). There are several lines of evidence that these two phases can be separately affected by experimental manipulations or genetic perturbations. A deficit occurring during unit formation produces a cortex with a small surface area but normal thickness, while a defect during the phase of ontogenetic column formation produces a thin cortex with a large surface (Rakic, 1988).

Relationship between Ontogenetic and Functional Columns

At later stages of development and in adults the initially simple radial organization of the cortical plate is distorted due to neuronal growth, development of their processes, introduction of afferent fibers, formation of synapses, myelination, proliferation of glial cells, and ingrowth of blood vessels. A severalfold increase in the cortical surface between completion of the migratory phase and maturity causes horizontal displacement of neurons which initially had a simple radial relationship. The anatomical and functional relationship between clonally-related cells in mature cortex remains a challenge to researchers in this field.

At present it is not possible to establish a direct relationship between ontogenetic columns and functional columns because we do not know their precise boundaries. For example, receptive field columns present in sensory cortexes are defined as a group of radially deployed neurons

that all have the same receptive field (Mountcastle, 1957, 1979). On the other hand some « columns » that are defined by the terminal fields of afferent input such as ocular dominance columns (Hubel and Wiesel, 1977) or callosal columns (Goldman and Nauta, 1977; Goldman-Rakic and Schwartz, 1982) are in reality stripes. Other types of « columns », such as orientation columns in the visual cortex, are morphologically less precisely defined and gradually merge from one to another (Hubel and Wiesel, 1977). In most instances, more than one ontogenetic column must be involved in a given functional column or, in the case of stripes, rows of columns (Rakic, 1988). The important common feature among the cellular compartments or modules described in the mature cortex is the principle of radial organization (Mountcastle, 1979). It has been repeatedly shown that the neurons in the upper and lower layers of the given cortical segment have a close anatomical and functional relationship in the adult cortex (e.g., Szenthagothai, 1983; Eccles, 1984). Although the relationship between ontogenetic and functional columns is probably not simple, available data reveal a principle of radial organization that has its origin in developmental events explicable in the context of the radial unit hypothesis. Embryological and lineage studies reviewed above show that neurons in a given radial compartment arise from the same sector of the ventricular zone. It remains to be shown directly, by double labelling techniques, whether clonally-related cells are preferentially interconnected.

The Concept of a Cortical Protomap

Perhaps the most relevant aspect of the radial unit hypothesis for understanding cortical phylogeny is that the larger the number of proliferative units in an individual or in a given species, the larger the surface of the cortex (Rakic, 1988). Theoretically, all units and columns of neurons could be initially identical or pluripotential. In this extreme case, differentiation of cortex into cytoarchitectonic fields must be imprinted on the developing cortical plate exclusively by the information derived from the afferents arriving from the periphery via thalamocortical projections (e.g., Creutzfeldt, 1977) or monoamine fibers from the brain stem (e.g., Ebersole, Parnavelas and Blue, 1981). Although there is little doubt that all cortical afferents must play an important role in shaping the size of cytoarchitectonic areas (Rakic, 1988), there are several lines of experimental evidence that suggest the existence of a basic bleuprint, a

provisionary cortical map, or at least a molecular heterogeneity of the cerebral wall. Since, as discussed below, the basic blueprint can be modified by competitive cell interactions, I termed it a *protomap* to underscore its primordial, malleable character (Rakic, 1988).

The first line of evidence for the protomap in the developing telencephalon comes from studies of normal development. A relatively well-preserved register between proliferative units in the ventricular zone and ontogenetic columns in the cortical plate suggests a definite spatial relationship between two structures. Furthermore, ^{3}H-thymidine autoradiographic analyses show that a portion of the ventricular zone subjacent to one area produces a different number of neurons than an equivalent size portion in the other (Rakic, 1976, 1982, 1988). Thus, a portion of the ventricular zone in the V1 area which contains a larger number of neurons in each ontogenetic column *anticipates* becoming visual by producing more cells (Rakic, 1988). The existence of some sort of map in the cortical plate prior to the arrival of axons is also supported by the common finding that specific thalamic afferents are attracted only to specific areas.

Another line of evidence for the heterogeneity of the ventricular and intermediate zones comes from the recent histochemical and immunocytochemical studies of the embryonic cerebral vesicles using a variety of molecular markers which show that various macro-molecules are expressed in a spatially restricted manner. Heterogeneous classes of molecules, including some oncogenes, glycoconjugates, vimentin, or several types of adhesion molecules may be distributed transiently in the cerebral wall in broad radial "patches", "columns", or barrel fields before afferents from the periphery had an impact (Cooper and Steindler, 1986; Johnson and Van der Kooy, 1989; Hutchins and Casagrande, 1989; Steindler *et al.*, 1989).

Our recent study of the distribution of a mitochondial oxidative enzyme — cytochrome oxidase (CO) — in the visual cortex of mature monkeys that were subject to prenatal binocular enucleation before neurons destined for these layers are generated provides experimental evidence that at least certain molecular features of the cytoarchitectonic areas may develop independently of the information from photoreceptors at the periphery (Kuljis and Rakic, 1990). In the normal adult monkey CO is distributed in layers II and III of V1 in the form of "blobs" or "puffs" that are interspersed with CO-free interpuff areas (Wong-Riley and Carroll, 1984; Livingstone and Hubel, 1988). In addition, neurons containing neuroactive peptide Y (NPY) are distributed predominantly

in the interpuff regions (Kuljis and Rakic, 1989). It is thought that neurons in the puff and interpuff regions subserve predominantly color and non-color vision (Livingstone and Hubel, 1988). In a cortex that has developed in the absence of the retina from an early embryonic age, before photoreceptor cones and rods that mediate these two visual functions have been generated or connected to the central pathways (Rakic, 1977; Nishimura and Rakic, 1987), these cytochemical features nevertheless develop normally (Kuljis and Rakic, 1990). Thus, at least some structural and chemical characteristics of neocortical modules are specified in the absence of input from photoreceptors at the periphery.

Modifiability of the Protomap in Ontogeny

The existence of a cortical protomap does not imply that every detail or the final size of each cytoarchitectonic area is rigidly prespecified in the ventricular zone. Recently, I provided experimental evidence of the role that thalamic input plays in regulating the size of a given cytoarchitectonic area in monkeys (Rakic, 1988). Due to transneuronal degeneration, early prenatal bilateral enucleation diminished drastically the number of geniculocortical afferents, which in turn caused a proportional reduction in the size of visual cortex. Nevertheless, V1 in enucleates was remarkably normal in thickness, layering pattern, synaptic density, and pattern of cytochrome oxidase reactivity, but had a considerably smaller surface (Rakic, 1988).

In spite of the smaller cortical size in early enucleates, CO-rich puffs retain the same size and similar packing density per unit area as in normal monkeys (Kuljis and Rakic, 1990). Our results, therefore, indicate that the reduction in the size of V1 cortex in enucleates is accomplished by deletion of a number of cellular modules rather than by their shrinkage. This suggests that the protomap which exists at the stage of unit formation is subject to modification through interactions with afferent inputs. The final number of ontogenetic columns devoted to a given area, and therefore its final size, can be regulated by the number of specific thalamic afferents present at the critical developmental stage (Rakic, 1988).

The cellular mechanism of the reduction of V1 in early enucleates is not fully understood, but some possibilities are illustrated in Figure 4: area V1 can simply lose a number of ontogenetic columns by diminishing the total size of the cortex (Figure 4B). Alternatively, V2, which nor-

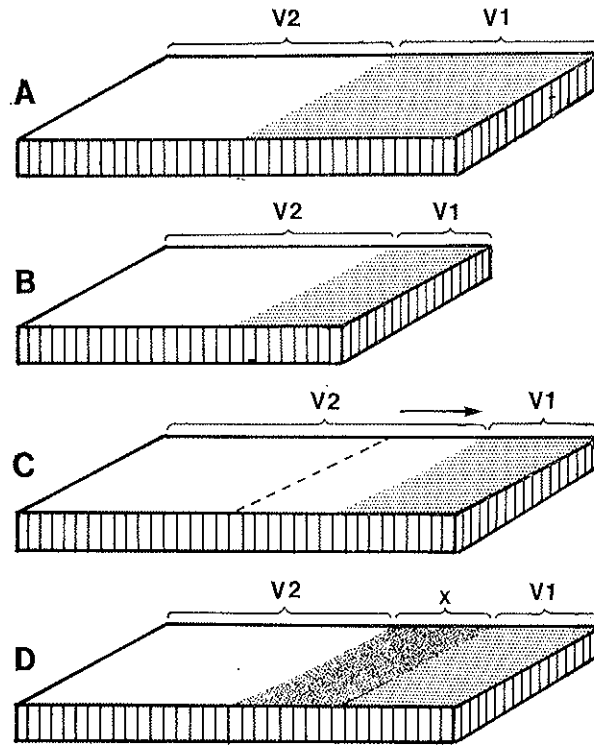

FIG. 4. Schematic representaiton of the possible modes of decrease in the size of V1 caused by experimental reduction of thalamic input. (A) Relation between areas V1 and V2 in a normal animal; (B) differential cell death; (C) encroachment of adjacent V2 into the territory of V1; (D) formation of an abnormal cytoarchitectonic area (X) that consists of neurons genetically destined for area 17 but which receive input characteristic for area 18. (From Rakic, 1988).

mally receives input from the adjacent thalamic nucleus (pulvinar) and from the other parietal and temporal cortices, could take over some of the territory from V1 (Figure 4C). Finally, a number of columns that were specified for V1 (X in Figure 4D) could, in the absence of normal afferents, receive input from the pulvinar and become a "hybrid" cortex that is genetically V1 and connectionally V2. This third possibility provides a model that could provide a useful, though indirect, way to test how novel cortical areas can be introduced during evolution. This model assumes an initial increase in the number of ontogenetic columns which subsequently serve as a substrate for completion for incoming afferent axons.

Implications for Cortical Evolution

There is probably little disagreement that between a common ancestor of Mesozoic mammals some 200 million years ago and living primates there must have lived a now-extinct species with numerous combinations of cortical cytoarchitectonic maps that eventually led to the present forms (Fleagle, 1988; Passingham, 1982). However, when it comes to providing the genetic or cellular basis of how this expansion of neocortex could have been achieved during the process of evolution, we have much less knowledge and much less agreement. There are several attempts to relate data from comparative neuroanatomy and contemporary research in neuronal plasticity to the cellular issues of brain phylogeny. (e.g., Armstrong and Falk, 1982; Ebbeson, 1984; Allman, 1989; Kaas, 1988; Finley *et al.*, 1987). The major drawbacks of such theories is that they can not be substantiated since experimental methods can not be used on fossils. The basic strategy of our approach is to extrapolate cellular mechanisms and principles of corticogenesis derived from embryonic development of living primate species to the possible cellular events that may take place during the evolution of cortical parcellation. Although the macaque species under study are not in the same phylogenetic line as humans, we do share with them a common ancestor. I will discuss below several aspects of cortical evolution that are explicable in terms of the radial unit hypothesis and our present knowledge of corticogenesis in normal, genetically or experimentally perturbed rhesus monkeys.

The neocortex in living primitive placental mammals that are thought to be close to early primates such as hedgehog is one thousand times smaller in surface area than in human. Yet the thickness of the cortex in the same period of evolution increases only about two times. I have argued elsewhere (Rakic, 1988) that this can be explained by the enormous increase in the number of proliferative units produced during the first phase (of unit formation) and only a moderate increase in production of neurons by each unit during the second phase (of formation of ontogenetic columns). Thus, during the first phase each symmetric division doubles the number of progenitors during each cycle (Figure 2A). While, during the second phase, when asymmetrical divisions predominate, an additional cycle adds only a single neuron to a given ontogenetic column (Figure 2B). As a result, an extra round of cell cycle at the end of corticogenesis produces only about 1% of the total cortical population. The difference between the linear increase which prevails at later stages

of corticogenesis stands in contrast to the exponential increase that occurs during the earlier phase. This distinction is important. For example, three divisions at the early phase would produce eight times more progenitor cells and as a consequence an eight times larger number of radial units (Figure 2A). Therefore, only slightly more than three rounds of cell division at the end of the first phase of unit formation can account for the difference in cortical size between rhesus monkey and homo sapiens. Theoretically, substantial changes in the total surface of the cortex can be attributed to a single or only a few heterochronic processes, but this hypothesis is not sufficient to explain the uneven growth of various cytoarchitectonic areas.

Remarkable variation in the number and size of cytoarchitectonic areas devoted to vision in living primates suggests that they are introduced during evolution sequentially and expand or retract independently (Allman, 1989). Accordingly, this area represents about 15% of the total cerebral surface in monkey and only 3% in human because other cytoarchitectonic areas differ even more in relative size, particularly association cortex, which is in man expanded more than in any other species (Blinkov and Glezer, 1968). Considering that about 22 million years ago the common ancestor of rhesus monkey and *homo sapiens* had a smaller surface of the cortex, how is this species variation achieved? What are the underlying cellular mechanisms?

I suggest that the differential expansion of the cortex can be explained in the context of the radial unit hypothesis (Rakic, 1988). According to this hypothesis, changes in the cytoarchitectonic map could be explained by the heterochronic process or modification of timing and proliferation kinetics in the ventricular zone coupled with competitive interactions with extracortical neurons. For example, extra rounds of mitotic divisions before E40 could produce a larger number of radial units. After additional ontogenetic columns of postmitotic neurons are added to the existing areas, this expanded cellular mass could provide a new synaptic territory with an opportunity for the spread, new combinations, and competitive interactions among incoming afferents. The last statement underscores that the enlarged cortex, without new input-output relationships, is not sufficient to provide extra functional benefits to the individual.

Although the radial unit hypothesis may be compelling in terms of what we presently know about cortical ontogeny, it is obviously difficult to prove its validity for phylogeny. Let's suppose that the entire, or only part of the ventricular zone undergoes an additional round of cell divi-

sion during the first phase of unit formation. Additional columns of cortical cells resulting from this event then could compete for the various afferent inputs and form novel input-output affiliations that can be adverse, neutral, or beneficial to an organism. This extra round of cell divisions, which can occur either due to genetic mutation or normal variation, must be inheritable so that new cell relationships could be enhanced through the process of natural selection. If additional columns turn out to present an advantage for the survival of the organism, it may be selected by preferential propagation of individuals with this trait. This hypothesis may not be directly testable, but some ongoing experiments in our laboratory are relevant to this issue.

Recently, we designed a model in which a larger than normal amount of cortex is devoted to a given function. In an initial study of the visual system in animals with prenatal monocular enucleation the remaining eye projects to the lateral geniculate nucleus which retains a normal number of neurons (Rakic, 1981). Geniculate cells in turn project to the visual cortex, which also retains a normal number of neurons but does not have ocular dominance columns. Since synapses seem to be ultrastructurally and biochemically normal in such cases, information from a single eye in these animals can be analyzed by a two times larger number of cortical neurons and synapses than in the normal monkeys (Rakic, 1981). It has been theorized that the computational ability of the V1 for the analysis of certain visual features, such as Vernier hyperacuity, depends on the number of local circuit neurons in the primary visual cortex in relation to the number of photoreceptors (Barlow, 1975; Crick, Marr and Poggio, 1981). We posed the question whether the change in numerical relationship in monocular enucleates is beneficial, neutral, or deleterious to the animal's visual cortical capacity. We first performed a 2-deoxyglucose experiment in behaving animals, which showed that all cortical neurons are active (Rakic, Friedman and Goldman-Rakic, unpublished). That is, a single remaining eye apparently drives a two times larger number of cortical neurons. After that we performed a psychophysical test of Vernier acuity, a specific function of visual cortex. Our preliminary evidence shows statistically better Vernier hyperacuity in monocular animals than in controls with both eyes, and the difference is even larger when the results are compared to a single eye in the control animals (MacAvoy, Bruce and Rakic, 1987). One can, therefore, speculate that thalamic input which is experimentally spread to a larger than normal area of the cortex devoted to a given

function may provide synaptic relationships that improve performance. In the context of an evolutionary hypothesis one can speculate that when new inheritable thalamocortical affiliations are formed, they also could provide the conditions for better performance with a presumed survival advantage for the individual that is fostered through selective breeding.

The purpose and limit of the present article precludes further elaboration of the radial unit model of cortical evolution and does not allow for provisions of additional examples of supporting evidence. However, I hope that the examples selected demonstrate how studies of normal ontogeny and experimental manipulation of cortical development can be used to suggest possible cellular and genetic mechanisms that could underlie phylogenetic development. I believe that this type of research will not only explain the pathogenesis of certain genetic and developmental disorders of higher cortical function, but could also provide insight into the evolution of cerebral cortex and the uniqueness of human mental capacity.

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DISCUSSION

ZEKI

What about area 18 stripes? Do you also get these in the absence of enucleation where you have got your sections through area 18?

RAKIC

No we don't.

ZEKI

What do you predict from your discoveries about area 17 so far?

RAKIC

I think that area 18 would have stripes.

ROLAND

Do you know any organizing principle for the ingrowth of aminergic fibres into the cortex, since these originate somewhere else down from the brain stem? Is there any general principle, for instance, for noradrenergic innervation of the developing cortex and serotonergic innervation?

RAKIC

We expect that they come normally. We are looking for receptor bindings and you see that receptors are present all over the cortex, even in area 17, except for that area close to it which is a little disturbed. So, they are certainly present but they might be disturbed.

SZENTÁGOTHAI

I am fascinated with your protomap concept. When you think it through, it should be something like that. Now, would you care to speculate a little

further in view of what we discussed in relation to speech development and speech areas? The early prehominid brain is more or less already a brain which theoretically could have the ability to generate speech, but how does it come about that these specific regions, which we find in the human, suddenly appear? We have to assume that new protomaps are generated. As was pointed out earlier in the discussion, not only speech developed, but also standing, loss of hair and a couple of other things. So would you speculate on how you could imagine that such things appear just de novo at the appropriate place?

RAKIC

I would like to speculate, since you ask me. I did think about that and not only in relation to the speech area. As Otto Creutzfeldt has pointed out, one has to deal with both the interaction between the periphery and the centre as well as with the interaction between the centre and the periphery. Supposing that in evolution, mutation occurs and that one or three areas during unit formation, that is before embryonic day 40, have extra cell division, the size of those areas is doubled. Later on when cells move to the cortex, thalamic inputs organize themselves. The cortex now provides larger analysis capacity, our "computer" brain has more chips, and if this is connected to periphery and if periphery can handle that, you have new possibilities of using it in a better way. If it is an advantage to animals, then it survives. Genes have to provide capacity, environment will provide tests, whether this is good or not.

ECCLES

I want to ask you, have you ever done this on the human foetus, looked at the neurotube, at the times when the mitosis was going on?

RAKIC

You see proliferative units, you see ontogenetic columns, and I have a beautiful picture of columns in the human at embryonic stage day 20. As far as the protomap is concerned, this is a concept. The evidence for it is indirect.

CREUTZFELDT

I was very impressed by your last experiments with enucleation, which indicate to what extent the periphery creates its cortex. As you know, there

is similar evidence in the somatosensory system, on whisker representation in the cortex after removal of single whiskers, and so on. It was, in fact, already quite clear to Brodman and to von Economo especially, that the cyto-architectural differentiation is created by connections of the respective areas. They realized that before the thalamic connections are established, every area of the cortex looks the same.

The question is, whether the whole visual cortex simply shrinks or whether something else takes over the "empty" space, turning it into new areas. It is a critical point, whether area and surface get lost or whether it stays the same. In your pictures one got the impression that the brains looked slightly shorter after enucleation.

RAKIC

It does not shrink. We also looked at cell death. It is re-arranged so periphery does play a very important role in it, but it's not sufficient alone. There has to be a protomap because visual cortex always attracts geniculate, and therefore must be different from pre-frontal cortex. Geniculate never goes to pre-frontal, so pre-frontal is different from visual. However, geniculate plays a role in the size of area 17 and therefore when you change the size of one, you change the size of all. In this respect I agree with you, but total surface area is not appreciably diminished in the six animals we looked at.

CREUTZFELDT

But as you know from your own lab, from Foster's and Su's work, one can turn an auditory into a somatosensory cortex or a somatosensory into a visual cortex by removing the normal input from these areas and by destroying the usual target areas of the respective inputs.

RAKIC

You don't make it a visual area, you just record visual responses from it. You can record visual responses from the spinal cord if you put visual input into it, but that doesn't mean that spinal cord is equal to visual cortex.

LEJEUNE

I was very interested when you mentioned the anophthalmia because in man, if you have a triplicate chromosome 13, you always have anophthalmia and it would be extremely interesting to know if the cortex of those children has been examined. It's a rather frequent disease, and you could check your model in man.

RAKIC

Yes, one could check it in man. It was examined in anophthalmic mice, which is a genetic mutation. These animals have a visual cortex. They have normal architecture, it is just smaller. This is in full accord with our report. I saw one anophthalmia of unknown origin and it also confirmed that.

INTERNEURONS OF THE CEREBRAL CORTEX AND TRANSMITTER REGULATION BY SENSORY EXPERIENCE

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Introduction

The neocortex of higher primates is a structure of relatively immense size and functional complexity. In the human, it represents the end point of a continuous evolutionary process that, for still undefined reasons, two to three million years ago induced in the advanced Australopithecines an incremental leap in brain size. In the ensuing period the hominid brain has apparently undergone an increase in volume of approximately 100% (Tobias, 1971), much of this increase being accounted for by the disproportionate enlargement of the neocortex (Stephan *et al.*, 1981).

It is a popular belief that this massive increase in neocortical size and the increasing diversity of cortical function that accompanies it is attributable in large part to the addition of new and more diverse circuit elements. The Spanish neurohistologist, Ramón y Cajal, had an important influence with his remarks that "the functional superiority of the human brain is intimately linked up with the prodigious abundance and unaccustomed wealth of the so-called neurons with short axons" (Ramón y Cajal, 1917). While it is incontestable that the cortex has advanced by the accretion of enormous numbers of neurons, among them the short axon interneurons, it is now arguable that this has been accompanied by the appearance of novel varieties of neurons. One of the purposes of the present chapter, therefore, is to present the case that primate cortical evolution has, instead,

involved the addition of huge numbers of neurons of the same types as are found in subprimate cortices, probably in the same relative proportions.

Circuit Elements of Primate Neocortex

The intrinsic circuit elements of the neocortex are the two varieties of cortical neuron: pyramidal and non-pyramidal (Ramón y Cajal, 1899a, b, 1911; Valverde, 1971; Lund, 1973; Jones, 1975; Feldman and Peters, 1978; Peters and Regidor, 1981; Peters and Jones, 1984; Fairén *et al.*, 1984) (Fig. 1). The former cell type, with its stereotyped morphology, is one of the more easily recognized cells of the brain. With it, by convention, are included certain less stereotyped forms such as the majority of cells of layer VI, which possess the pyramidal cell features of a long dendrite ascending towards layer I, a high percentage of dendrite spines and an axon that leaves the cortex (Ramón y Cajal, 1989a,b; Jones, 1975; 1984; Feldman, 1984). Also included by Ramón y Cajal in this group were certain large multiangular or stellate cells, largely confined to layer IVB of the visual cortex, that he regarded as a pyramidal type of cell with a rudimentary or absent apical dendrite. Such cells, like pyramidal cells,

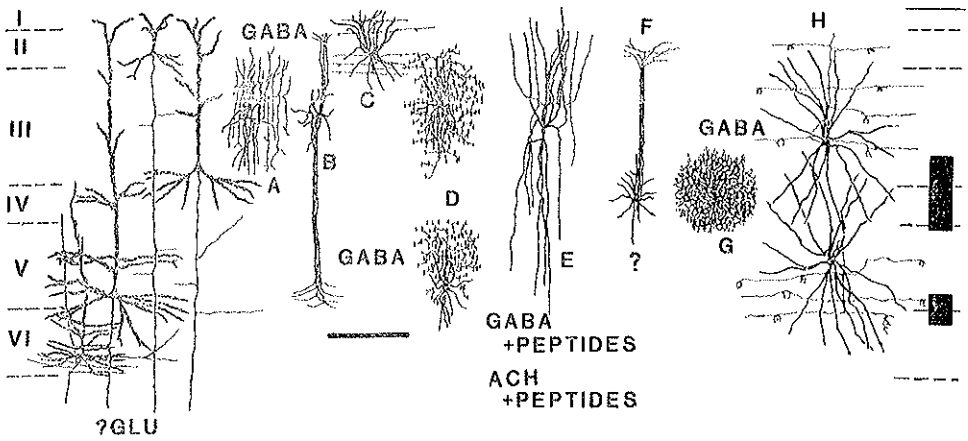

FIG. 1. Semi-schematic drawing of cell types and their known or putatively related transmitters and neuropeptides in the primate cerebral cortex (After Jones, 1975). Pyramidal cells (left) probably use glutamate. Non-spiny nonpyramidal neurons (A-E and G-H) are probably all GABAergic. Peptides tend to be colocalized with GABA in bitufted cell type (E) which in rats and monkey fetuses also contains choline acetyl transferase. Spiny nonpyramidal cell (F) is excitatory but transmitter is currently unclear. Bar 100 μm.

have high concentrations of dendritic spines and send axons out of the area of cortex in which they lie (Lund *et al.*, 1975).

The non-pyramidal cells fall into two classes: spiny and non-spiny. The spiny form is probably represented by a single form with ascending axon, whose dendritic tree assumes a stellate form in the visual cortex but is more elongated in other areas. It is largely confined to the middle layers of the cortex: layer IV and the deeper part of layer III. Other types lack significant numbers of dendritic spines and are divisible into approximately six distinct varieties. The distribution of the axon is the key to distinguishing these various forms although one, the basket cell, can also be identified by its large somal size, rivalling that of the largest pyramidal cell.

It would appear that the division of cortical neurons into spiny and non-spiny classes is a fundamental one. Such cells are distinguished by their biophysical properties, connectional relationships and transmitter characteristics. The nature of the discharges elicited from spiny and non-spiny neurons in slices of guinea pig cortex maintained *in vitro* and stimulated electrically suggests fundamental differences in membrane properties (McCormick *et al.*, 1985). Non-spiny cells are characterized by trains of brief spikes and little or no frequency adaptation. Spiny cells either display more regular spiking behavior or burst discharges.

The connections of cortical neurons are also distinctive and predictable. More than a decade of work with retrogradely transported tracers, allied with correlative physiological study, has enabled us to say that pyramidal cells, including the modified forms mentioned above, are the output cells of the cerebral cortex, sending their principal axon to subcortical sites or to other cortical areas, ipsi- and contralaterally (reviewed in Jones, 1984). Apart from the large layer IVB neurons of the visual cortex, which are only arguably "pyramidal", there are no examples of retrogradely labeled non-pyramidal neurons that cannot be explained away by incomplete filling of the cells or observer inexperience in recognizing the modulations of pyramidal cell form that normally occur.

Pyramidal cells, however, are also major contributors to intracortical circuitry via their far-flung axon collaterals. It is doubtful that the full extent of these collaterals had been revealed until the advent of single cell injection methods, but it is now clear that they can extend over relatively enormous distances. In the monkey postcentral gyrus, for example, individual collaterals 6-10 mm in length are regularly observed arising from the axons of cortico-cortical neurons (DeFelipe *et al.*, 1986a) (Fig. 2).

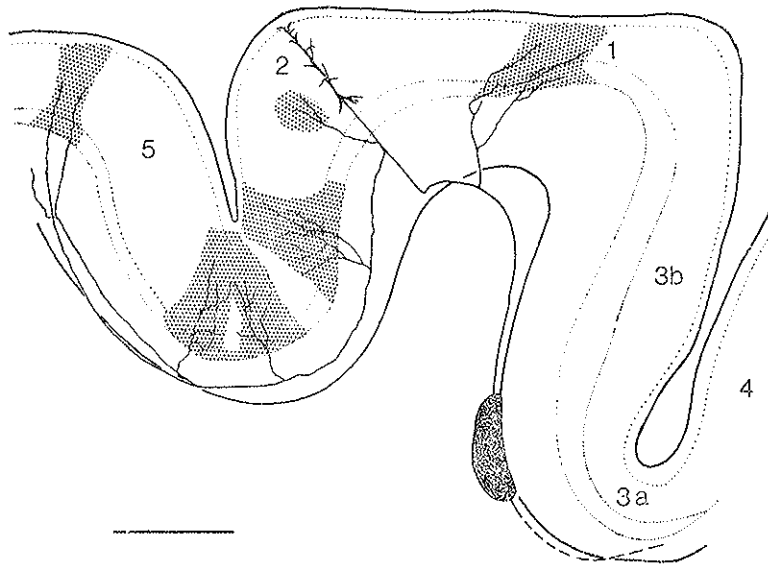

FIG. 2. Distribution of focused collateral terminations of a corticocortical neuron in area 2 of monkey somatic sensory cortex, the main axon of which projects to motor cortex (area 4). Cell and its collaterals were filled by horseradish peroxidase (black) injected into the damaged main axon. From material described in De Felipe *et al.* (1986a). Bar 500 μm.

These and similar collaterals in the visual cortex (Gilbert and Wiesel, 1983; Gabbott *et al.*, 1987) do not terminate indiscriminately but in focal patches of *boutons terminaux* at regular intervals. No axons of non-pyramidal cells have such an extensive spread, and the pyramidal cells, as a consequence, are probably the major contributors to the horizontal spread of excitation in the cortex.

The propensity for the collaterals to be given off, commonly selectively, in layers of the cortex other than that containing the parent soma, ensures that the collaterals are also major contributors to the vertical, interlaminar flow of cortical activity (Gilbert, 1983; Gabbott *et al.*, 1987; Jones, 1988).

The non-pyramidal cells, by contrast, have more restricted zones of influence since their axons are in general, all locally distributed (Jones, 1975; Gilbert, 1983; Martin, 1988). Even the basket cell, with its long horizontal axon branches, still appears to distribute the majority of its boutons in the general vicinity of the parent dendritic field (Martin *et al.*, 1983; De Felipe *et al.*, 1986b). While some of the non-pyramidal cell

types, e.g., the spiny and the double bouquet types, can be seen as mediating the interlaminar flow of excitation or inhibition, a potentially more useful view of their place in the neocortical circuitry can be obtained by considering that the axon terminals of each type seem to be targeted at specific parts of the surfaces of pyramidal cells (Hendry *et al.*, 1983; Houser *et al.*, 1983a; Somogyi and Martin, 1985) (Fig. 3). For example, chandelier cell axons end selectively on the axon initial segment, basket cell axons on the soma and bases of the stem dendrites, spiny cell axons and double bouquet axons on the dendritic spines of the apical and basal dendritic systems, and so on. The extent to which a pyramidal cell in a particular layer or projecting to a particular target receives a defined complement of synapses arising from each from of non-pyramidal cell remains to be determined. It is clear, however, that significant variation occurs. Layer III pyramids, for example, receive on average more chandelier cell axon terminals than layer V pyramids (DeFelipe *et al.*, 1985a; Fariñas and DeFelipe, 1988) and the variation per cell in each layer is very large.

Transmitter Characteristics of Cortical Neurons

The application of immunocytochemical methods to the study of the primate cerebral cortex has resulted in the localization of numerous neuroactive substances in that structure. Although the number and variety of neurotransmitters and neuropeptides found in the cortex is relatively large, a few simple generalizations can be made about their distribution. First, of the known "classical" transmitters only one, GABA, is regularly found in neocortical neurons of the primate (Fig. 4). This is found only in aspiny non-pyramidal cells and a case can be made that all the non-spiny types are GABA-ergic (Jones, 1986). The monoamines and acetyl choline appear to be confined to afferent fibers. Markers for cholinergic and aminergic transmission have, however, been described in neurons of the fetal cortex and in rodents (Hendry *et al.*, 1987a; Houser *et al.*, 1983b; Kosaka *et al.*, 1987).

Apart from GABA, the other major transmitter of neocortical neurons appears to be glutamate or a similar acidic amino acid (Baughman and Gilbert, 1981; Conti *et al.*, 1987; 1988a,b; DeFelipe *et al.*, 1988) (Fig. 5). There is also a very large number of neuroactive peptides in the cortex but these appear to be largely, if not exclusively, localized in a limited class of GABA-ergic neuron (Somogyi *et al.*, 1984; Hendry *et al.*, 1984b; Schmechel *et al.*, 1984; Jones and Hendry, 1986; Jones *et al.*, 1988a). This class

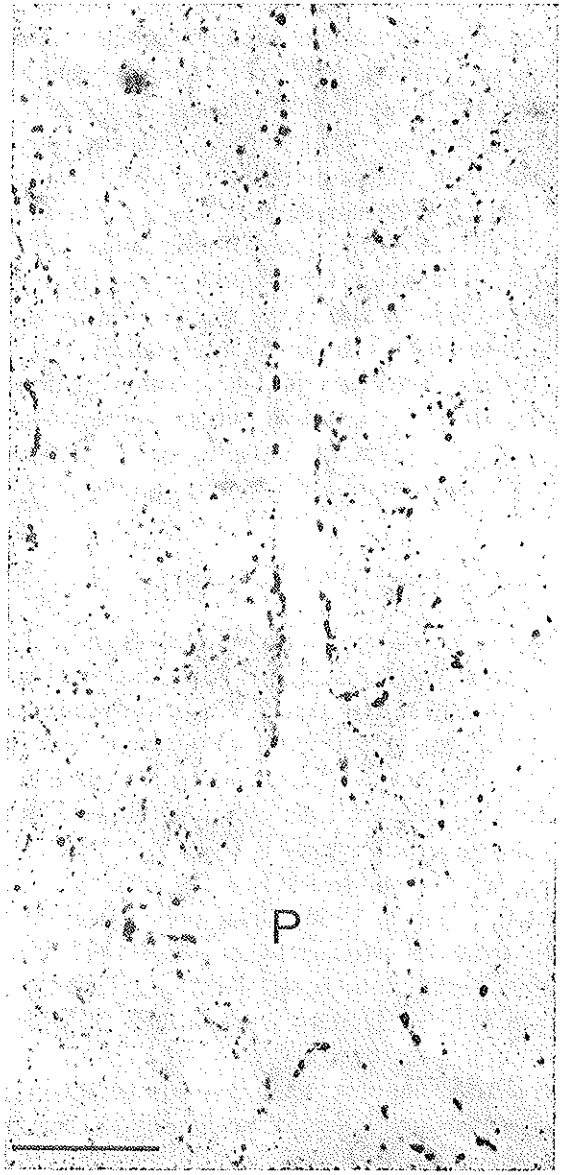

FIG. 3. Pyramidal cell (P) of monkey motor cortex whose soma, small and large dendrites and possible axon hillock are outlined by GAD immunoreactive terminals. Probably terminals of different types of GABA cell target different parts of the cell surface. From Houser *et al.* (1983a). Bar 20 μm.

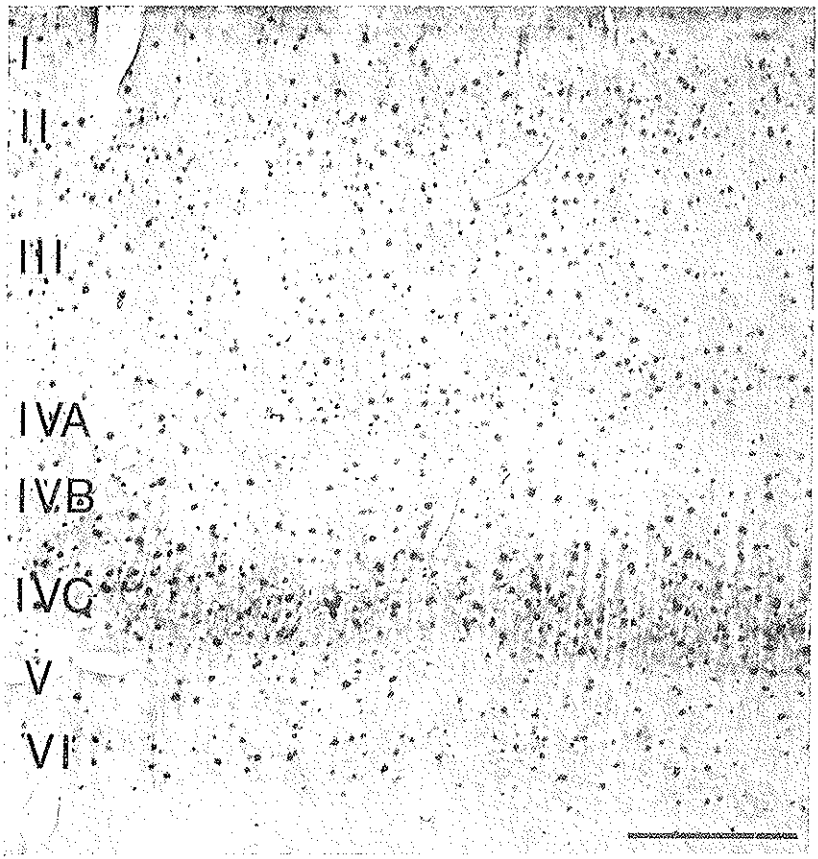

FIG. 4. GABA immunoreactive neurons in area 17 of monkey. Note concentrations in layers IVA and IVC. From Hendry *et al.* (1987b). Bar 250 μm.

is best described as bitufted although it can appear bipolar in some instances. Some cells of this class contain GABA and one, two or three peptides. Probably the group can be further broken down in terms of the placement of synaptic contacts of cells containing a particular peptide or particular peptides on the surfaces of pyramidal cells. Some, for example, appear targeted on more distal dendrites, others on proximal (Hendry *et al.*, 1984b).

The only cell variety that has not had a neurotransmitter reliably attributed to it is the small spiny intrinsic neuron. Although shown to display immunoreactivity for phosphate-dependent glutaminase in the rat

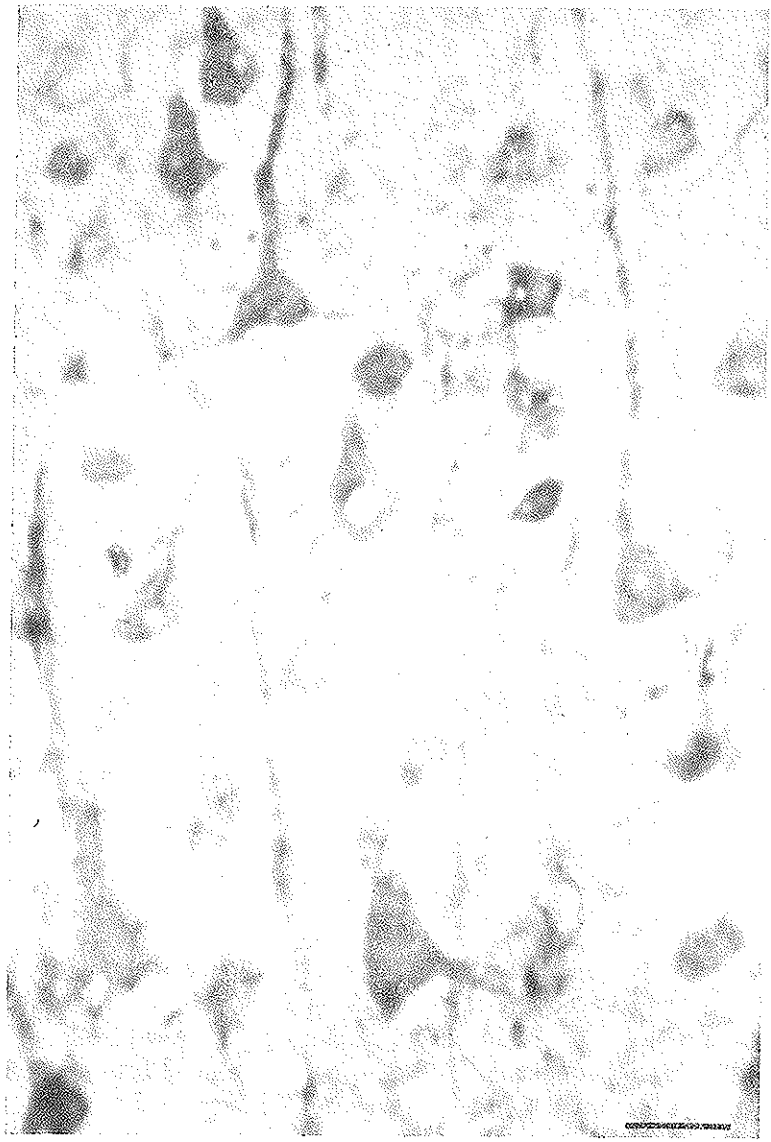

FIG. 5. Glutamate immunoreactive pyramidal neurons in monkey motor cortex. From unpublished work of the author. Bar 30 μm.

cortex (Donoghue *et al.*, 1985), it has been described as lacking immunoreactivity for glutamate itself in the cortex of several species (Conti *et al.*, 1987).

Studies of the localization of other molecules not directly related to the act of neurotransmission may yield further means of classifying cortical neurons. The known calcium binding proteins, for example, are confined to cortical GABA neurons (Celio, 1986; Stichel *et al.*, 1987; Celio *et al.*, 1986; Hendry *et al.*, 1989; DeFelipe *et al.*, 1989), and two of these proteins are differentially distributed, parvalbumin to basket cells and chandelier cells, calbindin to double bouquet cells (Jones *et al.*, 1988b; Hendry *et al.*, 1989; DeFelipe *et al.*, 1989 (Fig. 6). Type II calcium calmodulin dependent protein kinase, by contrast, is confined to pyramidal cells (Hendry and Kennedy, 1986) and various undefined neural antigens detectable by monoclonal antibodies characterize subsets of pyramidal and/or non-pyramidal neurons (Hendry *et al.*, 1989; Arimatsu *et al.*, 1987).

While allowing for the fact that immunocytochemistry may not reveal the full population of cells expressing a particular transmitter, it is possible to use the method in a quantitative manner to obtain an idea of the minimum number of cells in a transmitter-defined population. In a study of 10 areas of the Old World monkey cortex, (Hendry *et al.*, 1987b) the percentage of GABA immunoreactive cells was remarkably constant at approximately 25% for all areas, except the primary visual area, where, despite an almost doubling of the total cell population in comparison with the other areas, the GABA cell population fell to approximately 19% (Fig. 7). Similar studies on glutamate immunoreactive cells indicate a population that constitutes approximately 55% of the total neocortical population in the monkey (Conti *et al.*, 1987). Most neuropeptide cells are subsumed in the GABA population (Fig. 8). Those identifiable by peptide immunoreactivity without co-localization of GABA immunoreactivity, make up no more than 1-3% of the total neuronal population of the cortex. This leaves approximately 15% of the cortical neurons unaccounted for. One may provisionally assume that this represents the small spiny intrinsic neurons and it is probably a disproportionate increase in the number of these "spiny stellate cells" in layer IVC that accounts for the relative decrease in the GABA cell percentage in the primary visual cortex of primates.

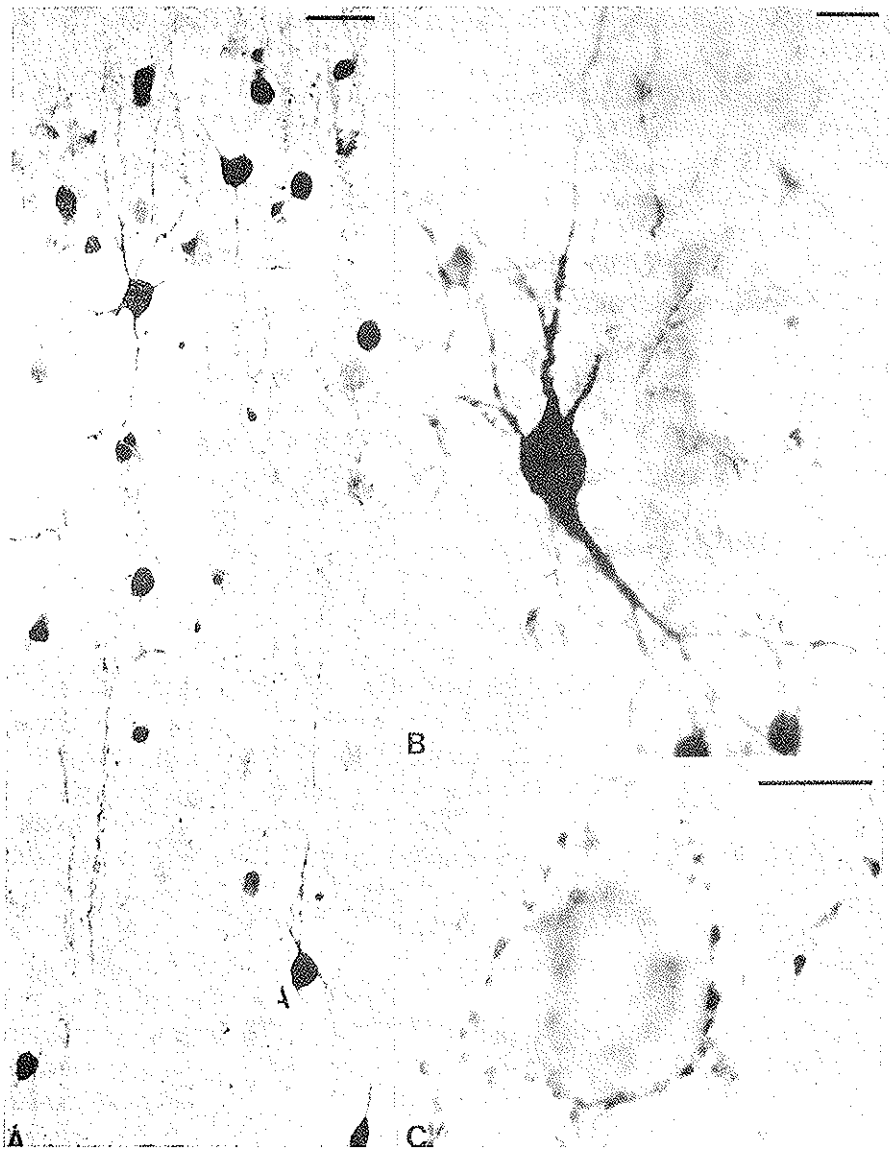

FIG. 6. A. Calbindin immunoreactive double bouquet cell in monkey area 5. B. Parvalbumin-immunoreactive basket cell and basket cell terminals (C) on a nonimmunoreactive pyramidal cell in monkey motor cortex. Colocalization of immunoreactivity ... (see following page).

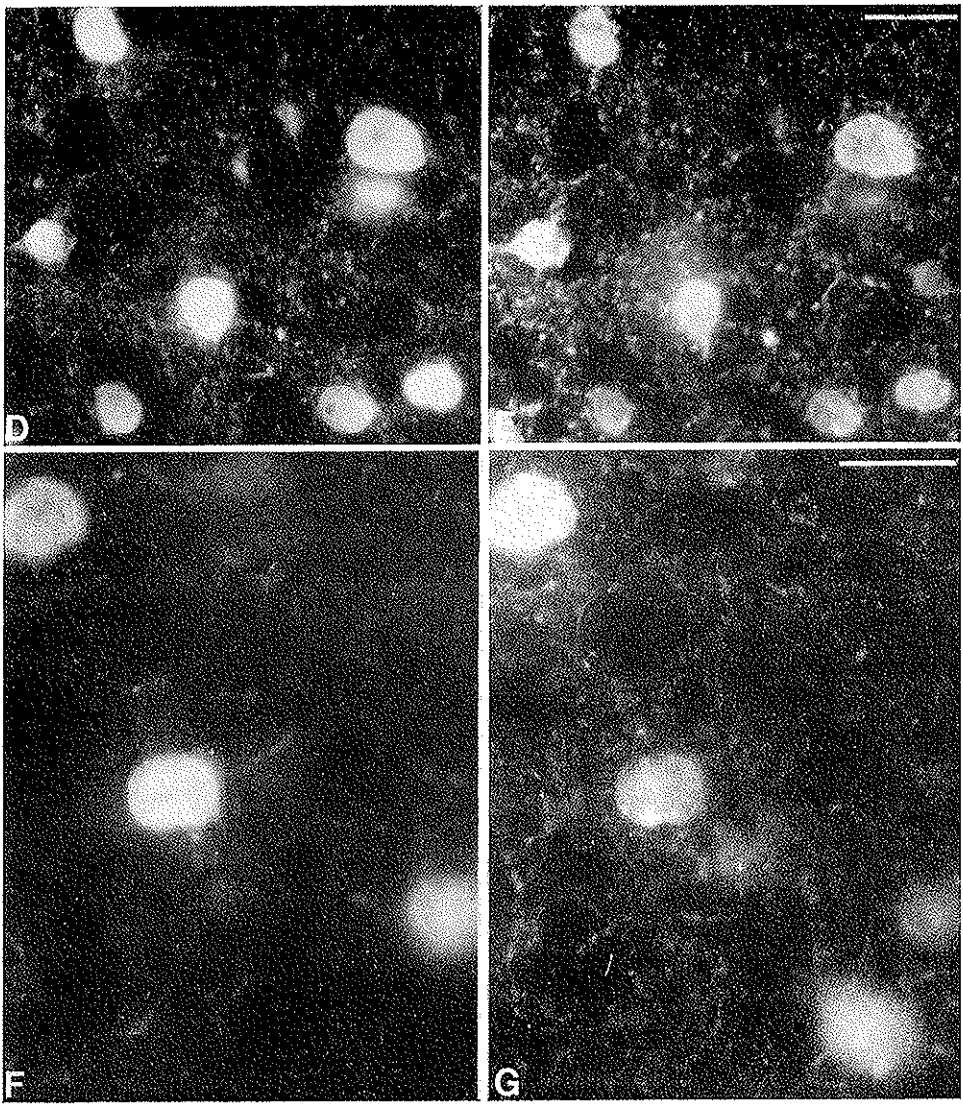

FIG. 6. ... parvalbumin (D) and GABA (E), for calbindin (F) and GABA (G) but lack of colocalization of immunoreactivity for ... (see following page).

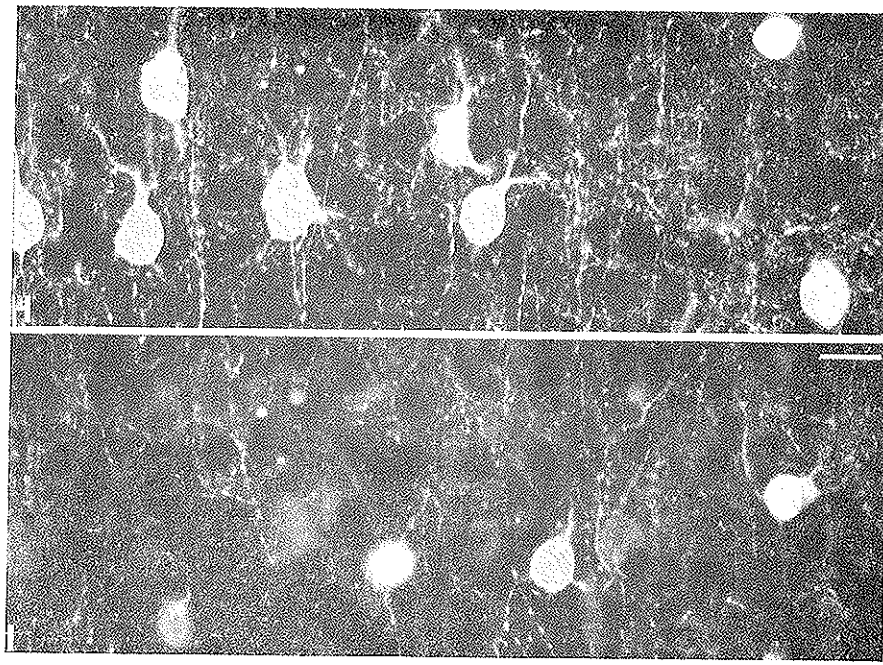

FIG. 6. ... parvalbumin (H) and calbindin (I). From Hendry *et al.* (1988a). Bars 25 μm.

Evolution of Neocortical Cell Populations

As pointed out at the beginning of this chapter, it is a popular belief that the greatly enhanced functional capacity of the neocortex in higher primates, as evidenced by their expanded behavioral repertoire, is accompanied by an increase in number and diversity of cortical circuit elements. The first intimation that this intuitive viewpoint may not necessarily be correct came in a study by Powell and his co-workers (Rockel *et al.*, 1974, 1980), in which they showed that for all cortical areas in non-primates and for all areas except the visual in primates, the number of neurons per arbitrary column through the thickness of the cortex is remarkably constant. In 30 micron-wide columns extending from pia mater to white mater, they found, on average, 110 neurons. In the visual cortex of primates the mean number was 268, and constant from species to species within the primate Order. As pointed out by Powell and Hendrickson (1981) and Peters (1987), these figures may be approximately 20% higher than normal on account of section shrinkage (sections were 25 μm thick).

	CM 181			CM 187		
Area	GABA	Total	%	GABA	Total	%
4	39.0 ± 2.9	158.9 ± 16.1	24.5 ± 2.0	39.4 ± 2.7	159.4 ± 16.3	24.5 ± 1.3
3b	39.9 ± 2.8	152.7 ± 11.9	26.1 ± 1.7	32.1 ± 5.9	154.9 ± 11.7	20.6 ± 1.2
1–2	40.1 ± 2.6	154.8 ± 14.2	25.9 ± 1.8	38.4 ± 4.0	157.9 ± 16.1	24.4 ± 2.1
5	40.4 ± 2.2	163.1 ± 10.6	24.7 ± 2.3	39.2 ± 2.0	160.6 ± 14.1	24.4 ± 1.9
7	38.4 ± 2.9	158.2 ± 9.4	24.1 ± 1.6	40.7 ± 3.7	158.8 ± 14.8	25.1 ± 1.4
18	38.1 ± 2.9	157.3 ± 10.1	24.4 ± 2.1	38.6 ± 3.6	157.9 ± 15.0	24.7 ± 2.1
17	59.1 ± 5.7	315.7 ± 19.4	18.7 ± 2.1	58.2 ± 5.7	309.9 ± 22.7	19.2 ± 2.0
	CM 183			CM 189		
Area	GABA	Total	%	GABA	Total	%
4	40.4 ± 3.9	161.7 ± 15.3	25.0 ± 1.7	39.4 ± 2.4	161.6 ± 17.0	24.3 ± 2.1
3b	33.1 ± 5.0	157.9 ± 12.2	21.0 ± 2.1	40.1 ± 3.0	156.5 ± 12.7	25.6 ± 2.3
1–2	38.0 ± 3.3	154.3 ± 11.6	24.6 ± 2.3	38.4 ± 3.3	158.8 ± 11.9	24.0 ± 1.9
5	39.1 ± 2.7	155.3 ± 9.4	25.2 ± 1.8	38.5 ± 3.4	155.1 ± 12.0	24.9 ± 2.0
7	39.9 ± 2.9	157.6 ± 11.8	25.3 ± 1.3	40.4 ± 2.4	160.1 ± 16.5	25.2 ± 2.4
18	38.4 ± 3.9	152.0 ± 9.1	25.3 ± 1.6	38.1 ± 2.9	157.5 ± 17.5	24.2 ± 1.7
17	61.1 ± 4.7	309.8 ± 17.1	19.6 ± 1.5	59.1 ± 5.7	321.3 ± 23.6	18.5 ± 2.2
	CM 184					
Area	GABA	Total	%			
4	40.7 ± 3.4	157.1 ± 15.5	25.2 ± 1.1			
3b	32.9 ± 5.7	160.4 ± 11.0	20.2 ± 1.9			
1–2	40.1 ± 3.1	154.9 ± 9.7	25.1 ± 1.7			
5	40.4 ± 2.0	158.1 ± 13.0	24.9 ± 1.3			
7	40.7 ± 2.8	159.9 ± 11.7	24.3 ± 2.0			
18	40.8 ± 5.0	158.4 ± 16.2	24.7 ± 1.8			
17	60.3 ± 5.3	319.6 ± 21.4	19.1 ± 1.0			

Counts of GABA-positive neurons and of all neurons were made at a magnification of 1250 from adjacent sections, and the percentages of GABA cells were calculated from the quotient of the 2 values.

FIG. 7. Table showing mean number (± SD) of GABA-immunoreactive neurons and of all thionin-stained neurons in 50 μm wide columns through various areas of monkey cerebral cortex. From Hendry *et al.* (1987b).

PERCENTAGES OF DEFINED NEURON TYPES IN MONKEY NEOCORTEX			
GABA	total		25-30%
	GABA only	17.5%-21%	
	GABA & peptide(s)	7.5%- 9%	
Glutamate			50-55%
Spiny stellate (small pyramids with arciform collaterals)			10-15%
Peptide(s) only			1-2%

FIG. 8. Assessment of percentages of defined neuron types in monkey neocortex, derived from sources discussed in text.

The principle of numerical constancy is, however, unaffected. This principle has been confirmed for Old World monkeys by Hendry *et al.* (1987b) who, in addition, found that the mean number of GABA neurons per arbitrary 50 μm wide column (in 15 μm thick sections) also remains constant at about 40 cells per column for all areas except the visual, in which it rises to 60 per column (Fig. 7). The range per individual column is quite large, ranging from 35 to 45 in the non-visual areas and 50 to 65 in the visual (see also Schwartz *et al.*, 1988). It has to be pointed out that the columns used in these studies are of arbitrary width and used as conveniences for quantitative assessments of cell numbers. They are not necessarily functional or morphological units of cortical organization. Nevertheless, one interpretation that can be drawn from the data of Rockel *et al.*, supplemented by that of Hendry *et al.*, is that the huge expansion of the primate cortex has occurred as the result of repeated reduplication of column-like groupings of cells of constant number and containing constant proportions of cell types.

To confirm the latter part of this conjecture, it would be necessary to show that in the course of cortical evolution, the proportions of defined neuronal types have remained relatively constant. There are, unfortunately, very few data germane to this question, although it seems clear that all interneuronal types are present in basal insectivores and in the higher primates (Valverde, 1986) and that pyramidal cell connectivity is similar (Jones, 1984).

Earlier reports of the relative percentages of pyramidal and non-pyramidal neurons in the rat cortex had suggested that the ratio of

pyramidal (85%) to non-pyramidal cells (15%) was much higher than in primates (Werner *et al.*, 1982;Peters *et al.*, 1985) although others had placed the nonpyramidal cell populations at closer to 30% (Winfield *et al.*, 1980a, b). The number of GABA cells in the rat cortex had also been reported at about 15% (Fairén *et al.*, 1986). More recent immunocytochemical studies of the rat and cat cortex, however, suggest that the ratios of nonpyramidal or GABA cells to pyramidal or non-GABA cells are approximately the same as in the monkey cortex (Conti *et al.*, 1987; Tömböl, 1974; Winfield *et al.*, 1980b; Gabbott and Somogyi, 1986; Hendry *et al.*, 1987b). In cats and monkeys the morphological results indicate that non-pyramidal cells make up approximately 35% of the population (Fig. 9). Pyramidal cells account for the rest. The immunocytochemical results indicate 25-30% GABA cells in rat, cat and monkey and 50% glutamate positive cells, all of which are pyramidal. Few of these data can be regarded as anything more than approximations, on account of the problems of accurate identification of cells in morphological preparations and the problems of sensitivity in immunocytochemistry. Immunocytochemistry for glutamic acid decarboxylase, for example, seriously underestimates the number of GABA neurons in monkey cortex (Fitzpatrick *et al.*, 1983; 1987; Hendry *et al.*, 1987b). However, the cell

RAT & MOUSE	CAT	MONKEY
Visual cortex	*Visual cortex*	*Visual cortex*
Peters & Kara, 1985)	(Gabbott & Somogyi, 1986)	(Hendry *et al.*, 1987b)
Pyramids 85%		
Non-pyramids 15% (nonspiny: 14%)	GABA positive cells 20%	GABA positive cells 19%
Somatosensory cortex		*Somatosensory cortex*
(Fairén *et al.*, 1987) GAD positive cells 14%		(Hendry *et al.*, 1987b) GABA positive cells 25%
(Conti *et al.*, 1987)		
GABA positive cells 44%		
Glutamate positive cells 51%		

FIG. 9. Percentages of GABA cells or of non-spiny non-pyramidal cells in the visual and somatic sensory areas of rat, cat and monkey.

percentages do not appear greatly different from species to species. Thus, if results in the series, rat-cat-monkey, can be taken as indicative of the course pursued by cortical evolution, then the ratio of cell types in the cortex may have remained relatively constant. It is then not too large a leap of faith to see the expansion of cortex and the creation of new and larger cortical areas as having occurred by the addition of new radial "units" or "modules" (see Rakic, this volume), each containing a fixed proportion of pyramidal and of interneuronal types. Ramón y Cajal's remark about the prodigious increase in interneurons can still be valid but not at the expense of a proportionate increase in the number of pyramidal or output cells.

Regulation of Transmitter Expression by Sensory Experience

It is a further popular concept that the neocortex of primates is a fixed structure in adults and not subject to the structural and functional modifications that can be wrought upon the developing cortex by sensory perturbations. In the visual cortex, for example, monocular deprivation which can have profound effects on anatomy and physiology in early life is reported to have little or no effect in adulthood (see Hubel and Wiesel, 1977). However, the representation of the body surface in the somatic sensory cortex of adult primates is remarkably plastic and subject to rapid modification in the face of sensory perturbations (Merzenich *et al.*, 1983a, b; Wall *et al.*, 1986). The mechanisms underlying this are not yet clear but results from a different type of experimentation suggest possibilities. Recent studies show that the interneurons of the visual cortex remain susceptible to visual deprivation into adulthood insofar as their neurotransmitter content is regulated directly by retinal activity. If an adult monkey is deprived of form vision by having the lids of one eye sutured closed for six weeks, GABA neurons in the relevant eye dominance columns of layer IV of area 17 show greatly reduced immunocytochemical staining for GABA and its synthesizing enzyme, glutamic acid decarboxylase (GAD), and for substance P (Hendry and Jones, 1986, 1988; Jones and Hendry, 1987, 1988; Hendry *et al.*, 1988a) (Fig. 10). An identical effect can be achieved much more rapidly (within 4-5 days) by shutting down impulse activity in the optic nerve as the result of injection of tetrodotoxin into an eye (Hendry and Jones, 1988). Restoration of binocular visual experience, by opening the eyelids or recovery from tetrodotoxin injection, restores the GABA, GAD and substance P immunoreactivity to normal

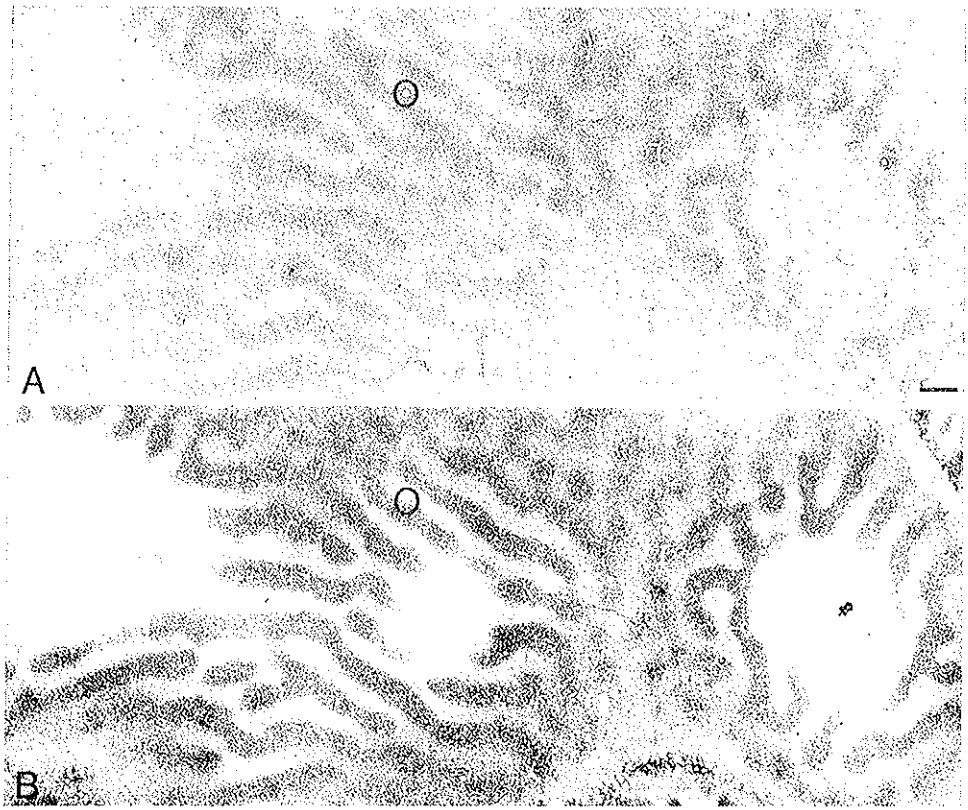

FIG. 10. Paired alternate sections taken from visual cortex of an adult monkey subjected to monocular deprivation, showing reduction in GABA (A) and cytochrome oxidase (B) staining in deprived eye dominance stripes. Bar 500 μm. From Hendry and Jones (1986).

(Hendry and Jones, 1988) (Fig. 11). The conclusion from these experiments is that there is an activity-dependent regulation of GAD and tachykinin production. Such an effect is likely to be mediated by the control of gene transcription and it is significant that immunoreactivity for at least one protein kinase actually increases in neurons of deprived eye dominance columns (Hendry and Kennedy, 1986), which may be a reflection of a change of intracellular phosphorylation pathways that ultimately leads to regulatory changes at the transcriptional level. It is possible that comparable changes in inhibitory transmitter expression may underlie the rapid reorganization of the body map that occurs in the somatic sensory cortex when the sensory periphery is modified. The regulatory

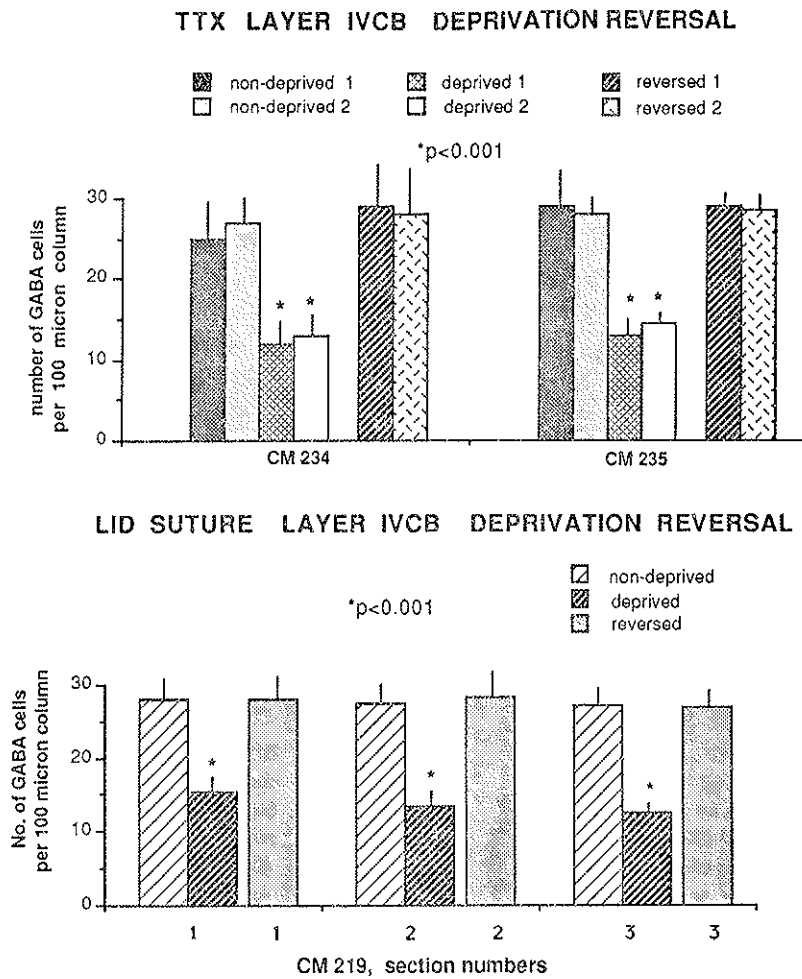

FIG. 11. Activity-dependent regulation of GABA immunoreactivity in adult monkeys subjected to visual deprivation by eyelid suture or intraocular injection of tetrodotoxin, followed, after biopsy of the visual cortex, by restoration of binocular visual exposure. Histograms show density of GABA cells in layer IVCB of deprived and non-deprived eye dominance columns of the biopsies (non-deprived, deprived) and in layer IVCB of the nonbiopsied cortex after recovery (reversed). From Hendry and Jones (1988).

effect demonstrable by extreme sensory perturbation in the visual cortex is, in any case, undoubtedly indicative of the existence of a finely-tuned molecular biological system whereby afferent activity controls transmitter expression in the neocortex.

Conclusion

The neocortex of the higher primate appears mainly distinguishable from that of nonprimates by its size. Although it is not possible to discount that in the course of its evolution the cells of the primate neocortex may have acquired connectional relationships more complex than those in the cortex of other mammals, the weight of evidence is that no new types have been acquired. Moreover, the newly emerging quantitative data suggest that there is preservation of cell numbers through the thickness of the cortex and that the relative proportions of cell types are maintained. Therefore, if the construction of the cortex is based upon a unitary columnarity, expansion of the cortex may have occurred as the result of accretion of additional units of relatively constant cell numbers and the same relative cell populations. These populations include both pyramidal neurons and non-pyramidal neurons; the former are not only the output cells but also the origins of the major long range intracortical connections, and the latter are the interneurons the vast majority of which appear to be inhibitory in nature. The inhibitory cells, since their transmitter levels seem to be subject to activity-dependent fluctuations, are probably major contributors to the process whereby cortical circuits are "selected" under the influence of afferent driving.

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DISCUSSION

ZEKI

I would like to throw open a general question. I have heard the word column used several times this morning and this afternoon. I have heard of Szentágothai columns, of Mountcastle columns, of your columns, and Pasko also used the word column. I wonder if there is such a thing, it's quite important to decide this, if there is such a unit which is applicable throughout the cortex because I suspect we are actually talking about different things.

MOUNTCASTLE

According to Powell there is a simple column which he calls an ontogenetic column. This is bound together in functional units of larger size which may vary in combining properties and in size in different areas of the cortex. So the sorts of column you see electrophysiologically or in these anatomical studies, may differ in different areas but the fundamental organizing unit is the same.

ZEKI

What is the common factor physiologically or anatomically if you go down a column?

MOUNTCASTLE

The columnar organizing factor differs in different areas and is largely due to the input properties.

ZEKI

Do the dimensions remain the same?

MOUNTCASTLE

No, they do not.

JONES

Can I just add to that? I have problems with columns myself, and although you will accuse me of using it, I think you'll agree it was used in a rather loose way and deliberately so.

MOUNTCASTLE

Yes. It's only used loosely by those who don't understand what I just said. I think it's very simple. The ontogenetic column is clearly defined. Now in the adult brain, after development, after experience, those ontogenetic columns may be combined in different numbers, in different shapes, in some places slabs, in other places round. So the concept does not say that the functional columns in the adult cortex are identical between different areas of the cortex.

JONES

Now I have got to be a bit cautious. The ontogenetic column is something which we see very clearly demonstrated by Pasko. It's a set of cell bodies. What I have problems with is whether that set of cell bodies is going to generate all my varieties of cells in the same proportions. I don't think any of us know that yet. The other thing I am not sure about is what is the unifying principle which does bring together those ontogenetic columns? I think when these kinds of concepts used to be discussed a few years ago, we all felt that probably the thalamic input was going to be something which would give us a homogeneous unification, but in fact I don't think you can even say that now, Vernon, because I think there is a lot of overlap. If we take the visual cortex, we're always, I think, forced into a greater rigidity.

MOUNTCASTLE

And that's probably the worst model for understanding cortex.

JONES

I agree, I think the visual cortex is totally unrepresentative of the rest of the cerebral cortex. We do have very rigid boundaries within ocular dominance domains, but within each domain individual thalamic axons overlap, and I think that is typical of the rest of the cortex.

SZENTÁGOTHAI

Yes, I think you have to look at it from the historical perspective. Originally Mountcastle was the first to talk about columns on the basis of receptive field organization in the somatosensory cortex. Then soon it was shown by Hubel and Wiesel that there are some kinds of field columnar organization in the visual cortex. I tried desperately from '67, '68 on, to get this anatomy straight as far as it was possible at that time. But it turned out that there was no equivalent. There was nothing which resembled that anatomically. So we had to explain it by the narrowing down of the input effect by inhibitory neurons. Finally Patricia Goldman showed us the beautiful experiments in '77 with real cortico-cortical columns.

Now these are completely different from the ontogenetic columns, that is an ontogenetically well-defined group of cells which come from a close neighbourhood, a group of cells in the ventricular zone which migrate to the surface. So a two-dimensional pattern in the ventricular zone is translated into a three-dimensional pattern of pyramids lying side by side.

JONES

I think the problem is that there has been for many years, at least certainly since 1980, the question, which is an important question: is there a fundamental unit of cortical structure? Now, if you call it the column, it turns out that what I was just complaining about is quite true, from what Professor Szentágothai said, because there is no definition of what it is. But if there is one, then we should stick to it.

ECCLES

Several types of cortical units have been described. Firstly there are minute anatomical structures in the whole of the neocortex. They were called mini-columns some time ago by Vernon but they are now identified by the bundling of the apical dendrites of laminae 5 and 3 pyramids in the neocortex. This bundling brings in perhaps 20 apical dendrites of lam. 5, but more in lam. 3, up to 80 shall we say. This is in a paper you haven't seen by Peters and Kara (J. Comp. Neurol., *260*, 573-590, 1987). These bundles or clusters are the basic units. They are about 50 microns across and 200 per mm^2. They are the mini-columns and they come from growth in the ontogenetic story that we heard about this morning from Pasko. Now that's the basic unit for

synaptic reception. I am going to propose on Friday that these units are there also for the purpose of mind-brain interaction.

Secondly are the well-known modules of Goldman and Nauta with Szentàgothai, which are about 20 times larger and are for a different purpose. They are the principal intracortical communication system.

The third system is in the area 17, the ocular dominance columns and the orientation columns at rights angles.

Finally, encompassing assemblages of modules are the very large units, usually of several cm^2 that are disclosed by metabolic and blood flow studies, the cortical field activations, that Per Roland will be telling us about.

JONES

I think one should comment on the bundling of dendrites, which is not novel. It's been known for a long time. It's really extremely variable, that's the first thing. There is no repeating pattern. What is perhaps more important is that even if it does repeat, I think it's inconsequential.

ECCLES

Why?

JONES

Because, for this reason — that's a bundle. (*The speaker refers to a slide projection.*) Maybe that's 50 microns, but look at all this. What about all these dendrites as well? I mean, it's meaningless. This is a trivial part of those cells. Those cells really have to get up to upper layers in order to ramify their dendrites. This is where the action is. If you want to use the bundling as some unitary module, you have got to save this line. Within this, there are a variety of neuronal types. Inevitably, layer 3 and layer 5 pyramids contribute to these bundles. They are different categories of cells and I think that even you will agree, Vernon, that if a cell receives a totally different input from another cell, it is probably not only anatomically different, but it is also functionally different and probably physiologically different.

ECCLES

The question is whether the bundles of apical dendrites of the lamina 5 and 3 pyramidal cells with at least 50,000 synapses on the apical dendrites can be diverse in their functions, or are they of the same class?

JONES

Certainly they are different in terms of their inputs, in terms of their outputs, in terms of their dimensions. These make for different cell categories to me.

ECCLES

How can you show that there is this difference in inputs into the apical dendrites of pyramidal cells so closely spaced as they are in the bundles?

JONES

But they're not. That's the point I'm trying to make. That they are only closely spaced at one very small part.

ECCLES

The bundling relationship is for at least 1 mm length.

RAKIC

When I started to work on columns I was very often asked how ontogenesis goes with Mountcastle columns. The visual cortex is no different from some of the sensory cortices such as the Mountcastle columns of 1957. When you look at what these cells have in common, it is that the cells below and above, on different levels, are related. It is true that they also connect other areas, but what is interesting is that they are related functionally, have a common sensory input and they come on top of each other and they migrate. Biology devised such a complicated system to put them one on top of the other by means of transient glia cells. The purpose was physiological, to put them together.

ROLAND

I would question whether it is legitimate to use the primary visual cortex with ocular dominance columns as a principle for organization of the whole cortex. After all, in man most of the cortex consists of homotypical areas. I see two problems. First of all, is it possible, electrophysiologically and metabolically, to identify functional columns in the homotypical cortex? I think

that Patricia Goldman-Rakic has done some experiments which clearly showed that there is what looks like a functional, metabolic functional organization, at least in some parts of the frontal cortex Secondly, I don't know if one should adhere to columns as strictly functional concepts, since we can modulate their widths and extents so much just by applying antagonists and agonists.

Can someone explain how these simple columns and complex columns get organized into these bands that we sometimes see metabolically in the cortex? Metabolically active bands running along seem to consist of active columns with inhibition areas in between.

MOUNTCASTLE

Everyone I think would agree that there is a small unit in the cortex which originally derives from what is called the ontogenetic column. It's important to remember how this is formed. Some processes combined these into the functional columns observed in electrophysiological experiments and in some tracer experiments. Completely mysterious is what limits the lateral process and that combines them into functional columns. Within such a functional column are a number of minicolumns, the number can be calculated. It varies from somewhere between 50 and 200 in different areas of cortex. It's important to remember that there are different intracolumnar processing channels. Some aim towards output to other cortical areas, some aim towards the spinal cord.

That's one of the major experimental objectives I have myself at the moment, to determine how the intracolumnar processing differs functionally towards different outputs. But there are certain defining properties of cells within such a column which are common and that's true for both cortices, motor cortex and the homotypical cortex. The most striking columnar organization I've seen was in the postcentral cortex. There the defining properties are very complex, and they depend upon the conversion input of many afferents to the cortex.

There's one point I would like to make apropos of anatomical observations. That is, I believe that when you say that the axonal distribution of a cell is x, that that does not define the functional distribution of that cell. We know already that the probability release of transmitter at terminals in cortical cells is about 0.3 and it's under dynamic control. So it's not correct, I think, to say that if you have a cell here, with an axonal distribution of 5 mm, this cell is influencing all other cells within the periphery of that axonal distribution. I believe that there really is no confusion, but a great deal to be learned, particularly about what are the mechanisms for bonding these ontogenetic

columns together into the functional ones we see in working adult animals. What limits them? I am absolutely sure that surround-inhibition with dynamic limitation is a most important factor.

ZEKI

You say that a functional column is a piece of cortex containing neurons with the same functional properties. In the old days when Hubel and Wiesel had published that picture showing everything was orientation selective outside layer 4c, a picture which we now know not to be true, it seemed quite straightforward. It was obtained by ignoring the cytochrome oxidase blobs which contain non-oriented cells. They lie throughout the cortex, but mainly and most visibly in layers 2 and 3. Now take layer 4b, which is well-known for having directionally selective cells, and wavelength selected. There is nothing further removed than motion and colour within vision. The cells which project to V5, which are movement direction selective, can lie underneath the blobs or outside. If you were to take a section through layer 4b and look at the distribution of cells going to V5, non-colour coded cells, you will find another system of patches which bears no relationship to those of layers 2 and 3. If we are going down this way, we have colour cells, wavelength cells, and then we hit motion selective cells, and then other cells which are not very well documented but almost certainly go to the superior colliculus. Nowhere is the functional unity there, except for two things. One is the ocularity, preferring one eye, and secondly is the receptive field.

MOUNTCASTLE

The dominating determinants are receptor field and modality, but the functional properties of cells in different layers differ strikingly. They have different outputs, different inputs. You would expect them to be different, but there are certain unifying determinants which say this is a column. They may be confused in the visual cortex.

GOLDMAN-RAKIC

When we published our paper we gave a name that was qualifying what we meant by a column: the afferent fibre column. The question is how it might be related to any other kind of column related to afferent input. What I find remarkable is that in almost every study of connections of the cortex, whether

it be pre-frontal or cortico-cortical or thalamo-cortical, the fibres enter the cortex and terminate in a particular distinct pattern of a given width of approximately half a millimiter. That constancy transcends regions of the cortex. It transcends species. We found the same width of afferent fibre columns in the rat and in the squirrel monkey which has a much larger cortical surface area. The physiological underpinning or counterpart of that afferent fibre column has only been studied in visual cortex, somatosensory and one or two other areas.

Later we came up with a basic principle which at least hints at an idea of what confines the width of a column and why you have alternating series. In every case I know of, it's a question of representing the contralateral versus the ipsilateral space. In the visual cortex, it's left eye alternating with right eye representation. In the case of cortico-cortical connections, it's ipsilateral afferent fibre columns alternating with contralateral afferent fibre columns.

ECCLES

The columns that you discovered and which Szentàgothai has developed are for communication. The axons of the pyramidal cells of the cerebral cortex are the only outputs from the cerebral cortex. 95% of that output goes to cerebral cortex. The axons are not projecting out and these are the projections of those columns that you talk of. The whole of the cerebral cortex is linked together by pyramidal cell axons.

JONES

Well, I think that the single comment I can make is that this has been a lively discussion. I am not sure that any of it is relevant to what I actually presented. All of us continue to struggle with the columnar principle. We have a columnar principle in the cortex, there is no question about that. The problem is in translating that into some common language that we can all agree upon. What I haven't seen in any of the discussion is the incorporation of these elements that I've presented as the fundamental elements of cortical circuitry into any column. I think of the physiological constraints on a column, of which there are several. The most important one is GABA transmission. There is no doubt about that, and it's in this that we probably have to seek for those changes which occur over short periods of time during the functional activities of the cortex.

FUTURE PERSPECTIVES OF RESEARCH IN NEOCORTICAL ARCHITECTURE

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ABSTRACT — Research into cortical architectonics is characterized by three major routes in technical development: (1) The cross correlation — on the basis of the strictest criteria and bridging the gap between light and electron microscopy — between physiological, anatomical, and transmitter-biochemical properties of individual neurons and synapses; (2) rapid development and refinement in techniques for tracing neuronal connections at long distances; and (3) a vastly improved understanding of the emergence of different cell lines and clones of the early medullary tube and the mechanism of their outward movement towards their final destinations, giving a better understanding of the general architectonic principles of various neural centers. By concerted use of these new techniques a coherent picture of the network of inhibitory interneurons has been already achieved and is recently beginning to take shape in our insight of excitatory neuron chains. The application of immunocytochemical methods gave clear evidence for the co-localizations of conventional mediators and various peptides. Although the studies are still in their beginnings, the possibility of a subdivision into different subgroups of apparently identical neuron types by chemical markers and hitherto unknown refinements in the mechanisms of impulse transmission has to be considered.

INTRODUCTION

The development over the last few years in neuroanatomical techniques has made it possible to cross-correlate physiological, anatomical, and biochemical properties of identified individual neurons and of many of their synapses — both given and received — down to the level of the electron microscope. Virtually any neuron or axon that can be penetrated by a microelectrode can now be labeled for a considerable part of its course (cell bodies, dendrites and local axon branches in the case of penetration of nerve cells, and virtually the whole terminal arborization of penetrated

axons) by horseradish peroxydase or phaesolus lectin. After having observed such cells or axons under suitable experimental conditions their light microscopy can be studied, and computer aided reconstructions of their arborizations can be made from section series, in order to gain a better understanding of their shape, volume, measurements, orientation, distribution, and local accumulation of their synaptic terminals in the occupied tissue space. This analysis can be carried further by the combination with the classical Golgi procedure (Freund and Somogyi, 1983) or various immuno-cytochemical procedures in order to define the shapes of the recipient neurons and the synapses given by the labeled neuron, as well as the synapses received by this neuron from other neurons of the network. In the same material any neuron or any synapse can be simultaneously studied by immuno-cytochemistry for the mediator (or modulator neuropeptide) that it might contain either separately or in co-existence with other substances. Most recently, not the mediators or modulators are the targets of study, but often the biochemistry of the subsynaptic receptor structures or the messenger RNA-s, carrying the genetic information to be expressed eventually in the production of any enzyme, peptide, or any other relevant molecule. We are confronted today with such an avalanche of new information every day that simple enumeration of the last few years' studies would go far beyond the space available for this report. It is suitable, though, to mention that this development of these new techniques originated in two papers by P. Somogyi (1977, 1978) and Somogyi *et al.* (1979) where we find the new strict criteria for the cross-identification of anatomical elements: i.e., to define any element showing some characteristic label or histochemical reaction not just by recovering it under the electron microscope, but that the identification be carried to a specific cell and specific synapses both received or given by the cell in question.

Another crucial step forward was a simultaneous dramatic development in the techniques of tracing neuronal connection at long distances, both retrograde and anterograde, by using various labels: either fluorescent dyes, or specific enzymes that can be made visible both for the light and the electron microscope, and uptake and transport of radioactive substances, generally of tritiated amino acids. Again, it would be impossible even to enumerate the most important studies in this field. We might mention, though, a comprehensive paper by Patricia Goldman-Rakic (1984) as representative for this line of research. The application of a modified cobalt technique (Görcs *et al.*, 1979) made it possible to label nerve cells,

both motor, vegetative and sensory from the peripheral arborization fields (Székely and Matesz, 1982; Matesz and Székely, 1983) not only in lower vertebrates but also in the mammalian. This offers an additional cue for tracing neuronal connections under circumstances that were hitherto inaccessible.

By the application of these techniques in suitable combination it is virtually possible already today, but will be increasingly so in the near future, to define any neuron system, or local network of the entire nervous system simultaneously physiologically (on the basis of recorded functions), anatomically, and biochemically. The limiting factor, for the time being, is the excessively high number of elements and the complexity of structures co-existing in the same piece of neural tissue. It remains still to show whether or not this kind of pragmatic and inductive approach to neural systems will give us a better understanding of the essence of neural organization, i.e., the key to an insight into its so-called "higher functions".

Considerable progress has been made over the recent years also in the field of tissue development in the major neural centers. The two cell lines emerging from the epithelium of the early medullary tube: the neuroblast line devoid of, and a neuroglial line containing the acid proteins characteristic for the glial elements (Rakic, 1982) could be separated in very early stages of development. By radiolabeling the several cell generations in their premitotic stadia, the outward movement of successive generations of neural and glial cells from the germinative inner zone of the epithelium towards the outer layers (mantle zone) of the medullary tube could be observed directly. It could be shown how the original neighbourhood relations of the various cell clones in the early medullary tube could be maintained, despite gross changes and distortions of the developing brain vesicle walls, by a system of radial neuroglia maintaining its original points of attachment at the inner and outer limiting membranes of the medullary tube. This radial neuroglia system serves as a scaffolding for the outward movement of neuronal and glial elements into the so-called cortical plate of the developing cortex. The logical consequence of this scaffolding system and its role as guiding "ropes" for the outward movement of nerve cells — so elegantly demonstrated by Rakic (1982) — is the transformation of a (quasi-) two-dimensional pattern of early neuroblasts in the germinative zone of the early tube into a topologically equivalent three-dimensional pattern of cylindrical (or more exactly prismatic) columns in which the successively generated nerve (and glial)

cells are distributed in depth according to the timing of their origin: the earliest cells being located in the depth and the younger cell generations in successively outer layers of the cortical plate. This mode of development is "self-explanatory" for the emerging columnar architectonic principle of cortical organization.

1. *Inhibitory Neurons*

The identification of inhibitory interneurons was greatly aided by the relative simplicity of labeling gamma-aminobutyric-acid (GABA) or its precursor enzyme glutamic acid-decarboxylase (GAD) by immuno-cytochemistry. Since virtually all identified inhibitory neurons and their synaptic terminals contain GABA, the list of reasonably well-studied characteristic types of inhibitory interneurons in the neocortex has run up to at least seven distinct cell types (summarized recently by Szentágothai, 1987), but it is very doubtful that we have arrived at the end of the list. A most characteristic feature of the axonal arbor of all inhibitory interneurons that are not confined to restricted tissue spaces (like, for example, the micro-gliaform cells) is that they have at least one major vertically descending branch, if the cell is localized in the upper layer of the cortex (lamina I-IV) and one vertically ascending branch if the cell is localized in the deeper (V and VI) laminae of the cortex (Somogyi and Soltész, 1986). There seems to be, hence, an intensive mutual inhibitory connectivity, organized strictly vertically, between the superficial and deeper layers of the cortex, while the tangential spread of inhibition is maximal (1.5-2 mm) in the depth of lamina III and in lamina V, ensured by a supragranular and an infragranular set of large basket cells.

2. *Excitatory Neurons*

Conversely, the identification of excitatory neurons, and particularly of interneurons, rests on less firm ground, due to the difficulties, so far, in demonstrating the excitatory mediators by histochemistry. Glutamate, one of the putative excitatory mediators, is too ubiquitous, so that its unequivocal immuno-cytochemical localization would require some very sophisticated quantitative measurements. The situation is more hopeful with the other putative mediator: aspartate, the first successful attempts apparently coming forth. Based on more circumstantial evidence, pyramidal

cells — 60% of the total cell population — have always been considered as the projective and excitatory neurons of the cortex. By the same token, the so-called spiny-stellate cells — especially frequent in specific sensory cortical areas and lamina IV — may be considered also as excitatory on the basis of the fine structural details of their synaptic terminals and their lack of GABA.

Most recently Kisvárday *et al.* (1989) have succeeded in tracing interlaminar and lateral excitatory amino-acid connections in the striate cortex of the monkey by taking advantage of the rather specific uptake from micro-injections of D-[^{3}H]-aspartate (D-[^{3}H]-asp) by axon terminals and retrograde radiolabeling of the cell bodies. This technique is considerably more specific than the earlier used analogous technique of radiolabeling by uptake of tritiated GABA, because GABA offered in such excessive local concentration is readily taken up by non-GABA-ergic neurons, whereas this is not the case for D-[^{3}H]-asp, which with few exceptions is not taken up by GABA-ergic neurons. The connections defined show certain parallelisms with the local and lateral inhibitory connectivity of the visual cortex in the cat (Kisvárday *et al.*, 1987). The most important finding, having no counterpart in inhibitory connections, is the termination in lamina I of a wide-ranging projection both from a cell population from lamina IV B and lamina V cells up to 1300 microns laterally. The cells in layer IV B could not, so far, be identified, but the pyramidal cells in lamina V that project to layer I have been suspected earlier (Szentágothai, 1962), but have been wrongly interpreted, and a single cell of this type had been reconstructed by Martin and Whitteridge (1984) in the cat visual cortex. Some specific layer II neurons appear to project in well-focused manners into lamina VI. These cells are probably pyramidal neurons. The focused excitatory projection between laminae II and VI has its mirror image in a similar localized inhibitory projection between the same layers, but only the cells of origin of the inhibitory projection are identified anatomically. The wide — up to 1300 micron — tangential spread of projection defined by high uptake of D-[^{3}H]-asp in lamina IV B cannot be translated directly into neuron types that could be defined anatomically. The same is true for the rather sophisticated excitatory connectivity between different sublayers of lamina IV. The findings of Kisvárday *et al.* (1988) are in fair agreement with earlier findings based on the application of less specific labeling methods, but for the details the reader has to be referred to the discussion in the original paper.

Fig. 1 taken from Fig. 1 of Kisvárday *et al.* (1989) attempts to

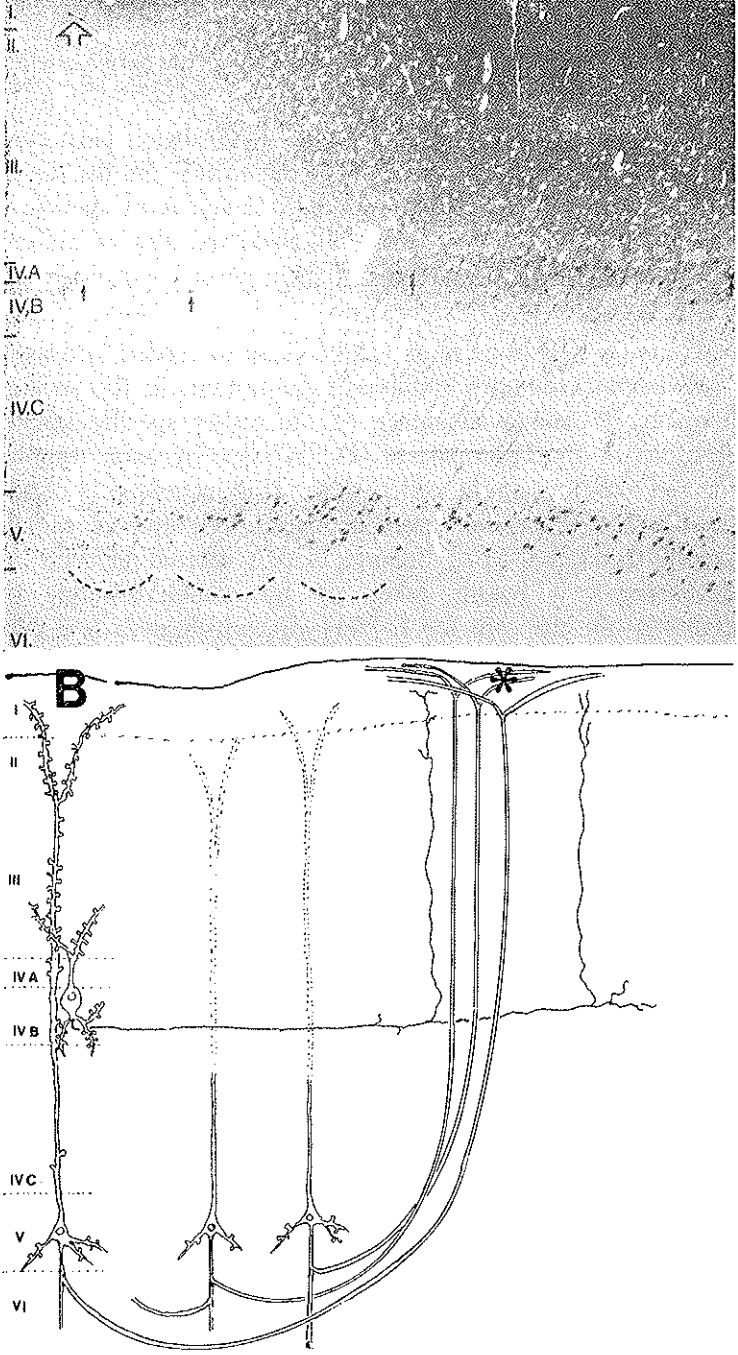

FIG. 1. Part of the original figure (Fig. 1) of Kisvárday *et al.* (1989) shown in A, and an attempt at an anatomical interpretation in B. - A is a light micrograph of a 1 micron thick section processed for autoradiography. Injection of D-[^{3}H]-asp into layers I and II, asterisk indicates injection site. Long range lateral labeling is seen in layer I (neglected here because this result is ambiguous) and in layer IV B (arrows) and in layer V (the clusters of retrogradely labeled cells are indicated with broken lines). Scale 200 microns. - Part B of the figure gives an anatomical interpretation showing some of the labeled cells (the cells are slightly enlarged, to show more details). A labeled cell in lamina IV B is assumed to be a spiny stellate cell with wide tangential spread of its axon and ascending terminal branches (as shown in the cat visual cortex by Martin and Whitteridge, 1984). Martin and Whitteridge (1984) have reconstructed a

interpret, in anatomical terms, the lateral projection of D-[^{3}H]-asp labeled pyramidal neurons to lamina I. Fig. 2 is a diagramatic illustration of the well-focused projection from lamina II to the bottom of lamina VI given by both excitatory and inhibitory neurons. The similarly large lateral spread of connection from and to lamina IV B cannot be interpreted with any degree of confidence.

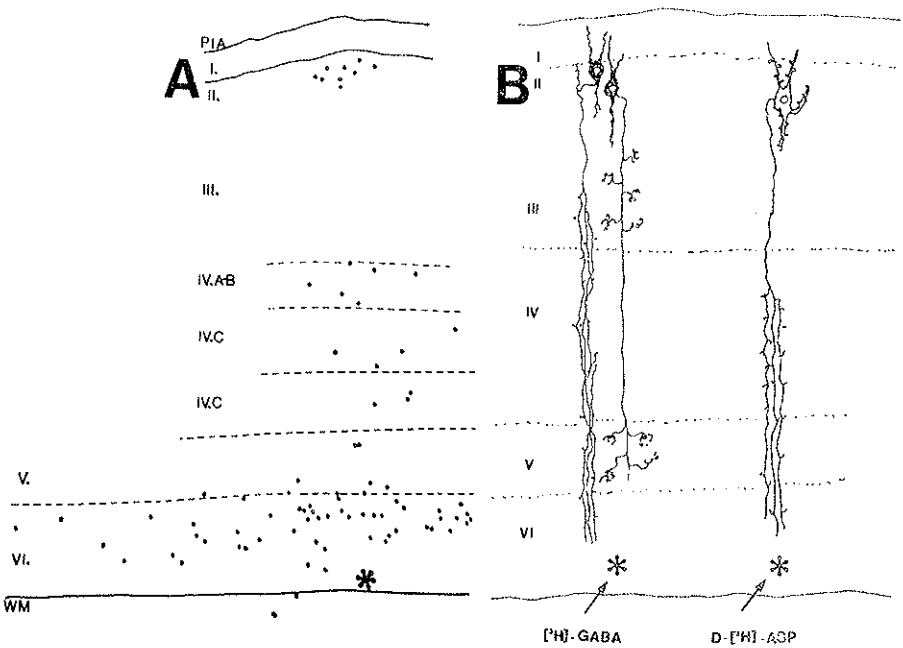

FIG. 2. Anatomical interpretation of vertically oriented connections between lamina II and VI. Part A is the reproduction of a drawing by Kisvarday *et al.* (1988. Fig. 7 C) with an injection site in layer VI immediately above the white matter, and a remarkably focused cluster of retrogradely labeled cells in layer II. Part B shows diagrammatically the results with [^{3}H] GABA (at left) where a similar clustering of retrogradely labeled cells can be observed. The two representative cells are a "cellule à double bouquet" of Ramon y Cajal (left) that is known to contain also CCK (Somogyi and Cowey, 1984), and so is the columnar basket cell (Freund *et al.*, 1986). Unfortunately, retrograde labeling with GABA is less specific than that with aspartate. The cell type labeled in layer II is anatomically not known, but similar spiny cells as shown in this diagram (right) have been observed by the present author, although never studied in any detail. The unequivocal observation shown in part A of this figure, and the similarity to the focused labeling of cells experienced with microinjections of GABA, forcefully suggest such a parallelism in excitatory and inhibitory connections.

3. *The Co-Existence of Mediators (and/or Modulators)*

There is convincing evidence for the co-localization of GABA and cholecystokinin (CCK) or of GABA and somatostatin, but never of the two peptide substances. (For reference, see Somogyi *et al.*, 1984, where the extensive literature is discussed). Unfortunately, only the position and not the anatomical identity of such cells has, so far, been identified. In the negative sense several well-known types of GABA-ergic interneurons can be safely discarded, such as the axo-axonic cells and, with high probability, the large basket cells, on the basis that their synapses, if immunoactive either to CCK or to somatostatin, would show up in consequence of their preferential localizations. Conversely, two very probable GABA-ergic interneurons, preferentially located in layer II are visible in the immune reactions to CCK: i.e., the cellule à double bouquet of Ramón y Cayal (Peters *et al.*, 1983, Hendry *et al.*, 1983, and Somogyi and Cowey, 1984) and a "columnar basket" cell (Freund *et al.*, 1986). Similar, although less convincing evidence for co-localization for GABA and peptide Y and encephalin has been suggested.

However this may be for the time being, it can be assumed with great confidence that similar co-localizations of two, and probably eventually more, synaptic transmitters (or modulator substances) will be found in the near future. The functional significance especially of transmitters (and/or modulators) in the same synaptic terminals, one (GABA) being inhibitory in function and the other (both CCK and somatostatin) being excitatory, gives rise to various speculations, many of which would be worth being tested. However, the hypothesis of modulation may be only one, and possibly not the most likely one among different options. Recent extensive studies in the peripheral vegetative nervous system, particularly the gut which is more amenable to experimental handling than the cortex or other central organs (see a recent summary by Furness *et al.*, 1987) very forcefully suggest a sophisticated system of chemical coding. The simple fact itself that there are three different types of noradrenergic fibers entering the gut from the coeliac ganglion: (1) containing noradrenaline (NA) and neuropeptide Y (NPY) that terminate on blood vessels, (2) those containing NA and somatostatin and supplying the submucous plexus, and (3) those containing only NA and terminating in ACh-ergic cells of the myenteric plexus, shows that co-localization of a traditional transmitter and two different peptides may itself subdivide the NA-ergic cell population of the coeliac ganglion into three totally different subgroups with distinct targets and functions. Further complications are caused by the fact

that cells in the submucous plexus may contain up to six different peptides together with cholineacetyltransferase (ChAT) which would make these neurons basically cholinergic. However, apart from serving as a chemical marker, each of these peptides may participate in the process of transmission. One might argue, of course, that such a labeling is more useful in simple neuron networks, where heavy restraints are imposed upon the possible number of neurons, while this would not be necessary in very highly complex centers, where the number of neurons and of different neuron types would be less restricted. However, considering the technical difficulties in analyzing the function of neuron networks in central organs, one might realize that similar and even more complicated functional subdivisions of the known characteristic neuron types might eventually become possible. Also the fact that several maps are superimposed upon and co-existent with each other in the visual cortex of primates, might suggest that at least similar refinements in chemical marking and delicate manipulations of the functional parameters of transmission could be expected in all parts of the cortex.

4. *Conclusions*

This cursory survey of the ongoing development in cortical architectonics clearly indicates that we are probably still at the beginning of unraveling its intricacies. It is certain that further studies, even if only with the technical means available to the researcher today, will soon bring forward a great wealth of hitherto unknown and unexpected new information. But even with this expectation in mind, I am not so confident for the near future about a radical breakthrough towards a better understanding of the really great riddles of neural organization: especially of the mechanisms of memory and cognitive functions. On the contrary, I would assume that even the fullest description of any nervous system; including the physiology, anatomy, and biochemistry of the entire neuronal network and of all synapses would not, by the same token include a description of its operations. It would be like the most complete description of a computer in terms of its physics and constructional aspects, but would not reveal to us the sense and meaning of the operation that it performs when properly programmed. The fact that the nervous systems are self-programming systems does not make the task any easier.

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DISCUSSION

CREUTZFELDT

I have a short comment. Could it not be that some peptides in the cerebral cortex are not necessarily involved in synaptic transmission as such, but that they are triggering off intraneuronal messengers? Still less specific would be an action of some peptides on capillary dilatation or constriction leading to changes in cerebral blood flow and so on. I think one should consider that some peptides may be rather unspecifically related to impulse transmission, but specifically related to other functions of neurons and their environment.

SZENTÁGOTHAI

Do you suggest that we have non-synaptic transmission? It has always been claimed that in the central nervous system many of the dopaminergic or monoaminergic or catecholaminergic neurons do not have real synaptic targets, but they have. If you reconstruct them in electronmicroscopical series, you always find synapses. Of course I wouldn't say that this excludes extrasynaptic action. In the periphery you do not need a direct contact with the smooth muscle or with secretory cells, so you can have general discharge of the mediator into the surrounding tissue fluid. But in the nervous system this seems to be rather rare. Well, I would have to see a really convincing example that somebody went through hundreds of sections and found, let's say, only varicose thickenings with many synaptic vesicles, but no postsynaptic sites.

LEJEUNE

Mine is a very naive question. I don't understand exactly what you mean by an aspartate neuron. Does it mean that it takes up aspartate, or does it mean that you know that its endings use aspartate as a chemical mediator?

SZENTÁGOTHAI

Nobody can say that. It was always suspected that aspartate may be a mediator used by many excitatory neurons. But now we don't know. They are highly specific uptake neurons. That's all we can say.

LEJEUNE

Is this the same for the glutamate?

SZENTÁGOTHAI

Yes; well more or less the same but the glutamate does not give you such clear pictures, that's the trouble.

LEJEUNE

I have a third part to my question. What would happen if instead of glutamate you were using glutamine? Does it go in or not?

SZENTÁGOTHAI

Well, I don't know. They have tried this. I think they have tried it all over the place and the results were not very conclusive as far as I know.

ECCLES

I would like to give a function for acetyl-choline in the cerebral cortex which is now well recognized (and I am speaking now for the McGeers, who should be here). They have shown, I think quite conclusively, that Alzheimer's disease is primarily due to the degeneration of the cholinergic input to the cerebral cortex, from the dorsal nucleus of Meynert and the diagonal of Broca. All of this is very well established now. So here is a function, you see. It's not a synaptic function. It's a trophic function. You have to think that the cerebral cortex is very much dependent on trophic influences of all kinds to keep it going. It's a subject that we know very little about, but this will make opportunities for these other transmitting agents that you speak about, VIP, etc.

JONES

I think there are many things one could add to the discussion which has just gone on. Perhaps just an aside in terms of these labelling methods: the advantage of aspartate is that it can be used in the D-isomeric form. This is not further metabolized and remains in the cell and therefore it is a wonderful marker. None of these other compounds are generally available in that isomeric

form so they go through the various metabolic stages, and you don't get a good label.

I wanted to come back to your comments about unconventional or novel transmitters, and I think when we raise these issues we must probably think about non-conventional transmission or non-conventional ways in which these other substances often co-localize and, we think, co-release. Now let's admit that we don't really know that some of these peptides are actually released because it has been shown in *in vitro* preparations that calcium-dependent mechanisms do determine that they will be released there. We don't know that they are released at that synapse where we see them, but we certainly don't know that they are actually active at that synapse. It's quite possible that the receptors for those compounds may well be situated not on the post-synaptic side but on the pre-synaptic side when of course there they could govern the release of the more conventional transmitters that they contain. Also, the receptors may be situated at some further distance away. So all of these are possibilities for which there are in fact some data in the peripheral nervous system to suggest that they are logical ones to pursue.

The question that was raised about vascular innervation by some of these peptide-containing neurons, we raised that initially when we found a lot of CCK cells closely approximated to blood vessels. I am a little less convinced about that now. Certainly NPY and VIP have various ways of acting on pial blood vessels. As yet they have not been shown to be operative on intracerebral vessels and so far as we can tell, there are really no terminals which come up against blood vessels. Well some cell bodies may. There are many other points of this kind that one could raise, but I don't think necessarily that because we are seeing these peptide-containing cortical neurons it means that necessarily we now have to look for more and more types of neurons. It may well be that the same types of neurons are able to enter into different functional states determined by the co-release or co-receipt of these other elements.

SZENTÁGOTHAI

I would agree in general, except for the last event, because at least in the cerebellar granular cells it was clear they had different targets, so that co-localization or non co-localization of something else means termination in different places. Of course, there is no evidence of how it is in the cortex. I agree with that completely.

JONES

Is there any connection with the possible way in which VIP might act on cholinergic mechanisms? There is in fact a simple model of this in the sympathetic ganglion. It's been shown that VIP enhances the response to acetylcholine, the muscarinic response and the enhancement lasting about 20 to 30 minutes. So without the VIP producing its own kind of postsynaptic potential, here's a clear kind of possibility for a straight modulator action on the action of another transmitter.

ROLAND

With respect to the question about whether these peptides like VIP, neuropeptide Y or CCK have any role in the regulation of the cerebral blood flow and local dilatation of capillaries, I'd like to point out that in our experience blood flow increases at about the same rate in the gray matter as in the cerebral cortex. You can achieve high blood flow increases almost anywhere in the gray matter through the proper stimulation. For such an unconventional role of peptide function, one has to demonstrate that the density of NPY neurons is about the same in the white matter as in the cortex. Is anything known about these NPY neurons? Is their distribution homogeneous?

SZENTÁGOTHAI

We have no direct evidence, but maybe Dr. Jones has some.

JONES

We found in fact that the majority of NPY neurons in the monkey are actually situated in the white matter beneath the cortex. There are some in the cortex, make no mistake about that, but the majority are in the white matter. They are fairly wide apart in the adult monkey but fairly evenly distributed. I don't think there is any evidence in our material for a preferential distribution beneath a particular cortical area.

CREUTZFELDT

I'd like to raise a general problem. If one looks at the afferent and intrinsic connectivity of a restricted part of the cortex, one would predict

that all neurons in such a modular volume are connected to the same input and with each other to some extent, directly or indirectly. The consequence would be that they all would have identical properties, either identical receptive fields or the activities from two neurons close together would be highly correlated. This is not the case, however. If you progress with a microelectrode from one neuron to the next vertically through the cortex, you find that each cell has its individual receptive field, although receptive fields may be overlapping. Neighbouring cells may have very different functional properties. In the visual system, one neuron may be an on-centre excited simple cell and another one next to it an off-centre type, since simple cells of all subvarieties are either on or off-centre excited. Complex cells of layers V and VI tend to have larger and more similar receptive fields, often with on- and off-centre input mixed. The same applies, *ceteris paribus*, to the somatosensory and the auditory cortex.

If you do cross-correlation between two cells you may find a few cell pairs with highly correlated activity, but this is the exception rather than the rule. All this, and even the special cases of highly correlated activities, speak in favour of a highly selective afferent and intracortical connectivity.

One then begins to wonder about the functional significance of the different anatomical connection schemes suggesting a unifying columnar connectivity. You have referred to Kevin Martin's and his colleagues' findings, which indicate to them that a single afferent fibre may establish only one en-passant synapse on a dendrite. In order to drive a cell one would need something like 100 synapses, consequently 100 converging afferent fibres. If this would be so, then I would expect that nearby cells would share the same afferents, and cell pairs with highly correlated activity should be abundant. But this is not what one finds.

With respect to inhibitory connections, neurophysiological findings are in better agreement with a more diffuse connectivity and large convergence. I pointed that out almost 20 years ago. If you go vertically through the cortex with a microelectrode, cells on top and next to each other tend to have the same large receptive fields. So one gets the impression that all neurons within a vertical penetration receive inhibition from the same receptive field region and thus from the same pool of afferents. In fact, what is most common to all neurons within a "column" is the area (not necessarily the strength) of their inhibitory receptive fields. Further support of a more diffuse organization of inhibitory convergence is the fact that negative cross-correlations between two cells are rare.

Thus, to sum up this lengthy interjection, I want to emphasize that in

spite of all anatomical evidence, each cortical cell has a highly selective, excitatory input which can sometimes be traced down to single or a few afferent fibres. This does not exclude some similarity in functional properties of nearby units such as orientation sensitivity in the visual cortex, which shows a high variability within a "column" anyway. It's not so, as many anatomical schemes suggest, that a large group of neurons within a vertical unit all share the same input, and that they are all driven by the same afferents.

SZENTÁGOTHAI

Thank you. You see, from looking at even the best preparations one always gets first the impression that between any given afferent and a postsynaptic target cell, the number of synapses is small. But if you really make correct statistics, then it turns out that it's much more. It's surprisingly higher. I was very much surprised. It seems that it often goes up to a hundred. I mean, a given neuron may have up to close to 100 synapses on one other neuron. So you see, I was always arguing the other way around, but I have come round to your original viewpoint.

GENERAL DISCUSSION

WIESENDANGER

There were several issues raised, and not so many answered. One which is near to my mind and which I think is really puzzling is this very rich recurrent arborization of pyramidal cell axons up to layer I. From what we know it's excitatory. Has anybody a guess as to the function of these collaterals?

MOUNTCASTLE

I think there is very old evidence, from intracellular recordings beginning with Phillips (recorded in the 1964 conference here), that recurrent excitation of the axons of pyramidal cells almost always imposes trans-synaptic inhibition on adjacent pyramidal and other cells so that the best candidate for action of the recurrent collaterals is the imposition of pericolumnar inhibition.

BROOKS

I just wanted to add to the point of the recurrent inhibition, that at the time that you see the long intracellular potentials you can demonstrate that the receptor fields of the neurons in the motor cortex become constricted.

JONES

Data on axon collateral ramifications for pyramidal cells in both somatosensory and visual cortex now would suggest that the majority of terminations of such collaterals are actually focused away from the cell of origin. Indeed, in the somatosensory cortex, the first major blocks of terminals come about 600 microns from the parent cell. Then there may be another 6000 micron gap and another cluster, and similarly so far as it has been studied in the visual cortex, blob-like territories in the upper layers are connected to other blob-like territories surrounding them rather than to the immediate adjacent regions. So I think we have to be a little cautious about intimating that all of the excitation mediated by these collaterals is focused very close to the cell. Now this is not

to say of course that what is close to the cell may not be more effective than at a distance, because there are some terminals there, but in general the anatomy is suggestive of something which is really rather precise and focused at a distance.

MOUNTCASTLE

Although I think that columnar inhibition is a very powerful organizing principle in the cortex, it's worth remembering that there may be others imposed dynamically. For example, there are certain conditions of slow-wave activity approaching sleep where there is a laminar dissociation in which, in the primary somato-sensory cortex, the supragranular layers can be driven from the periphery and the infragranular layers cannot. So we can imagine there are other modes of dynamic organization in the cortex imposed by control systems which might be superimposed upon a basic columnar organization and hence be quite different. I think this is a very dynamic thing. For example, the laminar dissociation which I described raises the possibility that we may operate with our cortex on our supragranular cortical connections in the absence of peripheral output from the cortex — that is, we can think without moving.

WHERE DO VISUAL SIGNALS BECOME A PERCEPTION?

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Lesions within the striate area cause scotomas or a total hemianopia, while prestriate defects can lead to an impairment of colour, movement or depth perception or a loss of object or face recognition. Riddoch (1917) spoke therefore of a dissociation of visual perceptions as light, movement and objects, implying that vision is composed of several subfunctions. Brodmann (1909) proposed for cytoarchitectonic reasons that "certain functions have a circumscribed regional localization". Taken together, these two proposals suggest that the processing of submodalities is done in spatially separated areas. Brodmann's statement led to a long controversy regarding the possibility of localizing higher brain function at all to some specific area(s) of the brain. Evidence from experimental and clinical neuropsychological studies supported finally his concept. Additional evidence for the visual system was provided by neuroanatomical and neurophysiological studies by Zeki (1975, 1976). He found independent projections from the first cortical receiving area (V1) to separated prestriate areas and that neuronal responses to colour stimulation were clustered in V4, to moving stimuli in V5 (1983a, b). Zeki suggested therefore that even a cytoarchitectonically uniform area as V1 must be functionally differentiated and proposed that V1 serves as a segregator for channelling the signals of visual submodalities in different cortical routes for further processing.

Functional Anatomy of Visual Pathways.

A functional inhomogeneity of V1 was already known to Poggio *et al.* (1975) and was confirmed with cytochrome oxidase staining by Wong-Riley (1979) and Horton and Hubel (1981) anatomically. Although the details are still discussed, different processing streams along the 12 cortical visual areas known so far have been principally confirmed by many authors (see Maunsell and van Essen, 1983; De Yoe and van Essen, 1985, 1988; van Essen, 1985; Mishkin *et al.*, 1986; Ungerleider *et al.*, 1983). More recently in V1 the well known orientation detecting system was added to by a non-oriented wave length sensitive system (Livingstone and Hubel, 1984a, b). This latter system has been traced to the cytochrome rich cells especially of layer 2 and 3, called "blobs". Livingstone and Hubel demonstrated also a specific reciprocal projection of blob and interblob regions from V1 to V2. In V2 they found a different pattern of the cytochrome oxydase rich distribution in stripes extending orthogonally from the V1/V2 border. These stripes are alternating thick and thin and separated by pale regions. Blob cells project to thin stripes, interblob cells to pale stripes and projections from layer 4 B cells are ending in thick stripes (Lund *et al.*, 1975; Livingstone and Hubel, 1987a). V2 in turn is connected with V3, V4 and V5 (MT) (Zeki, 1975, 1976, 1983a, b) and there is some evidence that the projection to V4 originates from thin stripes, the one to V5 from thick stripes (De Yoe and van Essen, 1985; Shipp and Zeki, 1985 Zeki, 1985). It has also been shown that the two magnocellular laminas of the lateral geniculate body with cells that are broadly tuned to wave length and activated by large retinal ganglion cells project to layer 4 C alpha. They are further relayed via 4 B not only to the thick stripes of V2 but also directly to V5. The colour blind magnocellular pathway seems to remain functionally separated therefore from the wave length selective projections to the neurons of the four parvocellular layers and the interlaminar areas of the lateral geniculate body activated by small retinal ganglion cells. They project via 4 C beta to layer 2 and 3 of the blob and interblob regions. The magnocellular and parvocellular systems both contribute probably to the interblob areas. The magnocellular neurons have larger receptive fields, respond phasically, have high contrast sensitivity and broad spectral sensitivity. The neurons of the parvo-cellular system have smaller receptive fields, show slow sustained responses, a low contrast sensitivity, and their responses are wave length dependent. On the bases of these characteristics, the spatial separa-

tion in V1 and V2, the large number of direction and velocity sensitive neurons in V5 and the colour coding neurons in V4, Hubel and Livingstone proposed that the magnocellular pathway is mainly related to movement and depth and the parvo-cellular pathway to colour perception (Hubel and Livingstone, 1987; Livingstone and Hubel, 1987a, b, 1988). The oriented cells of the interblob area and their projection to the pale stripes of V2 are supposed to transfer information for form. Such a segregation of the processing of elementary functions by keeping the contribution of the magno- and parvo-cellular pathways separated is suggested also by the possibility to separate form from movement perception. This has been shown by rotating gratings of low and high spatial frequency (> 16 cycles/degree) by Campbell and Maffei (1981) and is indicated by the disturbance of depth and form perception under isoluminant conditions (Koffka, 1935; Gregory, 1977; Livingstone and Hubel, 1987b, 1988) (Fig. 1).

Pathophysiology of Defects Within Cortical Processing Areas.

Visual defects after cortical lesions are strangely different from analog defects after interruption of the afferent pathways. While a sudden loss of afferent functions is instantly realized, a cortical defect may appear as a peculiar perceptive change, which cannot be clearly described or may not be perceived at all and denied. A sudden loss of one visual hemifield due to an occipital infarction, for example, may remain completely unrecognized. Such unawareness is most striking in the negation of a cortical blindness after a bilateral occipital infarction (Anton, 1898). It is often more difficult to assess for the loss of a subfunction as movement perception (Zihl *et al.*, 1983), but it is likely to occur also under these conditions. Cortical achromatopsias, for example (Damassio *et al.*, 1980; Zihl and von Cramon, 1986) are often not related by the subject to a defect, but to a change of colour in the surroundings. The loss of object recognition indicates a loss of meaning of any seen object. One would expect a panic reaction, if such an event would be still perceived and mentally integrated. But this does not occur. The patients seem to have lost also the awareness about the importance of the visual identification of an object although they are still able to discriminate objects by tactile or other cues. And in Anton's syndrome the denial of blindness seems to be combined with a complete loss of visual imagination and visual memory as well as visual dreaming. The question, if they cannot see, seems not to be meaningful any more, of no content and is simply denied. On the other side, if there

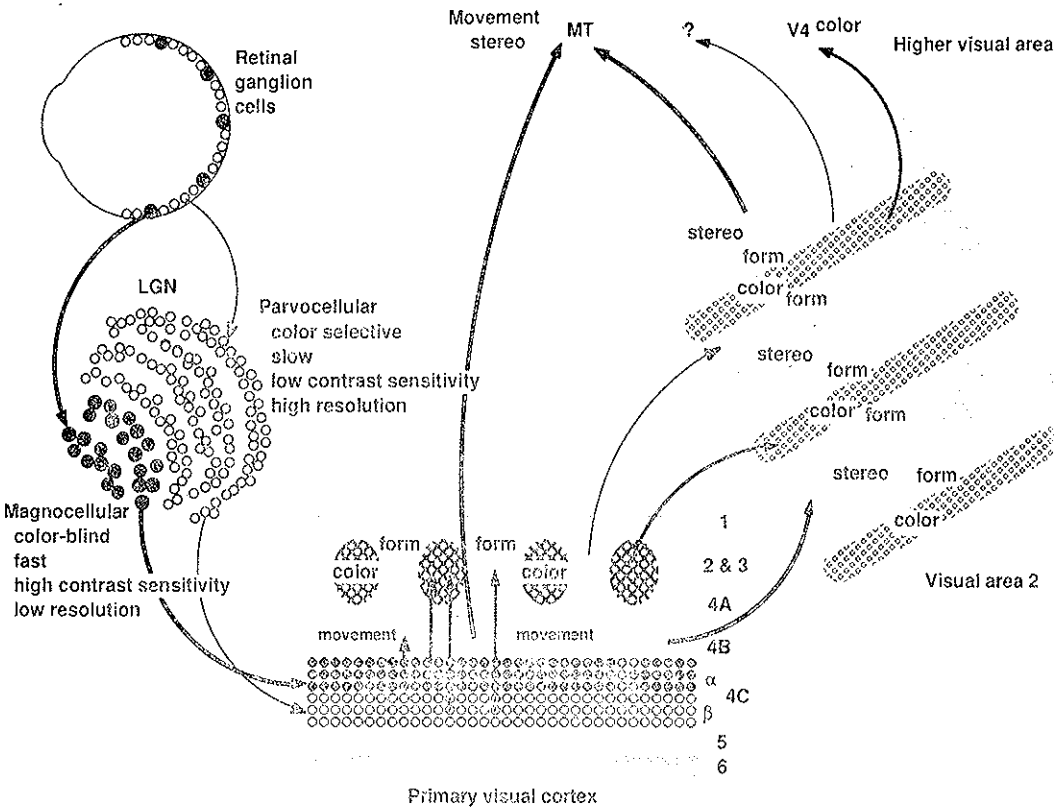

FIG. 1. Diagram of the functional segregation of the primate visual system. MT = middle temporal lobe (V5) V4 (visual area 4), LGN = lateral geniculate body, primary visual cortex (= V1, area 17). (Livingstone and Hubel, 1988).

is no destruction, but localized disorganization of activity as in focal epilepsies depending on the site of the focus, different kinds of fragmental visual percepts are reported.

Detection Versus Perceptions.

We conclude from these data that the neuronal activity in different visual areas is related to different visual percepts and that, after focal destruction, the perception of the related submodalities disappears as if they never existed. This is analogous to the point that we are not disturbed by the fact that only a limited band width of acoustic or electromagnetic

wave length is accessible. It implies further that our mental continuum is only apparent and in fact composed of many separable parts. Consequently we may ask where within the visual processing lines does the neuronal activity assume immediately perceptive relevance.

It can easily be shown that the bulk of afferent signals has no direct perceptive meaning and percepts can still be generated without them as eidetic experiences demonstrate. If one defines neuronal activity as perception-relevant, that is, meaning or generating shape, movement, depth or colour, one has to postulate that the activity of such neurons corresponds to perception, independent of biased input or without a corresponding input at all. A form related neuron should indicate a real or an apparent figure. A depth indicating neuron should be driven by disparity as well as other depth cues. A movement-related neuron should indicate a moving object, as it is perceived, independent if the movement is apparent or real (Movshon *et al.*, 1985; Mikami *et al.*, 1986). The activity of a true colour coding cell, as Zeki (1983a, b) pointed out, should correspond to a certain colour in its receptive area as long as we see this area within a complex coloured scene in this colour, independent of the wave length reflected from it. Under any such conditions the activity of these "perceptive" neurons does depend on information from outside of their conventionally defined receptive fields. The notion of the receptive field (Bishop, 1970) and its consequence, the detection of a certain stimulus of defined retinal localization, loses its meaning and cannot be related directly to perception. This follows also from the occurrence of identical illusions induced by different stimuli. They demonstrate that the receptive field becomes a variable parameter to "perceptive neurons".

If different stimuli can produce reliably the same perception, one has to assume that this is due to identical neuronal reactions as a consequence of the organization of the cortical network. Such an organization must be of utmost flexibility to guarantee the astonishing stability of the visual perception in view of the variable geometry and energy distribution of retinal images of even one object. One must postulate, therefore, mechanisms which establish invariances and constancy of space, shape, size, colour, depth and brightness. To make this possible, the system had to accept compromises. For the most obvious brightness perception, for example, it had to decide between the ability to discriminate small intensity differences and the ability to judge reliably the overall illumination. The decision was for the much more useful intensity discrimination and brightness constancy. In order to establish constancies within different sub-

modalities the network had to develop neuronal mechanisms which may generate perceptive values on its own. Their functions remain mostly unaware. Under certain conditions, however, they become manifest and produce illusions of shape, movement, colour and depth. Visual illusions therefore can tell us something about the algorithms involved and show, in addition, that the visual system is not a passive receiver, but a constructing device acting from inward out.

Neuronal Mechanisms of Form Perception.

We were interested to see where form related responses in this perceptive sense do occur, that is, where neurons begin to respond to real and anomalous or illusory contours as well. Since form is generated by contours, the first step was obviously to study simultaneous border contrast, the next to follow its transformation to field contrast and finally to illusory "contrast" (Frisby and Clatworthy, 1975). The experiments were done by single neuron recordings from the optic nerve, the lateral geniculate body (cat) and V1 and V2 (awake rhesus monkey).

As expected from the concentric center-surround antagonism of receptive fields of neurons from the retina (Kuffler, 1953) up to layer 4 C in V1 (Baumgartner and Hakas, 1962), border contrast was easy to detect in the neuronal activity at these levels (Fig. 2). One had only to assume that on-center neurons with broad wave length sensitivity are coding for brighter and off-center light inhibited neurons for darker in their receptive field center. This assumption was confirmed by the defect in the perception of light increments which follows selective blockade of on-center cells (Schiller *et al.*, 1986). Field contrast, however, that is, the increase or decrease in brightness of a surface depending on the direction of contrast gradients at its border, was not detected by neurons with concentric receptive field. If their receptive fields were completely inside the contrast area they respond as to diffuse illumination independent of the contrast gradient at the border.

Also cells with oriented receptive fields in V1 did not show field contrast either. Due to the balance between excitatory and inhibitory input they did not respond at all, if the receptive fields were within the isoluminant area. They remained silent irrespective of whether we perceived the surface brighter or darker. This left us with the paradox that a silent area in V1 may correspond to an increase or decrease of brightness perception. We had to assume, therefore, that neither border nor

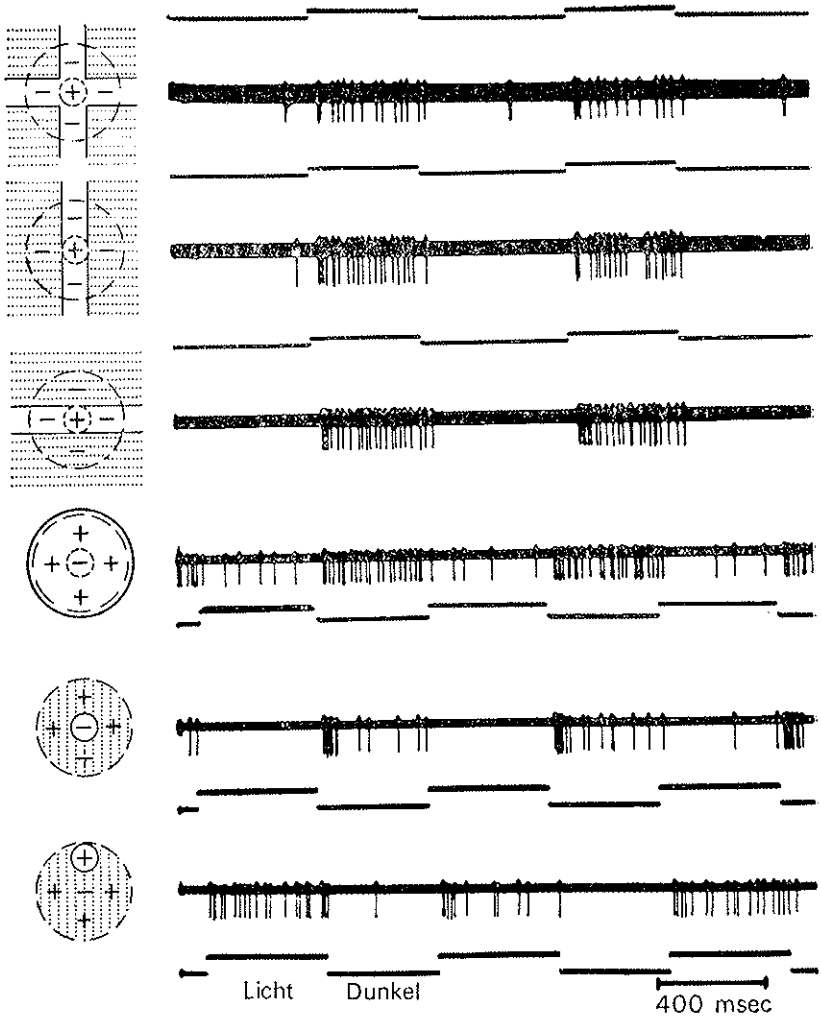

FIG. 2. On-center-neuron (upper 3 lines) and off-center neuron in different contrast illumination. The on-center-neuron is shown by stimulation with a horizontal and vertical bright bar and a bright cross of equal luminance. Due to increased lateral inhibition the activity in the intersection is reduced.

Off-center neuron after stimulation of the whole receptive field and stimulation with a light spot in the center and in the periphery. Complete inhibition after central illumination, activation after illumination in the periphery. (Dashed circles = receptive fields, + = excitatory, − = inhibiting regions, continuous circles = light stimulus). (Baumgartner *et al.*, 1988).

field contrast is perceived up to and including V1. Earlier experiments had shown that some cells with excitatory field axis were less active in the crossing area of two bright bars. This may indicate that cells within V1 with excitatory centers are still coding for brighter and with inhibitory field axis for darker. In the absence of any neuronal correlate for field contrast up to this level, we propose that V1 is still a detecting but not a perceiving device. It is suggested that the mechanisms of border contrast are used for improving contour detection in V1 and that field contrast is generated at the earliest in V2. Field contrast is thought to be the consequence of an extrapolation of brightness over space, that is, from border to border. Under this assumption, field contrast by stimulation with reversed contrast gradients on opposite sides of an isoluminant area should result in a perceived brightness in between the two uniform contrast conditions (Baumgartner, 1986). And this is the case (Fig. 3).

The assumption that V1 is still functioning on the detecting level is also supported by the strict dependency of the neuronal responses on the receptive fields, which does not fulfill the postulate of variable input dependency of perceptive neurons. We argued that a neuronal population which sees and not only detects, e.g., bars should respond to a real and illusory bar as well. To confirm this assumption we studied the reaction of cortical neurons to illusory contours. We consider those as a third order step along the contrast and form processing, which allows to perceive contours in conditions in which object and background are partially isoluminant (Baumgartner *et al.*, 1988). In addition, the mechanisms involved exclude more and more redundant information in order to reconstruct the objects based on crucial cues. Illusory figures can be induced by a variety of stimuli which trigger the impression of overlying occluding objects without corresponding physical equivalent. Consequently they induce also field contrast and depth perception (Fig. 4).

Neurons of V1 responding to a real bar of a defined orientation did not, as expected, show any response to stimulation with illusory bars of the optimal orientation. By contrast more than 30% of neurons in V2 which responded to a real bar did respond also to an illusory one of similar orientation (Fig. 5). The trigger stimuli for the illusory bar were clearly outside the boundary of the conventionally defined response field, that is, the area over which the neurons could be influenced with real bars of optimal length, width and orientation. Illusory contours as well as field contrast seem to be induced by the convergence of spatially separated neurons of V1 on neurons of V2 (Peterhans, von der Heydt and

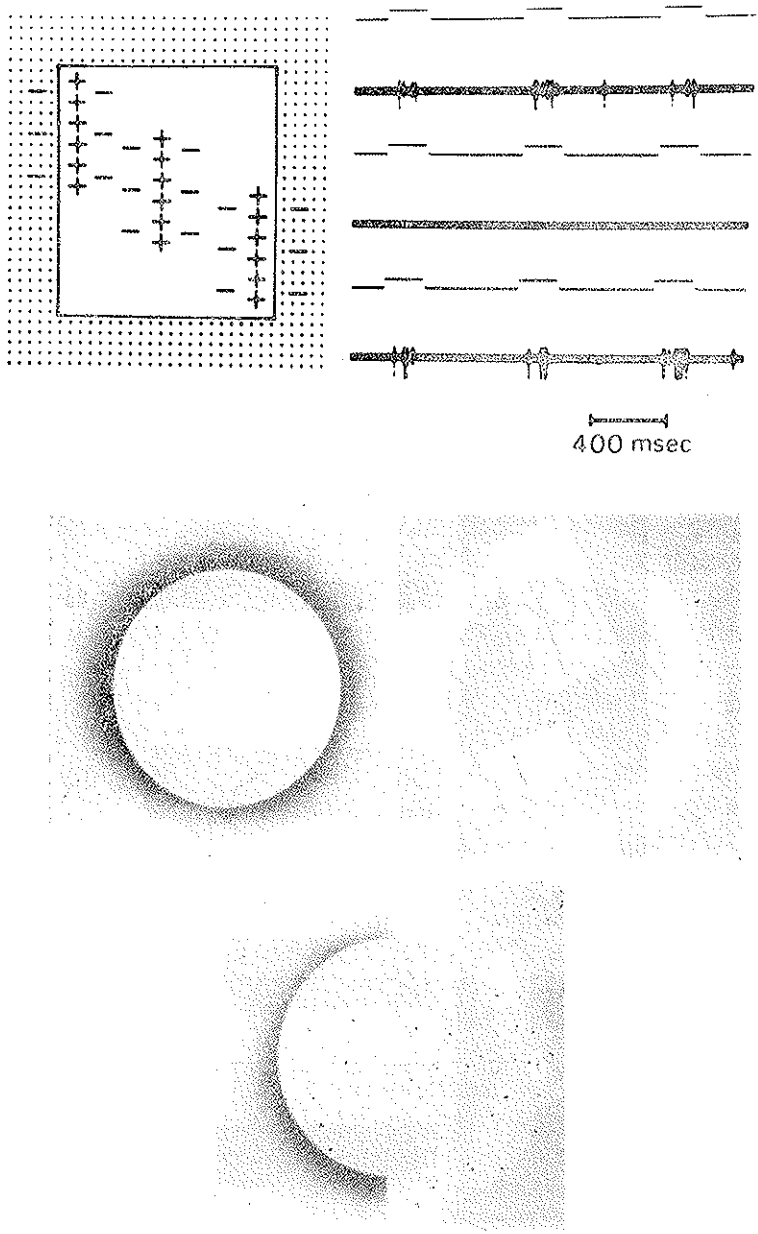

FIG. 3. Field contrast (Craik-Cornsweet illusion) and the response of a simple field neuron of V1 of the cat. Although the discs are equal in diameter and luminance, the left is appearing larger and brighter. The neuron is activated only at the borders of the bright rectangle, since activating (+) and inhibiting (−) zones of the receptive field are balanced. The line above the neuronal response indicates the photo cell (line up = light on). As it is shown below, reversing the contrast gradients on the opposite side of the disc results in an apparent brightness in between the two homogeneous contrast conditions (Baumgartner, 1986).

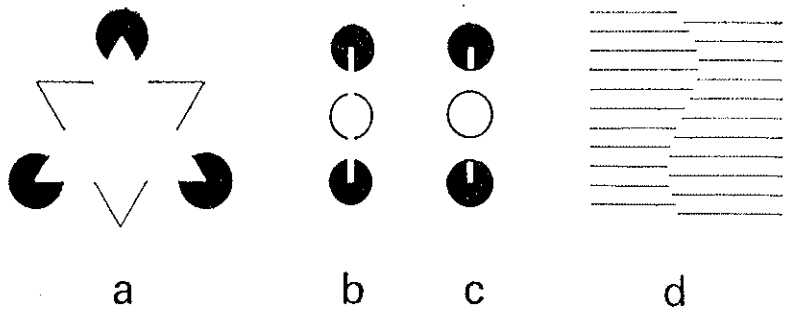

FIG. 4. Figures producing illusory contours. (a + d: Kanizsa, 1979; b + c: Smith and Over, 1975).

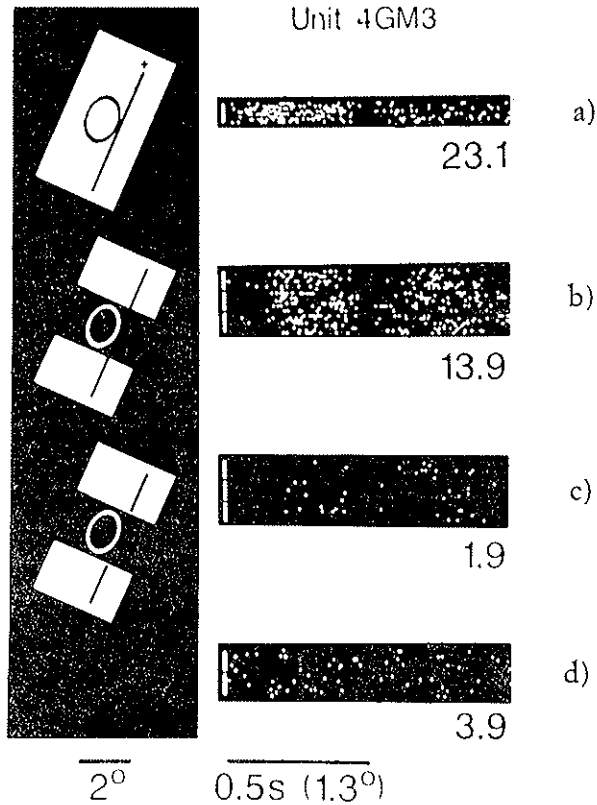

FIG. 5. Neuron of monkey's V1 responding to a bar (a) and an illusory contour (b) with the same orientation. After closure of the ends of the inducing lines (c) the activity drops to the spontaneous level (d). The dots correspond to an action potential. Each line of the dot display shows the response to a movement of the stimulus back and forth. The numbers indicate the averaged discharges/stimulation. The ellipses indicate the conventionally defined receptive field.

Baumgartner, 1986). Surprising and confirming the correspondence of the neuronal response to the illusory perception was the activation of neurons by an apparent contour induced by abutting gratings (Fig. 6). Such an illusory line is strongest to us when the inducing lines are orthogonal to it. This was valid also for neurons responding to an illusory line moved back and forth. The strongest response was induced by abutting lines orthogonal to the illusory one. The trigger features for vertical illusory lines under these conditions are horizontal lines which activate horizontally orientated neurons in V1 probably of the endstopped type (Peterhans and von der Heydt, 1987). That is, cells which respond best to a line of a defined length or the end of a long bar. The horizontal input is obviously transformed to give a percept of a vertical line without physical equivalence.

Illusory figures were often considered of cognitive origin and hence called cognitive figures. They were thought to be the result of a judgement of the visual input based on likelihood. Our findings show, however, that they are a consequence of the inherent organization of the system which modifies the incoming information and generates perceptive values

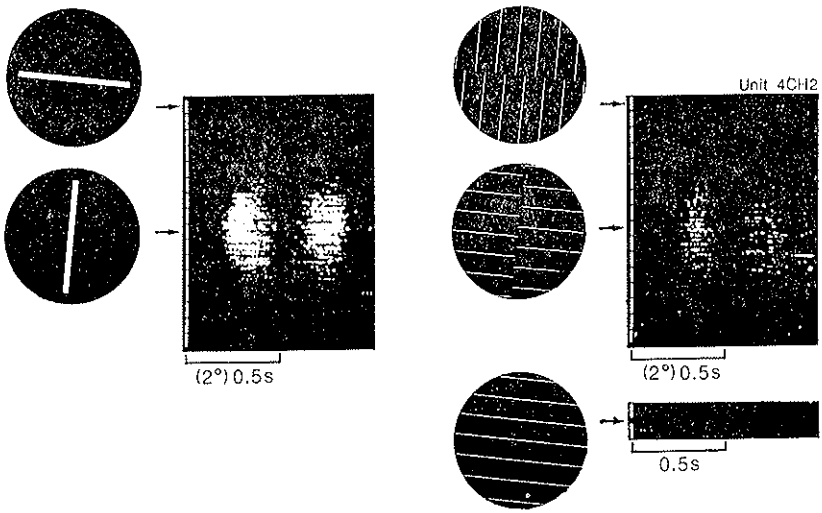

FIG. 6. Neuron of V2 of the monkey responding to a bar and an apparent contour of the same orientation induced by a grid of abutting lines (middle display). No response to a real or apparent contour (above) or to lines orthogonal (below) to the optimal orientation. The bar or illusory contour was moved back and forth orthogonal to the orientation (von der Heydt and Peterhans, 1989) (see legend figure 5).

of its own. In evolution this may have resulted for reasons of neuronal economy. An illusory contour corresponds in nature mostly to an overlying object and is so generated including its associated features as field contrast and depth by a minimum of neuronal activity. With respect to perception we have to assume that, since V1 neurons do not respond to apparent contours, perception related neuronal activity for seeing a bar appears at the earliest in V2. This would mean that form or object perception begins not before V2. The neurons responding to illusory stimuli lay within the thick and the pale stripes of V2 (Peterhans and von der Heydt, 1988). This may indicate that they are a part of the magnocellular system, which would serve as a "master form signalling channel" (Gregory, 1977). The stepwise development of contrast perception from border to field contrast and illusory contrast shows that the system processes information so that it becomes at the same time more specific and generalized. It is able to indicate an illusory contour of defined localization, depth and orientation, but the contour can be produced by many different trigger features. This may be one step to size and shape constancy.

The proposal that form vision arises first in V2 does not mean that it is completed there. One has to expect that depending on the complexity of a visual task, further processing is necessary. In this process only the essential information seems to be extracted in a stepwise manner. This is to derive from neurons responding to faces or facial attributes which are invariant for colour, movement, size, position and rotation (Gross, 1973; Perret *et al.*, 1984). One has therefore to assume that the specification of such submodalities is done by other neuronal populations, for colour possibly in V4, for movement in V5. For form and depth vision the parvo- and magnocellular input seems to be of importance with a clear bias to the colour blind magnocellular system. This is in agreement with the improvement of form and depth discrimination in brightness contrast compared to isoluminant conditions (Livingstone and Hubel, 1988).

Conclusion.

The neuroanatomical and neurophysiological data make it likely that the different attributes of vision are processed in parallel and are perceived in spatially separated areas. This could explain the occurrence of isolated defects of colour, movement and depth perception or object recognition

after focal cortical lesions in the prestriate regions. But the continuity and wholeness of our visual experiences is difficult to imagine under this assumption. It favours the postulation that the different visual submodalities must converge somewhere. However, the clinical experience may indicate that this is not necessary, since in case of convergence an isolated loss of one submodality should result in disturbances also in others. Partial unawareness could, however, be understood if submodalities are not only processed but remain perceptively independent. The integration of different submodalities to global perception could be the contribution of time. Time could serve as the unifying parameter by coincident activation (Phillips *et al.*, 1984) of neuronal population with different spatial coordinates. The rich interconnections between and along the different processing lines could be thought to act as a time control device for correlating local features within the visual field to different submodalities.

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DISCUSSION

DEECKE

When you have the patient who lacks movement perception *per se*, (he can see everything, but what he sees is not movement) — I have two questions. One, does he see this as stroboscopic vision? And two, if you assume that there is a specific brain area for movement perception, then you also have to assume that there is a "super area" in which all the different properties of vision are combined into conscious experience. Have you any idea where this could take place?

BAUMGARTNER

As to your second question, I don't see that there is a necessity for a "super area". If the different areas involved show covariant activation, I am completely satisfied to accept this as a basis of a continuous visual and whole experience.

As to your first question, this patient described his strategy in dealing with his problem. For example, as he realized that he could not fill his coffee cup without spilling it over because he did not see the movement of the coffee surface in the cup, he put a line on the inside of the cup, and stopped pouring as soon as the line was reached. He also described that if he poured out coffee, he couldn't see the coffee coming out of the pot like moving liquid, but it was like an icicle just hanging in the air, connecting the coffee pot with the cup. Also, he could not see the movement of cars in the street. He was therefore very anxious about crossing the street because he could not see the cars continuously approaching, but instead saw them first here and then there, and so on.

MOUNTCASTLE

Your description could fit well with a parietal lesion.

BAUMGARTNER

This was a retroparietal lesion. This patient is still alive. One can only

approximate the localization, and we cannot say whether it is MT (or V5), the exact location of which we don't know in humans anyway.

ECCLES

I am very interested in Professor Baumgartner's generalizations with respect to where is perception, after all the detailed knowledge of the visual areas, for example. I think that we can only regard this as moving into a different world, the mental world, the world of experience, mental experience and so on, which we derive from the neural performance. There is the great unknown between neural performances in the various areas of the brain and what we perceive as the result of that. For example, just look at this room here, the ceiling and all the rest of it. This is an immensely complicated neuronal performance that's going on but we see it as a unit, immediately. This is not explained by any of our ideas at present.

BAUMGARTNER

If you allow me a trivial analogy, one may consider the brain as an accumulation of around 5 billion small computers. The activity in this very complex system may generate substructures on its own which we cannot predict. If we have such a complicated structure as our brain, which is in my opinion the end point of the universal, then nature has obviously invented something like consciousness. Why it did invent consciousness I am not quite sure, but maybe it's a probe which makes it easier to sweep around, to focalize, to get out information from many different points. I think we will never know. We certainly will never understand it in terms of real understanding. It is, in my opinion, a question which is much more than our brain can access.

JEANNEROD

I wonder if there is not even a greater parallel processing in the visual pathways than you have shown in your talk. For instance, in our laboratory we now have experiments going on where we make complete blocking of area 17 by cooling and recording neurons in other areas. For instance, in V5 the neurons are still responsive to movement, they are still tuned to particular velocities and retain the direction coding. So I wonder where this information comes from because it can't come via the cortex.

BAUMGARTNER

I think this is completely correct. I was speaking in just a very simple way. I neglected all the input from the pulvinar and the tectum. If you discover motion-depending neurons in V5 after destruction of V1, this would in fact support the notion that V5 really has something to do with motion perception, even if it comes from somewhere else.

ROLAND

If one works with single-unit recordings, it's clear that one doesn't have the overview of what the whole brain is doing. With mapping studies of metabolism and blood flow, it has been a consistent finding that whenever perception is going on, be it auditory, visual or somatosensory, the prefrontal cortex is in some way also active. This doesn't mean to say that the prefrontal cortex is seeing what all the visual association areas are doing. I am not inferring that, but if one also puts one's attention towards shall we say a particular visual aspect, then there is an enhancement of the metabolism, particularly in visual association areas. This might be somewhat useful, that there is a kind of traffic between the prefrontal cortex and the visual association areas. One can actually have disturbed visual perception after lesions in the frontal lobe, and severe deficits in visual attention from prefrontal lesions.

Now I will come to a more specific question, and that is why are some of the patients aware of their hemianopia while others are not? I have a tentative hypothesis, and that is that if these patients' visual association areas are destroyed to a great extent, then they won't be aware of the hemianopia, but if they are preserved, then they will be aware of the hemianopia, the reason being that there are no direct retrograde connections from the prefrontal to the primary visual cortex, but there are several connections from the prefrontal cortex to the visual association areas.

BAUMGARTNER

Single unit and functional brain mapping studies concentrate on completely different time domains. You are dealing with minutes while seeing is going on, and we are dealing with milliseconds. When we see a neuron like this working, it does it in 40, 60, 80 milliseconds, and doesn't need the long back and forth traffic to the frontal cortex. The frontal cortex is certainly relevant for perception in some way such as concentrated visual exploration or directing

perception, but for immediate perception I don't think that it has great importance.

The other question was why some people don't perceive a visual field deficit. If the structure which is necessary to perceive is gone, the person is not perceiving the defect any more, but if the structure which is necessary to perceive is still okay, as after a lesion of the optic tract, for example, this structure immediately tells you that something is missing. That is my very naive explanation.

GOLDMAN-RAKIC

My question pertains to the phenomenon of blind sight with visual cortical lesions where you have an opposite kind of dissociation where verbally the patients report that they do not see, but it can be demonstrated that they do see. Would you comment on that as another evidence of dissociation and distribution of function?

BAUMGARTNER

It is well known that some patients with extensive right hemispheric lesions who are completely hemiplegic are telling you that they are okay. I remember such a patient. I came to his bed and said, "How are you?" He said, "I am fine." I replied, "But you can't move your left hand." Then he took the left hand with his right hand and said, "What do you want? I am moving it."

SELF-ORGANIZATION OF COGNITIVE STRUCTURES

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Principles of Self-Organization.

It has often been emphasized that the genes cannot contain, in any naive sense, the full information necessary to describe the brain. Cerebral cortex alone contains on the order of 10^{14} synapses. Forgetting considerations of genome size, one can hardly imagine how ontogeny could select the correct wiring diagram out of all alternatives if these were of equal likelihood. Besides, judging from the variability of the vertebrate brain structure, the precision of the ontogenetic process is not sufficient to specify individual connections. This implies that ontogeny has to make use of self-organization: of general rules for pattern generation and of simple principles of error correction.

The development of organs and organisms is based on a permanent, interactive exchange between the information stored in the genome and the information available in the cellular "environment" of the genome. The latter determines which of the genetic commands should be expressed at particular developmental stages. As the developmental process proceeds and organs differentiate, the microenvironment of the genome changes and hence modifies continuously the further expression of the genes. During early phases of brain development gene expression and post-translational modifications of gene products are controlled, as in any other organ, by the biochemical signals which are produced in the cellular microenvironment. Later, however, brain development starts to differ radically from the development of other organs because electrical activity is added to the biochemical messengers as a further signaling system in the self-organizing dialogue between the genes and their

respective environments. It has to be assumed that these electrical signals are capable of influencing gene expression and post-translational modifications.

This has a number of extremely important implications. Electrical signals are transported by neuronal processes over great distances and with high topological selectivity. This enlarges dramatically the range and the complexity of the "environment" that is available to the self-organization process. From a certain developmental stage onwards the brain possesses functioning sense organs which convert signals from within the organism and even from extracorporal space into electrical messages. Thus, the "environment" relevant for brain self-organization ultimately includes all domains with which the evolving brain is capable to interact and from which it can receive messages. Another important aspect is that the very same electrical signals which convey sensory messages are used by the brain as information carriers for computational processes. Hence, the powerful capacities of nerve nets to perform complex logical operations on large parameter sets become also available to the self-organization process. As the complexity of the brain increases, the computational power and the complexity of its interactions with its environment increase as well. As a consequence, also the set of parameters determining further brain development becomes more complex and capable of supporting self-organization towards even more differentiated structures. It is because of this spiral of reciprocal interactions between the genome and its increasingly complex environment that a rather small set of genetic rules suffices to promote the development of such highly differentiated structures as the human brain. As will become clear below, these very processes which support experience-dependent self-organization during development are closely related to the more general processes which serve to adapt the mature brain to its environment and are commonly addressed as learning.

The Visual System as a Model.

Most of our knowledge on activity-dependent specification of neuronal connections comes from the visual system. "Seeing" has to be learned during a critical period of early postnatal development. Experiments in visually deprived animals have revealed that certain cortical functions can only be developed if visual experience is available.

The following example illustrates this. Higher mammals and humans who have frontally positioned eyes with overlapping visual fields can compute from the differences between the images in the two eyes the distance of objects in space.

The basis for this function are neurones in the visual cortex which possess two receptive fields, one in each eye, that have the same features and are precisely superimposed in visual space. Thus, during development the one million afferents arriving from each eye have to be arranged so that only those pairs of afferents converge onto cortical cells which originate from precisely corresponding retinal loci. The problem is that there is no way to predict with any great precision which retinal loci will actually be corresponding in the mature visual system. Retinal correspondence depends on parameters such as the size of the eye balls, the position of the eyeballs in the orbit and the interocular distance. Clearly, these parameters are strongly influenced by epigenetic factors and they change during early development. It follows that genetic instructions alone, even if they were quantitatively sufficient, cannot in principle suffice to determine with the required precision the pattern of interocular connections. An elegant possibility exists, however, to identify fibers as coming from corresponding retinal loci by evaluating their electrical activity. When a target is fixated with both eyes, corresponding retinal loci are stimulated by the same contours. Therefore neuronal responses in afferents from corresponding retinal loci are more correlated than those in afferents from non-corresponding loci. What is required then is a developmental mechanism capable of consolidating selectively those retinal afferents which convey correlated activation patterns.

Hebbian Learning Rules in Developmental Self-Organization.

This activity-dependent shaping follows rules similar to those postulated by Hebb (1949) for adaptive neuronal connections in learning nerve nets. Connections are selected as a function of the statistical correlation between pre- and postsynaptic activation (Rauschecker and Singer, 1979, 1981). Pathways having a high probability of being active at the same time as the postsynaptic target cells become stabilized, whereas those tending to be inactive while the postsynaptic target is driven by other inputs weaken and eventually disconnect. These rules have the effect of stabilizing selectively those subsets of converging afferents which convey correlated activity and are capable of driving the postsynaptic

target and they lead to competition between afferents conveying non-correlated activity. In the latter case, one subset of afferents consolidates at the expense of the other.

There are further indications that the activation of the postsynaptic target must reach a critical threshold before modifications can occur. This "plasticity threshold" appears to be different from the threshold of sodium-dependent action potentials, and is most likely related to the activation threshold of dendritic calcium conductances (Geiger and Singer, 1986). A possible molecular mechanism for the implementation of this threshold process is the NMDA receptor, since selective blockade of this receptor system prevents use-dependent changes in binocularity (Kleinschmidt *et al.*, 1987). This mechanism is ideally suited for evaluating the contingency of pre- and postsynaptic activation and for activating Ca^{2+}-conductances when a critical level of cooperativity is reached. The ionophore coupled to the NMDA receptor opens and then becomes Ca^{2+}-permeable only when the receptor is occupied by its endogenous ligand and when the postsynaptic membrane is in addition sufficiently depolarized (Dingledine *et al.*, 1986; Thomson, 1986; Watkins and Evans, 1981).

Thus, the use-dependent modifications of binocular connections differ from the classical Hebbian postulates in at least two important aspects. First, there is a threshold for modifications. This implies that modifications occur only if a minimal number of converging pathways are co-activated. Second, the postsynaptic signal relevant for contingency matching appears to be a local dendritic event rather than the global output signal of the neurone.

Gating of Hebbian Modifications.

It has been postulated that the selection of appropriate binocular connections must not depend solely on locally available retinal signals, but also needs to be controlled by more globally organized gating systems if it were to be successful (Singer *et al.*, 1982). Obviously, selection may occur only when the two eyes are actually fixating a common target, and it must not occur when the eyes are moving or not aligned properly. In the latter case activity patterns from both eyes would be uncorrelated, and this would lead to a disruption of binocular connections. The same would be the case if the spontaneously produced bursts of activity that occur during certain sleep stages were capable of inducing changes in

circuitry. Moreover, to assure a sufficient degree of overlap of the images in the two eyes at the time of circuit selection, some evaluation of the best match between the coarsely prespecified retinotopic representations ought to be made prior to selection. This requires preprocessing of visual signals and control of eye movements, and hence an aroused and attentive brain.

In agreement with these postulates, it was found that proprioceptive signals from extraocular muscles which convey information about eye position and motility serve a gating function in ocular dominance plasticity (Buisseret and Singer, 1983; Freeman and Bonds, 1979). Thereafter, it was shown that central core projection systems whose activation is related to reticular arousal also have a permissive function in ocular dominance plasticity (Singer, 1982; Singer and Rauschecker, 1982). The initial proposal that this function is subserved by the noradrenergic projection alone (Kasamatsu *et al.*, 1979) has now been extended by the finding that both the noradrenergic and the cholinergic projections to striate cortex cooperate in this gating function (Bear and Singer, 1986).

Vision-dependent changes in circuitry can be induced only when these modulatory systems are sufficiently active, or when the corresponding neurotransmitters ACh and NE are substituted locally while the neurones are activated from the retina (Greuel *et al.*, 1988). This may account for the evidence that modifications occur under natural conditions only when the animals are alert and attentive to visual stimuli.

Thus, mechanisms are implemented which allow gating of local changes as a function of global states of the brain. As argued above, this is indispensable in this particular case of map matching, where two mobile sensory surfaces must be related to each other. It is also indispensable whenever local self-organizing processes are to develop functions which are embedded in a more global context.

Self-Organization at Higher Levels of Cortical Processing.

So far we have dealt with a self-organization process that essentially serves to generate an optimal match between ordered topographic maps. We shall now take this approach one step further and investigate the consequences of self-organization in the feature space in which "conceptual" rather than topological vicinity is the relevant selection criterion.

It has been known for a long time that one of the prominent features of cortical organization is the presence of an extremely dense network of far-reaching connections which are tangential to the cortical lamination. These pathways are thus capable of mediating interactions between cortical neurones that are nonadjacent and located in different columns and there are indications that these connections are organized in a selective way, linking neurone clusters that tend to be spaced periodically (Rockland and Lund, 1982, 1983) and that share the same orientation preference and/or the same eye dominance (T'so *et al.*, 1986; but see Matsubara *et al.*, 1985). Developmental studies in the cat have shown that these tangential connections essentially appear postnatally (Price and Blakemore, 1985), go through a phase of exuberant proliferation during which they are extremely numerous and far-reaching, and subsequently become pruned under the influence of visual experience. If visual experience is unrestricted, subpopulations of these pathways are stabilized; if visual experience is not available, only a rudimentary network of horizontal connections is maintained (Luhmann *et al.*, 1986, 1990a, b, c).

This intrinsic tangential network thus appears to develop in much the same way as the long-range connections between the eyes and their target structures (see above). We propose, therefore, that the system of horizontal connections self-organizes according to the same principles as the thalamocortical connections. We assume that those connections are stabilized selectively by coherency matching which extends between neurone clusters whose activation patterns show some statistical correlation. For neurone clusters too remote from each other to share a common input from retinocortical afferents, the degree of correlated activation does not depend upon particular neighborhood relations, but is determined essentially by coherencies between particular features of the visual scene. Consider, for example, an elongated contour. It leads to coherent activation of clusters of neurones which share the appropriate orientation preference. Because of the columnar organization of cortical representations, these clusters are distributed discontinuously along trajectories within striate cortex whose orientation on the retinotopic map depends on the position and the orientation of the contour border in visual space. Likewise, a slowly moving object coherently activates distributed clusters of neurones whose directional preference matches the object's direction of movement.

Selective stabilization of tangential intrinsic connections could thus generate a non-topographically organized map which matches the coherent

properties of "feature constellations" in physical reality rather than topographic coherencies. By virtue of selective connections between the eyes and cortical cells, the latter become "detectors" of coherency between pairs of corresponding retinal ganglion cells in the two eyes. In analogy the assembly of selectively coupled distributed clusters of feature detectors becomes a detector of coherencies within elementary constellations of features.

As in the formation of topographic maps, there will be competition between many possible constellations of features which all show some coherency, and only the most consistent and most frequently occurring constellations will win. Those which match best the already established connectivity pattern will have a competitive advantage. This leads to the development of a map which represents not only coherent relations in particular feature constellations, but also the statistical probability with which these constellations occur in the physical world. Furthermore, it is likely that the selection process at this level of cortical organization is also dependent on the activity of central gating systems, as this is already the case for selection processes at lower levels. This would provide the additional option to override the probability functions inherent in the structure of the physical world and to preferentially represent constellations relevant to the system in a behavioral context.

Thus, by simple reiteration of the very same processes of self-organization which at peripheral levels of the visual system lead to the establishment of maps encoding for topographic neighborhood relations, it is possible to generate non-topographic maps which represent dimensional neighborhood relations in feature space. All that is needed is an architecture of connections allowing for interactions between clusters of feature-specific neurones. Once such maps are established, they will serve as detectors of coherencies in visual scenes.

It is of particular importance and should be emphasized here that this map of "neighborhood" or "conceptual" relations in feature space actually coexists in the same cortical area as the retinotopically organized maps which represent the topological relations between features. It is thus not required to sacrifice retinotopy in order to decode coherencies between parts of a figure which are non-neighbors on the topographic map. As discussed more explicitly elsewhere (von der Malsburg and Schneider, 1986; Singer, 1985), such a network would be ideally suited to perform many of the segmentation processes required at the level of preattentive vision. Scenes must first be subdivided into what is most likely to be

coherent figures and non-coherent noise. The identification process of the figure itself can only start thereafter. However, during this segmentation process the topographic relations of the features identified as belonging to the figure must preserve their topological relation. Otherwise, the identification would not be possible. Hence, the mechanism which detects coherencies in the feature space must actually be implemented at a level of processing where topological relations are strictly preserved. The above-proposed organization of striate cortex therefore appears to be well adapted to perform segmentation of scenes while preserving retinotopy.

Synchronous Oscillations as Basis for the Formation of Coherently Active Cell Assemblies.

Recently we have obtained evidence which suggests that cell assemblies coding for coherent features in visual scenes may not simply be distinguished by the fact that the constituting neurones are simultaneously active. Rather it appears as if such cell assemblies are characterized by synchronization of oscillatory responses. We have discovered that a large fraction of neurones in the cat striate cortex engage in oscillatory activity in a frequency range of 40 to 50 Hz when activated with light stimuli to which the neurones are tuned (Gray and Singer, 1989). Units close enough to be recorded with a single electrode, if responsive to the same stimulus, always synchronize their respective oscillatory responses. In most instances oscillatory responses are also in phase for neurones aligned along the vertical axis of a cortical column. Of particular interest in the present context is the finding that the oscillatory responses can also synchronize across spatially separate columns and over tangential distances as large as 7 mm (Gray *et al.*, 1989).

So far three parameters have been identified which determine the degree of synchrony: The distance between the units, the similarity of their orientation preference and the coherency of the stimulus itself. When neurones are less than 2 mm apart, in which case their RFs are usually overlapping, they always synchronize their activation when they show the same orientation preferences, and they often synchronize even if their orientation preferences differ, as long as these differences are sufficiently similar to allow activation of both neurone clusters with a single stimulus. At larger distances, when the receptive fields are no longer overlapping, cell clusters tend to synchronize their oscillatory responses only when

they have similar orientation preferences and are activated by stimuli that have the same orientation and that move into the same direction. In such cases correlation decreases or breaks down when the two stimuli pass in opposite directions over the two receptive fields, and it gets maximal when both neurone clusters are activated with a single continuous stimulus. Thus, the amount of synchrony in the oscillatory responses of spatially separate neurone clusters signals the amount of coherency inherent in the stimuli that give rise to the responses. Even though direct proof is lacking, it is to be expected from these properties that cell clusters synchronize their respective responses if they are activated by spatially distributed pattern elements that share particular features, such as the same orientation, the same disparity, the same colour or the same direction of motion. The assembly of detectors which code for the coherent features of the figure would thus be distinguished from detectors coding for the non-coherent features of a noisy background by the fact that the oscillatory responses of the cells in the assembly coding for the figure are synchronous and in phase.

Expressing coherency by synchrony among oscillatory responses has several advantages. Oscillators that are tuned to similar frequencies can be entrained relatively easily to oscillate in phase. Thus, a high degree of synchrony can be achieved even if the connections which assure the coupling have only modulatory effects and relatively poor temporal precision in their transmission properties. Both are the case for the tangential intracortical connections. First, their coupling strength is low, as can be deduced from the fact that they do not produce discharges in cortical neurones. If they did, cortical neurones would have several spatially segregated receptive fields. Second, intracortical connections are slowly conducting and thus introducing considerable temporal scatter when associating cell clusters that are not equally distant (Luhmann *et al.*, 1990b). Another advantage of expressing coherency by synchrony of oscillations is that more than one coherently active assembly of cells can be represented simultaneously in the same cortical sheet without becoming confounded. It would be sufficient that the different assemblies oscillate out of phase in order to remain separated. The possibility to have more than one assembly represented at a time within the same cortical area may actually be crucial for low level visual processing such as scene segmentation and figure-ground distinction. In case both figure and ground consist of orderly structured patterns both should be represented simultaneously by two clearly segregated but simultaneously active cell

assemblies. In addition, it is likely that oscillatory responses serve as basis for dynamic processes which allow for very complex interactions between different cell assemblies. Coupled oscillators, even if their number is small, can engage in highly non-linear dynamics such as deterministic chaos and this in turn could be an exceedingly rich ground for the representation of patterns. The complexity of these dynamic interactions is still far beyond the reach of our experimental techniques, but I expect that it will be one of the major challenges in future work on higher brain functions to master the technical and theoretical problems inherent in non-linear dynamical systems.

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DISCUSSION

ANDERSEN

How do you entrain these coherent patterns of spike activity?

SINGER

We just present stimuli to the receptive fields of the respective columns. The neurons entrain each other, we believe, through the horizontal connections, or through back projections from other areas.

ANDERSEN

What is your preferred mechanism for entrainment? It may be the way in which far distant areas can produce the coherence that Baumgartner was alluding to today.

SINGER

We suppose that the tangential connections which go to the apical dendrites of pyramidal neurons use the NMDA receptor mechanism as a coupling device. This mechanism is operative as long as one column is active. Other columns would not see this activity because the NMDA receptor mechanism there is not activated. As soon as another column also gets an afferent input from below, then the coupling can become effective because the block is removed and the two oscillators entrain each other. We are about to simulate the constraints that have to be imposed on the coupling connections in order to establish coherency. What is quite clear is that the nervous system can do it with zero phase lag. These correlations are absolutely in synchrony over large distances. So it is not one driving the other. It's the two becoming synchronized.

LEJEUNE

I was very interested when you began talking because you first showed that you need a grid in which something is moving at the same time. Then

I was asking myself, where is the time keeper and then, finally, at the end of your talk, you proposed the synchrony between oscillators. Now, what is first? Is it the grid, which is a kind of Cartesian system, or is it the time keeper? Or could it be the same thing which is together, the flat space and the volume time?

SINGER

I wish you had an easier question for me! I think wherever one looks in nature one finds oscillators and pacemakers and I think that these set the time frame for evaluation and for contingency matching because, after all, all the brain can do is establish propositional, relational representations. There is no way to any formal analysis. What the system does apparently is to evaluate contiguities in space and time. So in order to do that it needs a fixed time frame over which it does this matching, and different animals may have different time constants. I guess these 40 per sec. cycles here are not just chance, because it's just above the flicker fusion frequency. In motor systems nobody would be surprised if one talked about oscillators that are tuned and interact and form coherent ensembles. Von Holst had already suggested that. I think the time frame is first.

MOUNTCASTLE

In the parietal cortex of monkeys I have also seen local oscillation, but it is restricted. You don't see it with every neuron. Do you suggest then that there are special cells which generate the oscillatory phenomenon and if so, how are they linked, how are they operating within the linkages of the columnar chains?

SINGER

One of our pet ideas was that not every cell is connected to every cell, but that there are some ambassadors who convey the message. It would economize circuits and then it would suffice that only those oscillate. On the other hand, we got the impression that oscillation is already a signal that indicates coherence along some dimensions, because cells oscillate much better when binocular convergence is assured than with monocular stimulation.

MOUNTCASTLE

But certainly there are many cells that do not show the oscillatory phenomenon.

SINGER

Yes; none of the simple cells in layer IV oscillates.

MOUNTCASTLE

Do you think the pyramidal cells do?

SINGER

We know that the layer V cells and the supragranular cells oscillate well. It should be the big cells, because the field that is generated by those which oscillate is enormous.

BAUMGARTNER

Do you think this oscillation has a linear base?

SINGER

It's highly non-linear. We have made analyses of the time sequence of the statistics, and what happens is that in the resting state these columns behave like a chaotic oscillator. They produce deterministic chaos. The attractor dimension is somewhere in the range of 7 to 9. I don't know what that means exactly, but when the stimulus comes, they switch into a limit cycle. Theoreticians tell me that this is what you want to do if you want to have quick transitions from an equal probability surface into attractor things. So if you want to make quick decisions bias-free, what you want to be is in a chaotic state with high temperature, as in the spin glass models, and then to stabilize in limit cycle resonant patterns.

CREUTZFELDT

Are these cycles independent of speed of movement and of contrast?

SINGER

If one runs velocity tuning curves, they have a preferred velocity where they operate best. In general one can say whatever is good for the amplitude of the single unit discharge is also good for the oscillations. The better the neuron response, the better it will oscillate.

CREUTZFELDT

In fact one can find such oscillations already in the geniculate, and you can find such recordings in my contribution to the 1964 conference on "Brain and Conscious Experience" (*).

SINGER

We have looked for it of course in the thalamus. We didn't see it very often, only occasionally, and it increases dramatically with arousal. If one stimulates reticular formation, then it really is like a spreading fire.

GOLDMAN-RAKIC

How far do your principles extend? If they are general and can cross species boundaries, can they also cross regional boundaries? Columns in the prefrontal cortex of the monkey are formed one full month before birth and in advance of ocular dominance column segregation in the visual cortex of the same species, which occurs only after birth. So how do these principles help to explain the organization of the prefrontal areas which seem almost to occur in advance of the visual? You can't explain it as a bottom-up transfer before birth.

SINGER

You can of course establish coherent activation without sensory stimulation. We know that the retina, for instance, in the embryo produces very rhythmic travelling waves, and these could be used to identify neighbourhood relations in the essential target zone. The same could be the case for cortical

(*) Semaine d'Etude sur Cerveau et Expérience consciente, 28 sept. - 3 oct. 1964, Scripta Varia 30, Pontifical Academy of Sciences, Vatican, 1965. See Fig. 10, p. 223.

projections. Everything is spontaneously active all the time. Now whether these oscillations can be generalized to primates, I don't know. But there are reports in the human EEG literature of a very prominent increase of power in the 40 cps range, mainly over the frontal and parietal cortex, under conditions of focussed attention, when the humans are very concentrated and performing something difficult.

A THEORY OF MULTI-STAGE INTEGRATION IN THE VISUAL CORTEX

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Introduction

One of the best established systems of facts relating to the basic design and operation of the cerebral cortex is that of the separation of functions in the visual cortex. Some twenty years of anatomical, physiological and behavioural work in the monkey and renewed descriptions of clinical evidence in man have established beyond reasonable doubt that certain basic attributes of vision, such as form, motion and colour — and possibly also depth — are processed in anatomically distinct parts of the cerebral visual cortex, findings which led us to the theory of functional specialization in visual cortex (Zeki, 1974a, 1978a). The description of functional specialization naturally entails a great puzzle, namely, how the signals processed in anatomically distinct parts of the visual cortex are subsequently integrated to give us our unitary perception of the visual world. Our attempt to put this great puzzle together has initially been anatomical. This may seem surprising, but there is much to recommend such an approach. It was anatomical evidence that gave the first clues to functional specialization in visual cortex. It was also (negative) anatomical evidence which led neurobiologists in the past to dismiss the available evidence for functional specialization (see Zeki and Shipp, 1988). In the same way, the anatomical evidence which we have accumulated over the past few years leads us to the prediction that the integration of signals in the visual cortex is a multi-stage process, occurring at several levels, including levels at which functional separation is first established in the visual cortex. This leads us to a theory of multi-stage integration in the

cerebral cortex,, a theory derived from the anatomical evidence alone (Zeki and Shipp, 1988; Zeki, 1989).

In this article, I first review briefly the evidence for functional specialization and then for multistage integration.

Functional Specialization

Separate Cerebral Pathways for Form, Colour and Motion.

The first evidence for the separation of form, motion and colour in the visual cortex came from studies of the prestriate visual cortex, a large cortical area of uniform cytoarchitecture surrounding the primary visual cortex (V1). The fact that early cytoarchitectonic studies had not revealed the presence of a multiplicity of distinct areas within the prestriate cortex was one reason, among others, why the early clinical evidence suggesting that a specific area of the prestriate cortex may be specifically involved in colour vision was dismissed — the area could not be distinguished cytoarchitectonically from surrounding areas (see Zeki, 1989, for review). The subdivision of the prestriate visual cortex into a number of cortical areas and the demonstration that each receives its own separate input from the striate cortex, led to the suggestion that these separate areas of the prestriate cortex must be executing different functions. The anatomically derived logic behind this was simple — it would be difficult to suppose that each one of these areas receives the identical signals from each mm of V1. They must therefore be receiving different signals, from which it follows that they must be functionally specialized to process different attributes of the visual scene. Such a supposition received powerful support from the demonstration, through direct recordings from cells in the anatomically distinct prestriate visual areas, that, as a whole, cells in different areas prefer different visual stimuli (Zeki, 1974a, 1978a). Chief among these areas is V5, where the overwhelming majority of cells are directionally selective, without being selective for the colour of the visual stimuli — positive and negative evidence which immediately suggests a separation of functions in the cortex (Zeki, 1974b; Gattass and Gross, 1981; Van Essen *et al.*, 1981; Albright, 1984) (see Figure 1). In another group of areas, V3 and its adjoining area V3A, the majority of cells are orientation selective but are not concerned with the colour of the stimulus (Zeki, 1978a, Baizer, 1982; Burkhalter *et al.*, 1986), again positive and negative evidence which suggests that colour must be processed elsewhere.

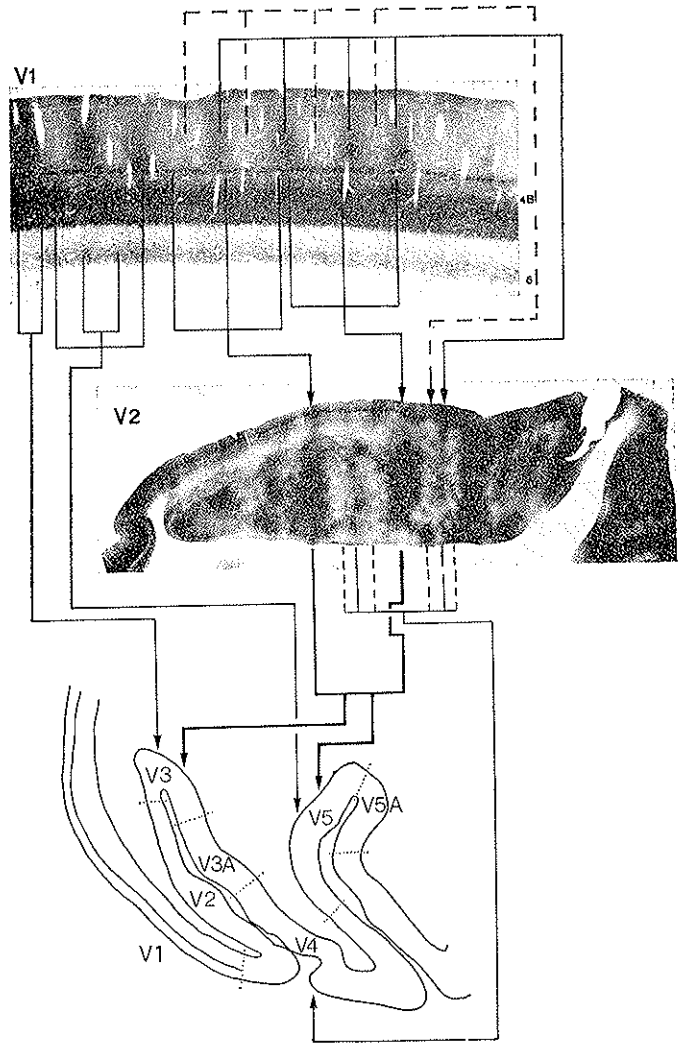

FIG. 1. Diagrammatic representation of the separate pathways leading from the striate cortex (V1) to the specialized visual areas of the prestriate cortex, either directly or through V2. The sections through V1 and V2 have been taken at angles which reveal their cytochrome oxidase architecture to best advantage. Layer 4B of V1 projects to V5 (which also receives input from layer 6 of V1) and to V3, either directly or through the thick stripes of V2 (heavy lines). These pathways are derived from the M system. The blobs of V1 project through the thin stripes of V2 to V4 (thin lines) and the interblobs of V1 project through the interstripes of V2 to V4 (dashed lines). There is also a direct projection from V1 to V4 (not shown). These pathways are derived from the P. system. From Zeki and Shipp, « Nature », *335*, 311 (1988).

In contrast to these areas, the areas that comprise the V4 complex contain heavy concentrations of cells which are wavelength selective (Zeki, 1973). These areas also contain orientation selective cells (Zeki, 1975; Desimone and Schein, 1987) but even most of these are, to a greater or lesser degree, wavelength selective.

In summary, anatomical and physiological evidence shows that there are three pivotal groups of visual areas in the cytoarchitectonically uniform prestriate cortex: Area V5 and the adjoining area V5A, which are concerned with the analysis of motion; the areas of the V4 complex, which are concerned with colour, and with form in association with colour; and the V3 complex, concerned with form but not in association with colour. It would naturally be naive to suppose that these are the only functions of these areas, although they are among the more prominent of their functions. It would also be naive to suppose that the functions listed above are unique to these areas, since each area forms part of a more extensive, and segregated, pathway.

These anatomical and physiological results can account for the specific visual defects seen in man. The restriction of form and colour processing to separate areas and pathways may explain the fact that, at least in man, one can obtain specific perceptual scotomas affecting colour or motion vision exclusively, following specific lesions in different prestriate areas (Pearlman *et al.*, 1979; Damasio *et al.*, 1980; Sacks *et al.*, 1988; Zihl *et al.*, 1983). The fact that both the V3 complex and the V4 complex are involved in the analysis of form, the latter in association with colour, may also explain the fact that a pure form defect is rarely, if ever, seen. Presumably, to obtain such an effect, a much more widespread lesion would be necessary, encompassing a great deal more of the prestriate cortex.

These results, together with the results on areas V1 and V2, reviewed below, also explain the fact that the detection of visual patterns when stimuli generating them differ in colour alone (isoluminant stimuli) becomes difficult, if not impossible, a topic that has recently been ably reviewed by Livingstone and Hubel (1987). Thus, the detection of depth in Julesz random dot stereograms is compromised when isoluminant red and green random dots are used (Lu and Fender, 1972). Equally, the detection of moving gratings is compromised when equiluminant gratings are used (Ramachandran and Gregory, 1978; Cavanagh *et al.*, 1985). This is no doubt due to the fact that the depth and motion systems in the visual cortex do not use colour information to differentiate stimuli.

More Recent Confirmation of the Separation of Form, Motion and Colour: Functional Segregation in the Striate Cortex (V1).

The physiologically demonstrated separation of form, colour and motion in the prestriate cortex was incongruous with the most detailed picture of V1 available at the time, obtained from Hubel and Wiesel's extensive work (Hubel and Wiesel, 1977). They had reported V1 to be functionally uniform, with all cells outside of layer 4C being orientation selective, one orientation succeeding another in a regular sequence. Because the functionally diverse visual areas of the prestriate cortex receive their inputs from the striate cortex, such a uniform functional architecture seemed improbable. It was therefore suggested that a further function of the striate cortex, beyond that of analyzing contours and bringing the input of the two eyes together (Hubel and Wiesel, 1977), must be to segregate different types of signals and parcel them out to the different, specialized, visual areas of the prestriate cortex for further processing (Zeki, 1975). The demonstration of a functional segregation within V1 would naturally be a confirmation of such a supposition. In fact, there were hints in the published evidence of the time that the striate cortex may not be so uniform in its organization. In particular, the evidence of Dow (1974), Dow and Gouras (1974) and of Poggio *et al.* (1975) had suggeested the presence of many non-oriented cells in the striate cortex, and Michael (1978) had reported that wavelength selective cells are grouped together and separated from non-wavelength selective cells, although he considered many to be orientation selective. But compelling evidence for the segregation of form, motion and colour in the striate cortex came only after the demonstration that the striate cortex, which appeared to be cytoarchitectonically homogeneous when stained for Nissl substance, was far from so when stained for the activity of the metabolic enzyme cytochrome oxidase. When so stained, the striate cortex is characterised by a set of blobs running from surface to white matter and especially prominent in layers 2 and 3 (Horton, 1984; Livingstone and Hubel, 1984). It has been found that most cells inside the blobs in layers 2 and 3 are non-oriented and about 50% are wavelength selective. By contrast, most cells outside the blobs are orientation but not wavelength selective (Livingstone and Hubel, 1984). Thus, whereas the picture of V1 provided by Hubel and Wiesel (1977) did not contain any hint of the separation of form, motion, and colour — even though such a separation had, at that time, already been demonstrated in the prestriate cortex — the later picture of Living-

stone and Hubel (1984) not only confirmed that the segregation of colour, form and motion is a general phenomenon in the visual cortex, but also confirmed its presence in the striate cortex. The question as to why such non-oriented cells were dismissed in Hubel and Wiesel's earlier studies has been discussed by Livingstone and Hubel (1984).

Cells involved in processing information relating to motion are segregated into separate layers, 4B and 6, which project to V5 and (the former) to V3. Cells projecting to V5 are directionally selective and occur in patches whose dimensions are similar to the cytochrome oxidase blobs, though they do not bear any systematic relationship to the latter. They are therefore segregated from cells projecting to V3, most of which are probably orientation selective. It thus seems that there is another system of segregation in the striate cortex, within layer 4B (Shipp and Zeki, 1989).

Functional Segregation in Area V2.

Area V2 surrounds area V1 and receives a systematic and topographically organized input from it (Cragg, 1969; Zeki, 1969). Physiological recordings from it suggest that, like V1, it contains a functionally heterogenous population of cells, including direction, wavelength and orientation selective cells (Baizer *et al.*, 1977; Zeki, 1978a). Moreover, it projects to the very same functionally specialized visual areas of the prestriate cortex that V1 projects to, namely V3, V4 and V5 (Zeki, 1971). By analogy with V1, and using the predictive power of anatomy, one can suggest that V2, like V1, is functionally compartmentalized, with cells subserving different functions being grouped together in anatomically identifiable parts of V2. The development of cytochrome oxidase histochemistry has shown that V2, like V1, possesses a distinctive cytochrome oxidase architecture (Tootell *et al.*, 1983). This consists of a set of heavily staining thick and thin stripes, separated from each other by the more lightly staining interstripes. Anatomical evidence has shown that the thick stripes receive their inputs from layer 4B of V1 and project to V5 and to V3. The thin stripes receive their inputs from the blobs in layers 2 and 3 of V1 and project to V4. The input to the interstripes is from the layer 2 and 3 interblobs of V1. They also project to V4, though they may have other cortical destinations as well (Livingstone and Hubel, 1984, 1987; Shipp and Zeki, 1985, 1989a, b; DeYoe and Van Essen, 1985) (see Figure 1).

Thus it can be said that the projections from V1 to V2 are *patchy*

in the sense that functionally specialised groups of cells, occupying definite cortical patches in V1, project to cells with a corresponding function in V2, which also occupy definite cortical patches. The projections from V2 to the specialised areas of the prestriate cortex are also patchy, one set of patches, for example in the thick stripes, projecting to V5, while another set, also in the thick stripes, projects to V3. By contrast, cells in the thin stripes and the interstripes project to V4.

Parallel physiological studies have shown that about 50% of cells in the thin stripes, which project to V4, are wavelength selective and none is orientation selective. By contrast, cells in the thick stripes and the interstripes are orientation but not wavelength selective. Direction selective cells are found in the thick stripes only, the very ones that project to V5 (Shipp and Zeki, 1985; DeYoe and Van Essen, 1985; Livingstone and Hubel, 1987). The physiological evidence thus confirms the anatomical evidence in showing that cells subserving different visual functions are grouped together and maintained segregated from each other, each functional grouping having its own separate projection to the more specialised visual areas of the prestriate cortex.

Functional Inferences from Anatomical Studies.

It is perhaps worth noting that many inferences about the functional organization of cortical areas can be made by observing the pattern of anatomical connections between them, even without reference to functional studies. All cortical areas project to two or more other cortical areas and most of these projections are patchy, both in origin and termination. In V1 and V2, these patchy projections can be correlated with a definite modular architecture, revealed by cytochrome oxidase histochemistry. One can infer from this that if an area has divergent, patchy, projections to several areas, as well as a modular architecture, it is also likely to contain functionally distinct and segregated groups of cells. *If any one of these features is observed, it may be inferred that the others may also be present.* An interesting example is V5. This specialised visual area receives patchy inputs from V1 and V2 and is the origin of widespread, and patchy, cortical projections to other areas. Further, at least in some species, it has a lattice-patterned cytochrome oxidase architecture. Hence one can predict that functionally distinct groupings of cells, occupying anatomically distinct subdivisions within it, will be found, sooner or later. Similar predictions can be made about other cortical areas.

Functional Segregation in Subcortical Visual Centres.

It is perhaps an irony that it was studies of the higher visual areas in the prestriate cortex that first revealed the functional segregation of form, colour and motion rather than studies of the retina, lateral geniculate nucleus or striate cortex. This seems odd because the number of studies undertaken on the latter structures exceeds by far those undertaken on the prestriate visual cortex. It seems odd, too, because functional segregation is present, at least in incipient form, in the retina itself as well as in the lateral geniculate nucleus.

There are two types of ganglion cell in the retina which project to the lateral geniculate nucleus, known as the Pa and Pb cells. Pa cells are not wavelength selective, have greater sensitivity to contrasts, large receptive fields and fast, transient responses. Pb cells have slow tonic responses and are wavelength selective. The Pa cells project to the lower two, magnocellular (M), layers of the lateral geniculate nucleus whereas the Pb cells project to the upper four, parvocellular (P) layers. The P and the M layers project, in a topographical manner, to different layers of the striate cortex and there generate new, and segregated, selectivities. P cell outputs are relayed to layers 2 and 3. Here a new kind of wavelength selectivity is generated inside the blobs in the form of double-opponent, or pseudo double-opponent cells which lack orientation selectivity (Livingstone and Hubel, 1984; Tso and Gilbert, 1988). By contrast, orientation selective cells which lack wavelength selectivity are generated in the interblobs. The M cell output is relayed to layer 4B, where, once again, two new and segregated selectivities are generated — orientation and direction selective cells (for review, see Zeki and Shipp, 1988).

Further Cortical Projections from the Specialised Visual Areas.

It is thus common now to speak of two basic systems, the P and the M systems, which can be identified by certain characteristics present in the geniculate layers from which the terms derive, as well as in the striate cortex and beyond. The parvo-blob-thin and interstripe-V4 system is called the P system while the magno-layer 4B-thick stripe — V5 and V3 system is called the M system.

It is also commonly supposed that there are two, isolated, serial and hierarchically organized "streams" in the visual cortex — one derived from the M system, directed to the parietal cortex, and concerned with

where an object is and the other derived from the P system, directed towards the temporal cortex and concerned with what it is (the "what" and the "where" systems of Mishkin *et al.*, 1983). In this scheme, V5 and its satellite areas belong to the M parietal "stream" whereas V4 belongs to the P temporal stream. V3 is put alternately into one stream or another, or both, and V3A is omitted altogether.

While there is no doubt of the specialization of the temporal and parietal lobes for different visual functions, this division into two exclusive, isolated, serial and hierarchically organized pathways is perhaps an oversimplification. In the first place, recent anatomical evidence shows that both V4 and V5 project to the temporal cortex *and* to the parietal cortex. As well, V3 and V3A also project to the parietal cortex which, itself, is connected with temporal cortex (see Zeki and Shipp, 1988; Zeki, 1990, for reviews).

Moreover, recent physiological evidence, ironically from area V3A, the one area that is not accounted for in this schema, suggests that such a functional dichotomy between the *what* and the *where* may itself be an oversimplification. Most cells in this area are orientation selective and disinterested in the colour of the stimulus (Zeki, 1978b). One might conclude from such a result, perhaps somewhat simplistically, that V3A is interested exclusively in what an object is. But recordings from V3A in the awake, behaving monkey show that about one-half of these cells in V3A are gaze locked. In other words that they will respond to a line of the appropriate orientation only when the animals gaze in a particular direction (Galletti and Battaglini, 1989). Since this is a means of identifying the position of the object with respect to egocentric space, it follows that V3A can be more accurately described as being involved in both the *what* and the *where*. Gaze related cells were thought to be a property of higher visual areas in the parietal cortex — the where system (Andersen and Mountcastle, 1983). That they should be found as early as V3A, in an area with a high degree of topographic precision, implies that the processes underlying integration occur earlier than had been envisaged. It also implies that the specialised pathways in the cerebral cortex must interact at earlier levels.

Functional Integration

In fact, anatomical evidence shows that the problem of integration is not quite as straightforward as one might suppose. In doctrines which

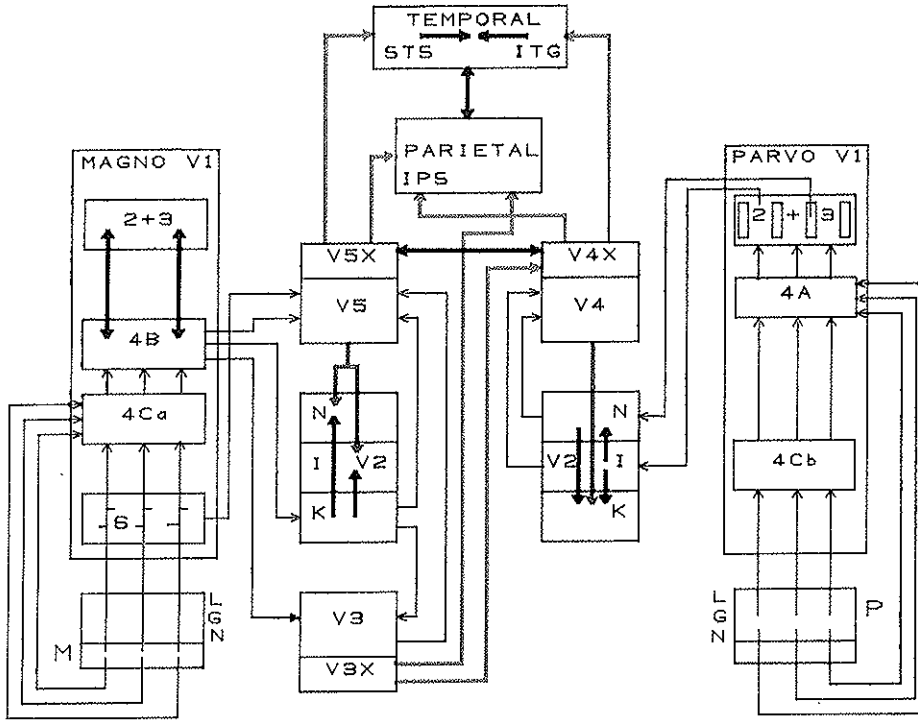

FIG. 2. Diagrammatic representation of the connections of the visual cortex to illustrate the many levels at which the specialized visual areas can communicate with each other. Connections in green lines are forward. Like the connections shown in black, they are all reciprocated by backward connections but these are not shown. Connections in red are backward and those in blue are lateral or intrinsic. The diagram shows the lateral geniculate nucleus (LGN) divided into the magnocellular (M) and parvocellular (P) portions; V1 with its several layers and the cytochrome oxidase blobs (small cylinders shown to the right); V2 with its thick (K), thin (N) and inter (I) stripes; areas V3, V4 and V5 as part of the third, fourth and fifth visual complexes (X - connections shown to arise from V3X, V4X, and V5X include the whole complex and do not exclude the areas proper); and the higher visual areas in the parietal and temporal lobes, the former including the intraparietal sulcus and the latter the cortex of the superior temporal sulcus and the inferior temporal gyrus. From Zeki and Shipp, « Nature » *335*, 311 (1988).

imagined that there is a single hierarchical system the problem of integration was no problem at all. Integration was envisaged to occur progressively in the transition from one area to the next. With the demonstration of functional specialisation, one might have been tempted to modify this doctrine and suppose that each specialised area will project to a single area, which would then be the integrator stage. It is easy to dispose of this notion by the simple anatomical observation that there is no single area to which all visual areas uniquely project.

The available anatomical evidence shows that integration might start much earlier, even at the levels at which functional segregation is first established in the cortex, that is, in V1 and V2 (see Figure 2). There are three important anatomical points which are of crucial importance in considering integration:

1. *No single cortical area connects with one other area only.* Instead each connects with a multiplicity of areas. This rules out the notion of a single area to which all other areas report and compromises the notion of two isolated, serial pathways in the visual cortex. It also suggests that any given function must be widely distributed in many different areas and that the nervous system must consequently tap information from a variety of sources in building its visual constructs.

2. *The specialised areas of the prestriate visual cortex have direct connections with each other.* For example, V4 (P system) connects directly with V3 and with V5 (M system). V5, in turn, has direct connections with the other areas. This immediately suggests that direct interactions between areas may be one strategy for achieving integration.

3. *Whereas functional groupings of cells are segregated in segregator areas such as V1 and V2 and project in a segregated way to the specialised areas such as V4 or V5, the return inputs from V4 or V5 to V2 are not similarly segregated but invade the territory of all functional groupings.* The thick stripes of V2, for example, which do not project to V4, nevertheless receive an input from it. Equally, the thin stripes of V2, which do not project to V5, nevertheless receive an input from it. Finally, the segregated cells of layer 4B of V1 which project to V3 probably receive an input from V5 and those projecting to V5 might receive an input from V3, although this has yet to be demonstrated (Shipp and Zeki, 1985) (Figure 3). In other words, using these return projections, one visual area can inform another of the results of its action and modify the input to the other area before it gets there.

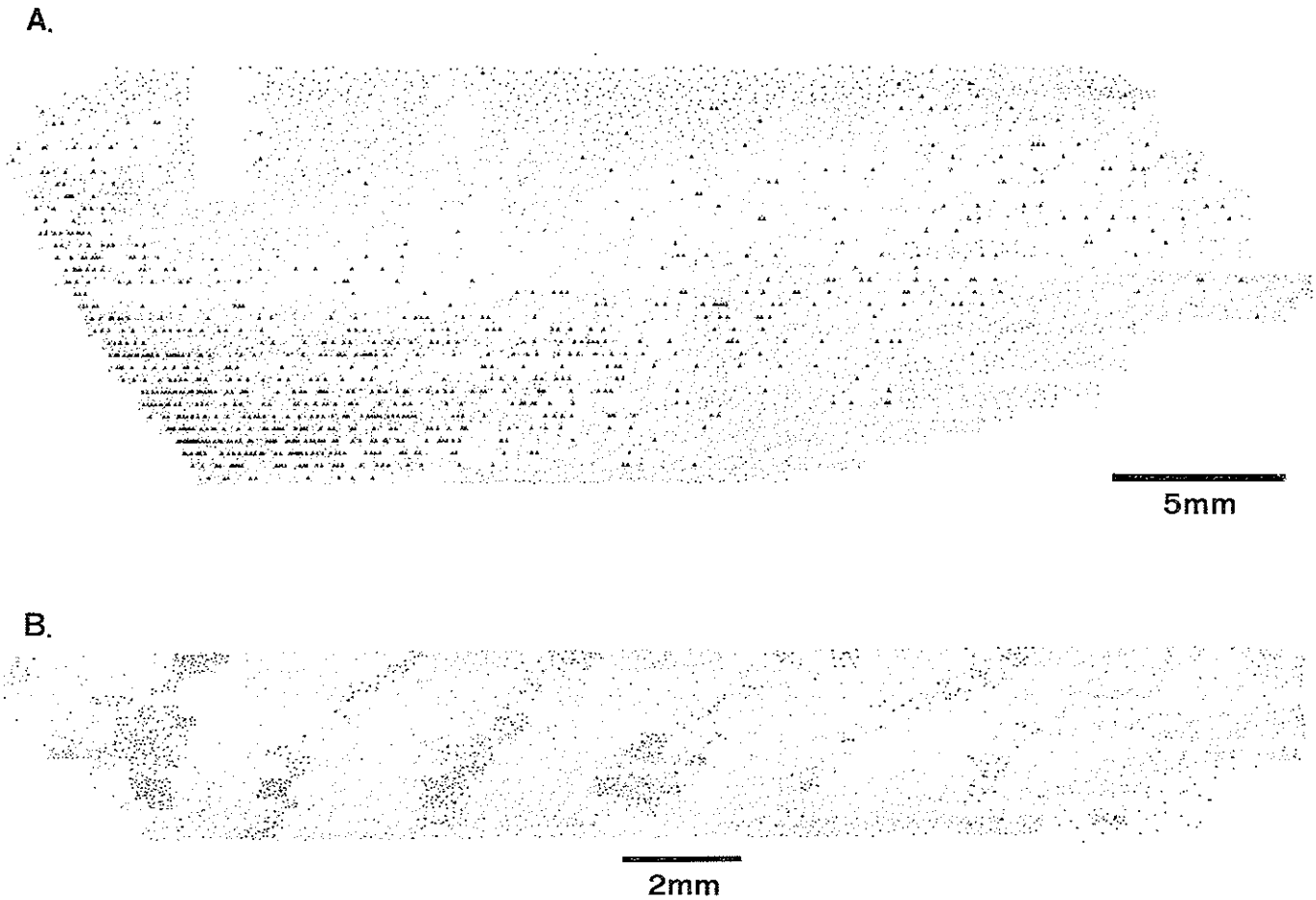

FIG. 3. A computer aided reconstruction of the distribution of labelled cells (triangles) and terminals (stippling) in layer 4B of V1 (A), and in area V2 (B), following an injection of label into area V5 of macaque monkey visual cortex. Note that the prograde label, representing the return connection from V5 to V1 and V2, is continuously distributed and involves the territory of labelled cells as well as the territory of other cells. From Shipp and Zeki, « Eur. J. Neurosci ». *1*, 318 (1989a).

The anatomy of integration.

The anatomical machinery underlying integration is convergence. There appears to be two predominant types of convergence which operate at all levels (Zeki and Shipp, 1988):

a. *Topical convergence* operates within a specialized pathway and involves integration across space, that is, collects information on the same attribute of vision, for example colour, from different retinal locations. The result is that the signals in the specialised areas are themselves, in a sense, integrated. This entails the progressive elaboration of increasingly more complex response properties in a specialized pathway by a pattern of spatially convergent connections repeated at each stage, a strategy that also leads to larger receptive fields and a less precise topographic representation. In the colour pathways, for example, many blobs in V1 project to a thin stripe in V2 and several thin stripes to a small part of V4. The physiological consequence of this is that cells in V4 have much larger receptive fields than their counterparts in V1 or V2. Moreover, some cells, at least, in V4 have the property of colour constancy, whereas the wavelength selective cells in V1 do not. The property of colour constancy depends on a comparison of the reflectance of one surface with that of surrounding surfaces for lights of different wavebands, i.e., a comparison of information from wide parts of the field of view (Land, 1974). The widespread intrinsic connections within V4 may also contribute to this process. Such intrinsic connections could also be classed as topical convergence since they probably serve to collect information relating to the same attribute of the visual scene from different retinal locations. The same principle underlies the proposed simple-complex-hypercomplex scheme for the progressive elaboration of the orientation, position and length of a contour (Hubel and Wiesel, 1965).

Topical convergence does not operate in one direction, e.g., from V1 to V5, only. It also operates in the opposite direction, e.g., from V5 back to V1. The presence of such a backward projection is known (e.g., Shipp and Zeki, 1989a,b). Its purpose is still not clear. But one of its functions might be the creation of larger surrounds for cells, such as found by Allman *et al.* (1989) in V1.

It is thus obvious that topical convergence can be discerned in forward, intrinsic and backward connections.

b. *Confluent convergence* operates between specialized pathways and involves integration between different attributes, e.g., colour and motion.

An example is the convergence from areas V4 and V5 to the cortex of the parietal lobe or the inferior temporal lobe. It is still not clear whether the inputs from V4 and V5 actually overlap in the territory of these third areas or whether they are merely contiguous. If only the latter, they would still be within the range of lateral interactions subserved by the local, intrinsic connections within these third areas. Like topical convergence, confluent convergence can also operate in the backward direction. A good example is to be found in the return projection from V5 to V2, which, as discussed above, is not restricted to the territory of the thick stripes but invades the thin stripes and the interstripes as well, an anatomical convergence that could help unite information on colour, form and motion. Another example is to be found in the widespread return input from V5 to layer 4B of V1, which invades the territory of cells projecting to V3, and thus helps unite information on form and motion. Finally, the direct connections between V4 and V5, for example, provide for direct topical (lateral) convergence between specialised areas.

From this, it becomes obvious that confluent convergence, like topical convergence, can be discerned in forward, backward and lateral connections between the visual areas.

We are now able to classify all the connections subserving integration in a simple manner, using topical and confluent convergence as the main subdivisions, and dividing each category into forward, backward and lateral (see Table 1). Just as one can make inferences about the functional organization of areas, and the segregations within them, by observing

TABLE 1 - *Examples of the two types of convergence* (abbreviations as in Figure 1).

	Topical	Confluent
Forward	blobs → thin stripes → V4 V1 → V5	thin stripes + V3 → V4 V4 + V5 → IPS + STS
Intrinsic lateral	in V4	in V1, V2 and IPS V4 ↔ V5
Backward	V5 → V1	V3 + V5 → V1 (4B) V4 + V5 → V2 (K + I + N stripes)

the projections from an area or its modular architecture, so the observations described above, between areas subserving the same submodality of vision and areas subserving different submodalities of vision, naturally lead to a theory of multi-stage integration in the visual system, *without reference to functional studies* which, indeed, remain to be done. Such is the predictive power of anatomy.

Perhaps mirroring this rich variety of anatomical connections, the processes involved in integration are themselves varied. The one presenting the greatest puzzle is how it is that the different attributes of the visual scene, analyzed in separate parts of the visual cortex, are integrated to give us our unitary perception of the visual world.

In addition to integration of information within a specialized pathway, such as the colour pathway, and between pathways, for example, the motion, colour and form pathways, there is a third, and more subtle kind of integration. Here attributes belonging to one subdivision of the visual system are generated from another, good examples being the generation of structure and of form from motion.

Why is There Functional Specialisation and Multistage Integration?

It has been argued that functional specialisation is a consequence of the fact that the requirements for constructing different attributes of the visual scene are sufficiently different that, in terms of efficiency, the cortex assigns different areas for constructing different attributes (Zeki, 1989). In trying to account for why it is that the cerebral cortex uses a strategy of multi-stage integration, we note:

1. That there are several steps within each specialised pathway. For example, there are several successive steps in the colour pathways leading from the blobs of V1 to the infero-temporal cortex. The responses of cells at each level may contribute to perception directly and explicitly and that contribution must be integrated with explicit contributions derived from other sources. The simplest way of achieving this is to allow integration to occur at that stage rather than at a later stage, when the output of the cells may have been further transformed. Hence information must be accessible to integration at every stage.

2. For whatever reason, the precise local sign is lost in topographic terms as one proceeds from areas such as V1 and V2, which have a very detailed topographic map of the retina, to higher areas such as V4 and

V5, in which the retinal maps are far less precise. Yet the local sign is not lost perceptually, since even minute objects can be referred to precise positions in space. The backward topical and confluent projections might help in preserving the local sign perceptually.

An implicit logical conclusion from this multistage process is that perception cannot be confined to the higher areas, but might even include lower visual areas, such as V1.

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DISCUSSION

FREUND

Do you have any idea what the further stages are after the various sequential steps in the visual cortex? Could ITS and IPS be a further linkage to the motor system?

ZEKI

First of all, I actually forgot to say that the same strategy that I have been talking about is probably used repetitively in the cortex, throughout the cortex. So I think that the multistage integration strategy is probably something that you can generalize about the cortex as a whole.

With respect to your question of infratemporal and intraparietal sulcus, we have found, like Boullier in Lyon, that there are direct connections between the infratemporal and the intraparietal cortex. So you see the problem — that if all areas report to area B and area B reports to C, by the time you get to area Z you are out of areas. But the fact that these areas can interact with each other at different levels, including previous and forward levels, means that it is that interaction which leads to the percept.

JEANNEROD

I don't know how this relates to your framework, but there is a clinical anecdote that I might report to you. A long time ago I observed a patient who was having epileptic seizures originating from his occipital lobes. So the patient, after the occipital lobes had discharged for quite a long time, had cortical blindness. He could not report any vision for several minutes, and then he would recover from this blindness and we could observe this gradual recovery. He would first report seeing moving shadows and then he was seeing fuzzy shapes, and then grey shapes. He would see the things as they were, but without colour. The colour would return last. We observed this several times. I don't know if this would represent an example of reactivation of several of those modules that you are describing.

ZEKI

Yes, you know this is the very evidence that Teuber dismissed as showing any segregation of function, this very evidence that you are giving. Now I think that it does indicate segregation of function, but what is not clear is the exact mechanism of why it is that colour always returns last or first, I can't remember which it is. There are other problems about colour vision which in fact no theory of colour vision deals with or is able to explain. One of them is, for example, the nature of the cerebral achromatopsias, because the cerebral achromatopsias are very different from the retinal colour blindnesses. They usually affect the blue-green region but sometimes the red only without affecting the blue-green. There is no adequate explanation, any more than there is an adequate explanation for the successive emergence of these different attributes of vision.

May I use this occasion to make one other point which I forgot to make, which is that there is the reverse of achromatopsia, which is until today treated as a hysteria. I've had three patients who have come to me in desperation because they thought someone was not listening to them seriously, and this is a phenomenon which I shall call phantom chromatopsia. Now these are blind patients. They are blind patients who have these visual hallucinations which start in a small part of the field of view, which consist usually of gold or purple colour, and they invade the entire field of view and drive the patients absolutely suicidal, mad. One person did actually seek frontal leukotomy to get rid of that. It turns out that this syndrome was documented first by Boss in Germany in the 1930's.

ROLAND

Can you indicate the location of V4 and V5 in man?

ZEKI

When you have damage to the lingual and fusiform gyri in man, a cerebral achromatopsia results. I believe some people would now restrict it to the lingual gyrus, but I don't know whether that is because of anatomical evidence. V5, I am told, is somewhere in the superior temporal sulcus. I think John Allmann and his colleagues have tried to locate it using PET-scans, but so far that has not proven all that easy or successful.

SINGER

This is a comment that may turn into a question. One may wonder why nature has not developed a metacortex with 12 layers in which all this is beautifully mapped and everything is kept together. One suggestion has been that neurons have a very limited dynamic range, so they can't digest too many different inputs and still integrate activity, because they will be either saturated or not active at all. Therefore the amount of convergence must be limited to small numbers, and I remember Patricia Goldman-Rakic having mentioned that no cortical patch receives more than three different inputs.

Then, if we assume that cortical modules are always doing the same, namely correlating something, comparing something with something, then the only degree of freedom which one has in order to compute new things, is to change neighbourhood relations. So the only degree of freedom one has in order to establish other representations or different representations is that one has to map the same thing with a different neighbourhood relation, and this can only be done by opening up a new area.

ZEKI

I don't have a straight answer to your question because there isn't one. You can conceive of various different ways of doing that. Ultimately, you must build an efficient system so that using the same kind of genetically specified distribution you can generate a number of different constructs. Of course I can see that you could arrange a system whereby instead of having all these visual areas, you can pull everything into the primary visual cortex, give it 12 layers and get every cell connected with many other cells. The brain just doesn't do it like that and I don't know why.

GOLDMAN-RAKIC

We know from the work of Gilbert, Wiesel, Martin and others that collateral branches of geniculo-cortical fibres often terminate in alternate columns, about two or three of them. In our own studies, after small injections into one area of the cortex, we often see a triad of columns labelled 2 or 3. Could there be a general rule that neurons in a single column might send axon branches to 2 or 3 other columns? It seems as though it's not one-to-one.

ZEKI

The question about these numbers touches an important point. After injection into V5, for example, the number of labelled little blobs within the thick stripes is usually about five. If you look at the number of stripes labelled, it can be anywhere between 2 and 8. Where you have a single patch after a big injection (for example, when you inject V6, an area which I have not talked about) and you look at the intraparietal cortex, you have what I call an operational connection. By that I mean that an area is undertaking an operation, but not the whole of this area needs to report to the other area. It reports the results of the operation only to a small region there, and it's only that region which needs to report to the other area. I believe that the connection between V3 may be of the operational variety, and certainly connections of V6 are sometimes of the operational variety. But that's purely speculation. However, I think it's very interesting to look at why it is that in some cases you get only one patch.

CREUTZFELDT

My first comment is aimed at emphasizing the thalamic input into all these various association areas which is usually discounted in this type of discussion. It is a strong input and is topographically organized. One finds in all animals including monkeys, as we just heard in Jeannerod's comment, pretty good representation of various aspects of visual stimuli after you take away areas 17 and 18, especially in cats. Neurons in the respective thalamic projection nuclei (the LP/Pulvinar complex) also show similar properties to neurons in the respective cortical projection areas.

The next comment I want to make is that one disregards in this form vs. colour distinction very much the question of texture representation. Texture is a very important aspect, and probably the most important aspect for distinguishing objects from each other and from the background. It has a perceptual quality like colour, and is a uniform, global property of surfaces. In texture representation the same neurons are involved which are sensitive to contours and orientation. Thus, the same cells which in one case code for contours are also representing global properties of a stimulus. This also applies to more global representations in one specialized area. V4, for example, is not only a colour area, but patches with colour-sensitive neurons alternate with patches of texture-sensitive neurons, and so on.

A final comment is related to the multiple representation of functions. Here, we are always talking about the multiple representation of inputs, but

I think we should also take into account that there is, even in the various areas of the visual cortex, a multiple representation of outputs. Each visual area has a specific output, not only into other cortical areas but into motor control systems. That means it sends something directly into behaviour control. MT/V5 is a good example. It contains movement-sensitive neurons and is probably involved in movement perception, but its output is connected to the eye movement control system in a very direct way. This can be generalized, and you may say that activation of a neuron may represent cognitive properties on the one hand, but at the same time represent a motor command, e.g. for aligning the eyes, for directing the gaze, etc. Thus, perceptive properties or features are at the same time command properties to do something with that stimulus. This is of course most obvious in the parietal association area, where neurons can be defined as sensory or motor depending on the test you apply. The motor cortex, on the other hand, also receives sensory inputs in a very clear topographic manner. So in pointing out the segregation of global sensory properties in different areas, one should also take into account that all these areas have a sort of command function, whether directly or indirectly, for appropriate behaviour.

ZEKI

I agree, of course, that texture is extremely important, and it is an important feature of V4. I think you must distinguish between texture and form. They are two different things. And when you come to the question of colour, you have now opened the Pandora's box because you cannot really separate colour from form, and the evidence for this is very simple. You can never have a form which does not have a colour, be that colour black or white, because every object must have a lightness and the lightness is determined by the reflectance of that object for the light of a given waveband. You've got to have reflectance. A surface must have reflectance.

Number two, any colour that you see is confined within space and therefore has a form. Now, what happens to patients when they have hallucinations and they have got no form to attach that colour to? That colour attaches itself to another sensory attribute. It's got to attach itself to something. Colour and form must obviously not be separated. Let us start off with the physiological observations that colour goes to V4, that the vast majority of cells in V4, whether they respond to oriented lines, whether they respond to textures or not, are colour sensitive and that you cannot really separate colour from form in the way that you can separate colour from motion.

I think we are in essential agreement there. On the question of the multiple output, I think that is a very nice point and it actually makes the point I was trying to make slightly more emphatic because you see, let us take V3, V3A, V5, V5A and V6, each one of these areas, as you know, has got an output to the frontal eyefield — each one of these areas. In other words, each one of these areas, whatever it is doing, is doing something else which becomes explicit for the eye movement control system. On the thalamus I have no response. I don't know.

BAUMGARTNER

Where do you think, within this line of processing, is space defined? On which level?

ZEKI

It's amazing. I had the impression, like everybody else, I think, that it happened in the parietal areas. But it looks like the beginning of the definition of egocentric space occurs in V3 and is elaborated from there, because responses are locked to the position of the eyes.

ORGANIZATION OF NEURONAL WORK IN THE HUMAN BRAIN: NEURONAL POPULATION ACTIVATION AND CORTICAL FIELD ACTIVATION

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What is Meant by Neuronal Population Activation and Cortical Field Activation?

The cerebral cortex participates in brain work in awake human subjects by activating multiple cortical fields. Each activated field has the size of a few hundred mm^2. Activation means that the neurons in a field increase their biochemical activity. This leads to increases of the regional cerebral metabolism (rCMR) or regional cerebral blood flow (rCBF) and to increases in transmembraneous ion transport. This is the cortical field activation hypothesis (Roland, 1985a).

The hypothesis says that neurons in the cerebral cortex always change their biochemical activity not scattered and single, but in large ensembles covering some 100-400 mm^2 of the cortical surface. How the active neurons and active synapses are organized within the field is not considered. Presumably the active synaptic regions form columns and bands of raised metabolic activity (see below).

According to Cragg (1967) such a field contains about $2\text{-}4 \times 10^7$ neurons. In normal brain work, of course, only a minor proportion of these are active. It is however not in the soma of the neuron that the most intensive biochemical changes take place. By far the major increase in, for example, glucose metabolism takes place in the synaptic regions in the neuropil (Hand *et al.*, 1978; Mata *et al.*, 1980). If we assume that an active cortical field covers an area of 300 mm^2 and the thickness of the

cortex is 3 mm, such a field of 900 mm^3 contains about 10^{12} synapses (Hüttenlocher, 1979). It is not to be expected that all these synapses are active in physiological brain work. When the brain goes from a resting awake state to work with specific information transformation and a cortical field then becomes active, the synaptic activity can increase in two ways: the number of active synapses can increase and the transmitter traffic between already active synapses can increase. Presumably some synapses will also decrease their biochemical activity due to inhibition of lateral neurons (see later). Usually, however, the net result is an increase in regional metabolism.

From our studies (see below) it appears that even in subcortical structures, such as the basal ganglia and thalamus, neurons do activate in larger populations if one should judge from changes in rCMR and rCBF.

One can support the field activation hypothesis by showing that all *kinds* of brain work in the awake state are produced by neuronal population activation. To do so, one has to apply a measurement method by which one can measure biochemical changes simultaneously in all parts of the human brain. One such technique is positron emission tomography. Here we will present some recent results of biochemical and biophysical measurements which support the field and population activation hypothesis. The measurements are of rCMR and rCBF. The synaptic work during specific brain work results in a net increase in rCMR. It has been demonstrated in subhuman primates that such active fields consist of many single metabolically active columns. Locally, within the field, a metabolically active column and the increase of rCBF are exactly spatially congruent. In other words: there is a tight spatial coupling between the rCMR and rCBF even down to columnar level (Greenberg *et al.*, 1979). Measurements of rCMR and rCBF are thus sufficiently accurate to delimit active neurons spatially.

Experimental Evidence for Field Activation and Population Activation

Some of the experimental evidence for cortical field activation with the intracarotid ^{133}Xe-injection technique was summarized earlier (Roland, 1985a, 1985b). With this technique it was impossible to measure rCMR and rCBF in subcortical structures. Now that positron emission tomography is available, one can measure rCBF, rCMR and other biochemical parameters simultaneously in all parts of the brain.

In the experiments we report here, a Scanditronix PC-384-7C posi-

tron emission tomograph was used. The spatial resolution in the plane was 8 mm. The slice thickness was 8 mm for cross slices and 11.5 mm for direct slices. The spatial resolution tells how many mm apart two point sources have to be in order to be detected as separate. All subjects participating were equipped with a stereotaxic helmet (Bergström *et al.*, 1981) which secured a repositioning of the head in the tomopraph with an error less than 1 mm. The rCBF and the regional cerebral glucose consumption (rCMRglu) were measured in normal young volunteers at rest and while they performed a somatosensory discrimination test (Roland, 1976). Briefly explained, the test was a two-alternative forced choice discrimination of the oblongness of rectangular parallelepipeda. The subjects discriminated the parallelepipeda with their right hand and then decided whether the first parallelepipedum or the last was the most oblong. The time resolution for the rCBF measurement was 60 sec. The rCBF at rest was then subtracted, pixel by pixel, from the test image such that an image of changes in rCBF (in ml/100g tissue/min) was produced (Fig. 1).

A closer analysis of the image of changes revealed that these were of different magnitude, shape and extent. Obviously some of the changes were just noise due to small fluctuations in blood flow beyond reproducibility. From a series of examinations of rCBF in subjects at rest ($n = 25$) it was clear that changes above 15% in any region of an individual brain were significant ($p < 0.05$). Once this level of the extent of random variations was set, it became clear that the changes in rCBF from rest to test, with few exceptions, all were increases. The histogram in Fig. 2 shows that the majority of the increases were between 100 and 300 mm^2 in size. Seventy-seven percent of the increases were above 100 mm^2. Since the spatial resolution of the PET-camera was 8 × 8 mm, none of the increases included in these 77.5% could have been produced by point-like elevations of the rCBF. One might argue that these fields could have been produced by clustered point-like elevations viewed with poor spatial resolution. If this would have been the case, the rCBF increases should consist of a high increase corresponding to each point surrounded by a halo of lower rCBF increases. Certainly some fields of rCBF increases seemed to contain one or more intense spots, but these intense spots often had a size above 100 mm^2. Furthermore, from Fig. 2b it is seen that by far the majority of fields contained no intense spots.

The shapes of the fields were most often oblong, irregular, covering more than four, five and even six coherent spatial elements of resolution (8 mm × 8 mm) (Figs. 1, 2 and 5). Statistically, such patterns of increases

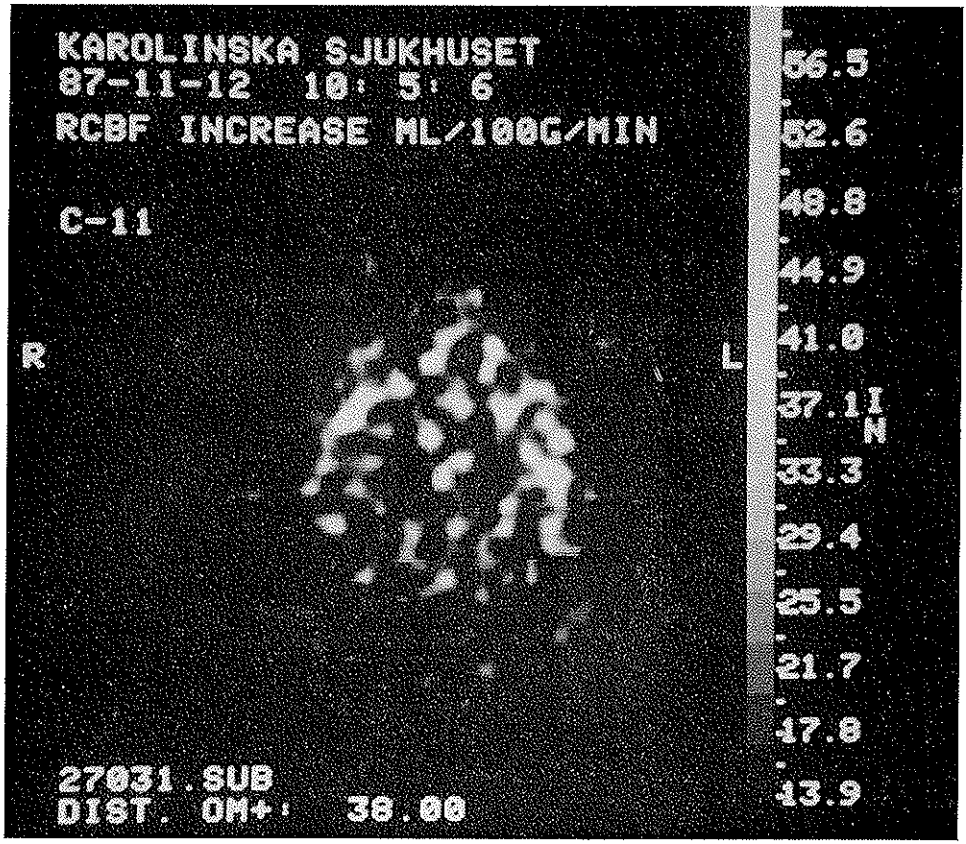
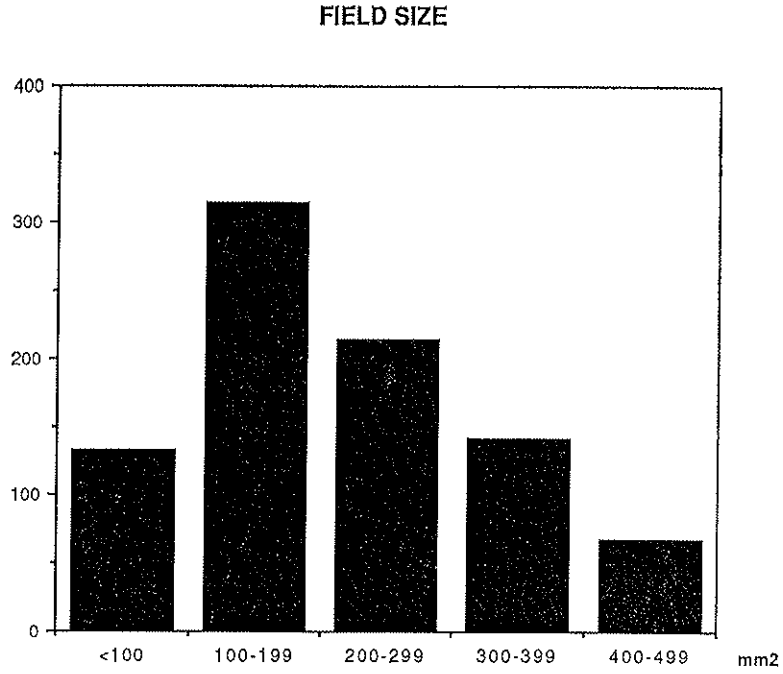


FIG. 1. Substraction image, rCBFsomatosensory discrimination - rCBFrest, of a young volunteer. The section goes through the sensory-motor hand region and the supplementary motor areas. Note the increases of rCBF bilaterally in the premotor areas, supplementary motor areas and supplementary sensory areas. All increases shown are above rCBFrest +15%. Black and white display will not reproduce intensive spots.

cannot be produced by random, point-like or scattered point-like elevations of rCMR. The only possibility was that the increases were organized to cover a field.

If instead of the rCBF, the regional cerebral metabolic rate for glucose was measured with C1-labelled glucose (Blomqvist *et al.*, 1989) the somatosensory discrimination test gave rise to the same size of fields and distribution of intense spots (Fig. 3). The field activation was, thus, independent of the physiological metabolic parameter measured.



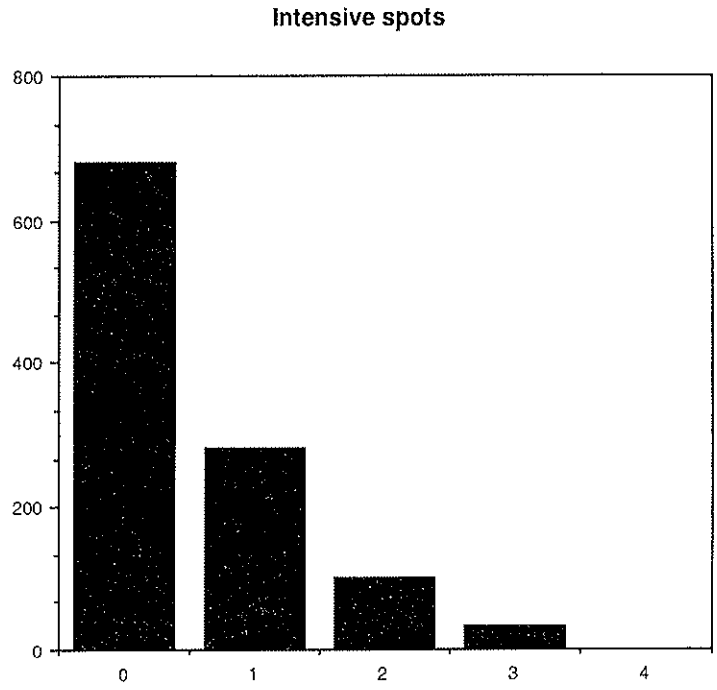


FIG. 2. Histograms of the distribution of (A) field sizes and (B) number of intense spots per field in six subjects performing somatosensory discrimination. The spots were identified in each field of rCBF increase on original color displays of the subtraction images.

Still one could argue that the size of the increases would depend on the general increase of rCBF or rCMR from rest to somatosensory discrimination. If, for example, the rCMR and rCBF increased strongly in all regions due to an arousal accompanying the test situation, the subtraction would give rise to big fields which were just amplifications of the rest pattern. That this was not the case was shown in Fig. 4. Here the rCBF in rest was "normalized" by division of each pixel with the mean rCBF during rest. A similar "normalization" was done for the rCBF during somatosensory discrimination. The resulting subtraction

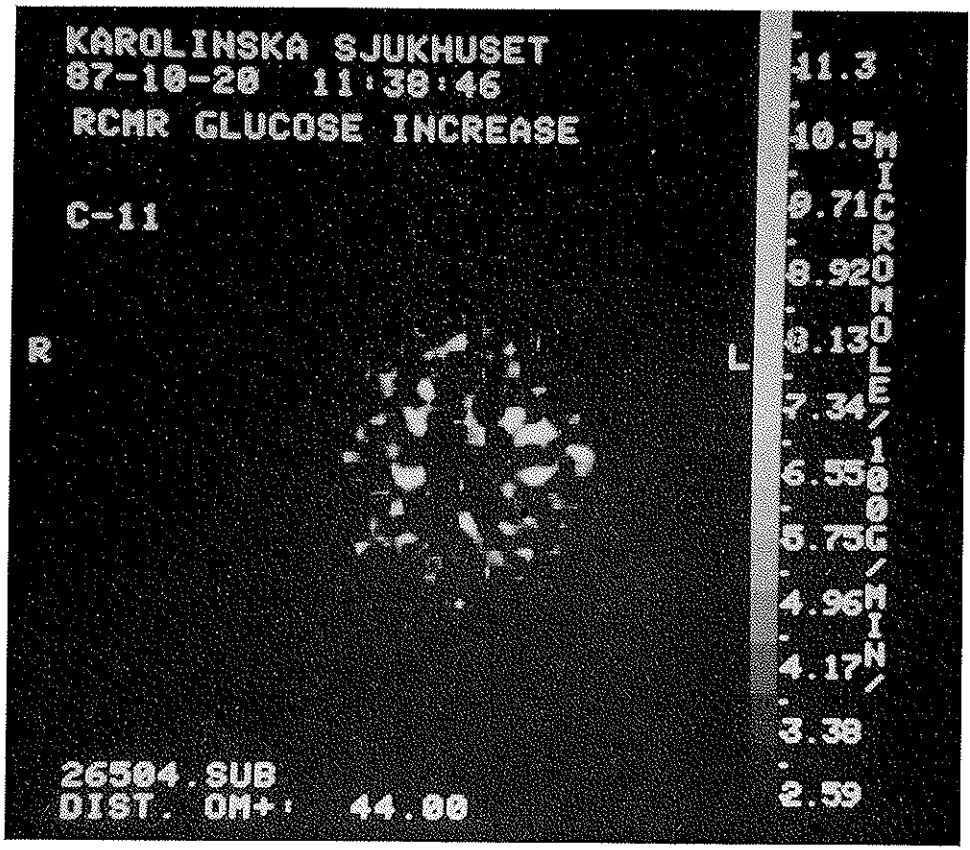


FIG. 3. Substraction image of the increases in regional cerebral rate of glucose consumption in a subject performing somatosensory discrimination with the right hand. The glucose consumption was measured after injection of glucose labelled with 11C in the 1-carbon atom position.

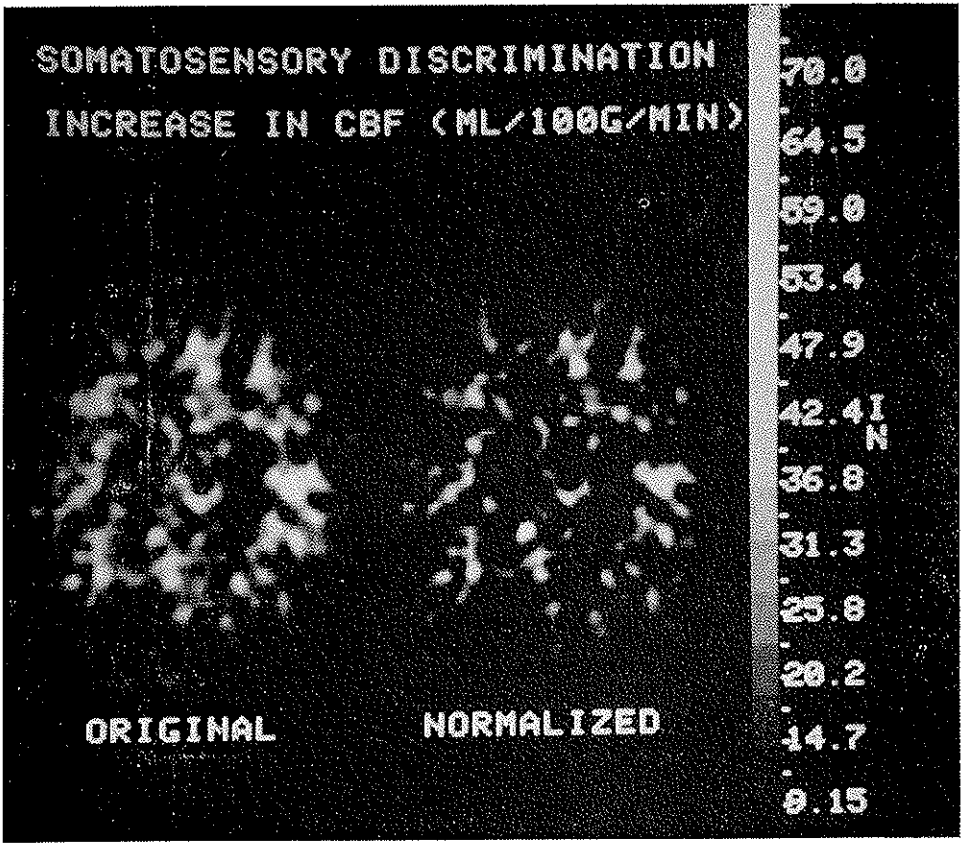


FIG. 4. Original and normalized changes in rCBF due to somatosensory discrimination. In this case the normalization reduces the halo of minor increases surrounding the core of the field.

images still showed the same sizes and shapes of fields (Fig. 4). The field increases thus were not produced by such arousal or general tuning effects.

Finally, the field increases in rCBF and rCMR were also seen in other types of information processing within the brain. Figure 5 shows the sizes of field increases in subjects trying to learn to recognize colored geometrical shapes (Roland *et al.*, 1988). This independence between the phenomenon of field increase and type of information processing was also noted with other techniques (Roland, 1985a,b). The observed increases in rCMR or rCBF were not induced by the spatial or temporal

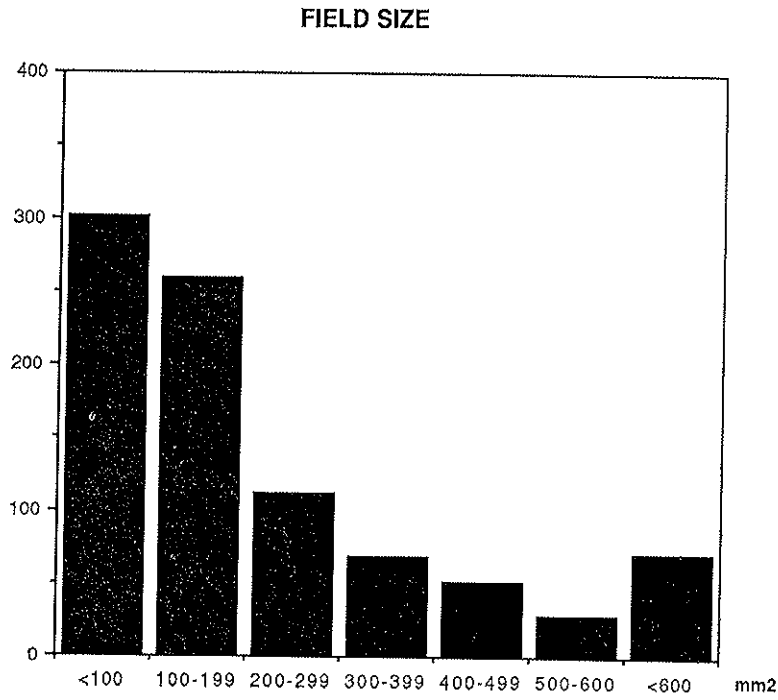


FIG. 5. Histograms of the distribution of (A) field sizes and (B) number of intense spots per field in four subjects performing visual learning.

characteristics of the stimuli. This was evident not only from the present examples of somatosensory and visual information processing, but also from earlier PET studies in which temporal and spatial characteristics of visual, auditory and somatosensory stimuli or motor performance were widely varied (Reivich *et al.*, 1979; Phelps *et al.*, 1981; Mazziotta *et al.*, 1982, 1983; Fox and Raichle, 1984; Fox *et al.*, 1987; Lauter *et al.*, 1985; Roland *et al.*, 1982, 1989). Cortical fields of rCMR increases also appear when information stored in the local neurons is retrieved (Roland *et al.*, 1987, 1988).

Thus, in the cerebral cortex the normal mode of work is activation of fields of 100-400 mm^2. Even neurons in the basal ganglia and thalamus seem to activate in populations. The thalamus, caudate, putamen and globus pallidus are subdivided in rather small anatomical and functional subdivisions. Each of the thalamic nuclei, for example, is smaller than the element of spatial resolution (7.8 mm × 7.8 mm × 8.0 mm). This implies that the PET cannot distinguish between a strong increase of rCMR in a small number of neurons and a moderate increase spread out over the whole nucleus. From animal autoradiographic studies, however, it is known that the increases in rCMR of thalamic and striatal neurons are of the same intensities as in the cortex (see later). This means that the increases of rCMR and rCBF in thalamus and basal ganglia that have been observed during voluntary movements, somatosensory stimulation, visual stimulation, thinking and learning (Roland *et al.*, 1982, 1987, 1989; Mazziotta and Phelps, 1984; Roland and Seitz, 1989) all probably stem from larger populations of synaptic activity.

By the use of the computerized atlas of Bohm *et al.*, (1986) it is possible to adjust all individual brains to the size and shape of a standard atlas brain. Having done this for the six subjects discriminating the oblongness of the rectangular parallelepipeda, we could produce an image of mean changes of rCBF for all subjects (Fig. 6). Since this mean image conforms to the standard atlas brain, we could determine the exact localization of the anatomical structures producing significant changes in rCBF ($p < 0.02$). These were: rt + lt sup. frontal gyrus, rt + lt middle frontal gyrus, lt inf. frontal gyrus pars opercularis, lt inf. temporal gyrus, rt + lt supplementary motor area, rt + lt premotor area, lt motor hand area in the precentral gyrus but also rt (ipsilateral) motor hand area, lt somatosensory hand area, lt + rt anterior part of lobulus parietalis sup., lt supplementary sensory area in anterior part of precuneus, rt + lt secondary somatosensory area, rt + lt parietal operculum. Subcortically

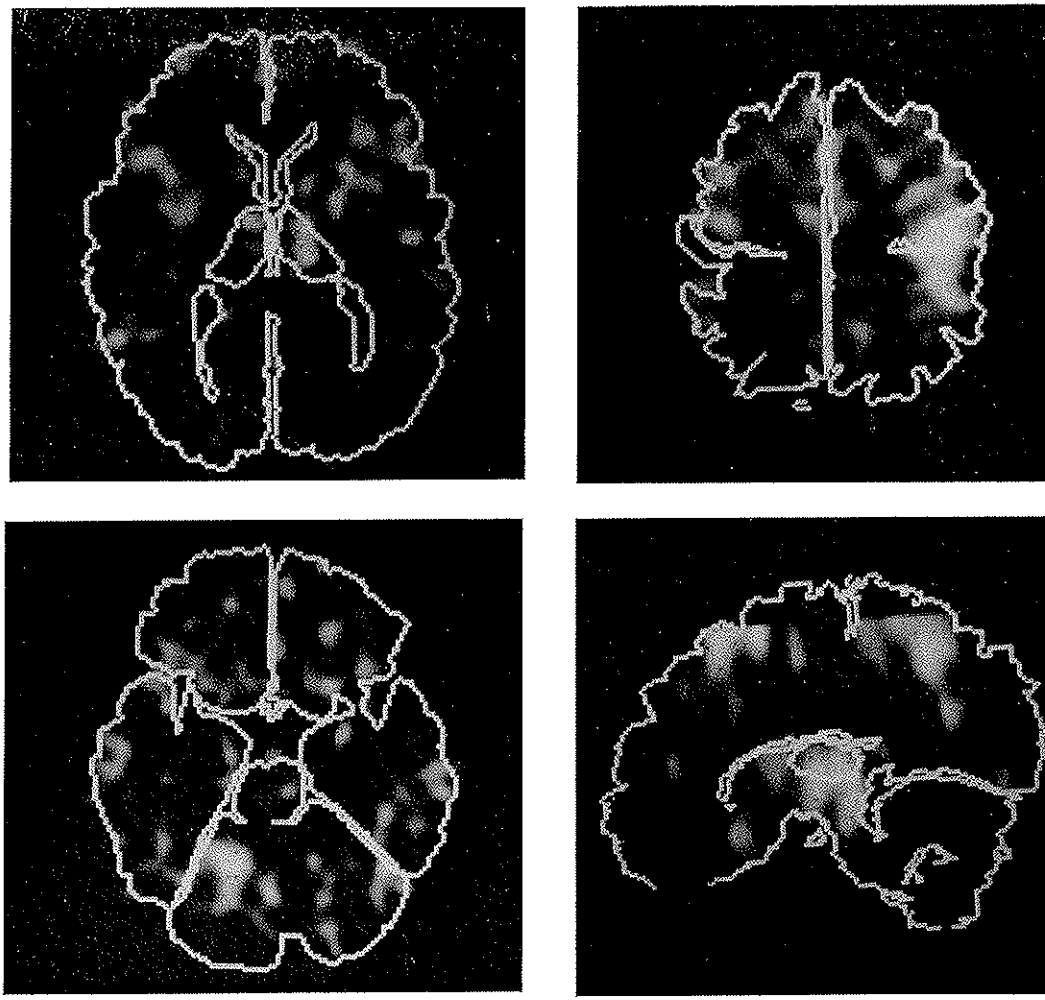


FIG. 6. Atlas images of the mean changes of rCBF in six subjects performing somatosensory discrimination with their right hand. The left hemisphere is shown to the right. Top left: section through ventral thalamus. Note the left thalamic increase, the increases in the basal ganglia, anterior insula and left secondary somatosensory area. Top right: section through the sensory-motor hand area. The central sulcus is shown. Note the small increase in the ipsilateral (right) precentral gyrus. Lower left: section through anterior lobe of cerebellum. Note the larger parasagittal increase in the right anterior lobe. Lower right: sagittal section through thalamus and left nucl. ruber. Note the increases in the supplementary motor and supplementary sensory areas. Please also note that the field sizes of the mean increases in most instances are well above 200 mm^2.

the rt + lt hippocampus, lt putamen and pallidum and the lt ventral thalamus showed rCBF increases (Fig. 6). It is evident from the figure that the mean increases in rCBF also cover areas of cortex ranging from 100 to 500 mm^2

Evidence from Brain Lesions in Man

For this particular task of somatosensory discrimination of rectangular parallelepipeda, Roland (1987a) measured the increases in discrimination thresholds arising from circumscribed lesions of the brain. It was found that lesions of the contralateral thalamocortical connexions to the somatosensory hand area in the postcentral gyrus produced severe increases in thresholds. More moderate increases were observed after lesions of the cortex lining the postcentral sulcus, the anterior part of the sup. parietal lobule, the supplementary sensory area, the parietal operculum, the superior and middle frontal gyrus (Roland, 1987a). Not all lesions to these areas produced discrimination deficits however. In the postcentral gyrus the somatotopical organization and parallel projection to different anterior-posterior sectors made it impossible to delimit a region to which damage always produced threshold increases in shape discrimination. For the somatosensory association areas in the cortex lining the postcentral sulcus, the anterior part of the superior parietal lobule, the supplementary sensory area and the parietal operculum, it was required that more than 2/3 of one of these areas be lesioned to cause a measurable discrimination loss. Minor lesions encroaching less than 2/3 of the area did not produce any changes in discrimination thresholds. Furthermore, it did not seem to matter which part of a given somatosensory association area was damaged as long as the defect was below 2/3 of the area. Also a whole section of the prefrontal part of the superior frontal gyrus had to be lesioned to elicit a shape discrimination loss. Similarly, only lesions of a large sector of the prefrontal part of the middle frontal gyrus caused shape discrimination loss whereas smaller lesions of any sub-sector were without measurable defect.

In a similar study of detection of electrical threshold stimuli to the tip of the index finger of patients with circumscribed unilateral lesions of the brain, it was found that lesions of the anterior part of the contralateral gyrus postcentralis (hand area) always caused increases in thresholds (Roland, 1987b). The larger the lesion was, the greater the threshold increase. This size effect could have been due to parallel projection of

skin afferents to a larger part of the finger area and spreading of information by collaterals. In addition, lesions of the fibres to the superior and middle part of the prefrontal cortex and lesions which undercut or destroyed a large sub-sector of the prefrontal parts of the middle or the superior frontal gyrus increased the detection threshold. Smaller lesions of the fibres to these prefrontal areas and smaller lesions of the middle and superior frontal gyri themselves did not change the thresholds (Roland, 1987b). Finally, larger lesions of the inferior and orbitofrontal cortex and hippocampus also increased the thresholds. Outside the anterior sector of the postcentral gyrus it did not matter which sub-sector of any of these structures was damaged. The issue seemed to be that a major part of the functional contributing cortex had to be damaged in order to elicit a threshold increase.

Since, in both these investigations, it did not seem to matter which sub-sector of a given contributing part of cortex was damaged and since, with the exception of the anterior sector of the postcentral gyrus, it was impossible to delimit any area of overlap to which lesion was always associated with detection or discrimination loss, it was concluded that there was no particular subset of cortical neurons within a contributing area responsible for the crucial information transformation and representation necessary to conduct the discrimination and detection. The synaptic transfer and transformation of information, thus, must have been spread over the whole cortical area or field in a quasi-redundant way. By quasi-redundant is meant that all active neurons and synapses contribute to the information transfer and transformation, but the elimination of a few neurons will only add minute noise to the discrimination or detection. Elimination of larger amounts of neurons and synapses will cause moderate noise. Only elimination of more than say 70% will cause so much noise that the detection and discrimination capacities of the patient now are clearly distinguishable from those of normals. The noise added is non-linearly related to the area of destruction. Severe noise arises when only very few neurons or fibres have to convey the function of the field (Roland, 1987a).

Evidence from Experiments Conducted in Animals

The studies of cortical field activation and field lesion above made it unlikely that the active field should consist of information processing in several independent neuronal clusters within the field. However,

neither the lesion studies nor the PET measurements of rCBF and rCMR tell about the anatomical and functional metabolic micro-structure of the activated fields. Such information can be obtained from autoradiographic and anatomical studies in other primates.

Sharon Juliano and co-workers vibrated the tip of the index finger in awake monkeys and found cortical "patches" of activity not only in the postcentral region but also in the somatosensory association areas in the parietal cortex, the secondary somatosensory area and the retroinsular cortex (Juliano *et al.*, 1981, 1983a). In three-dimensional reconstructions the patches were arranged in more or less longitudinally oriented bands with zones of less metabolic activity in between. These bands in turn made up an irregular field of high metabolic activity. At higher magnification the patches of high metabolic activity were seen to be composed of columns of high metabolic activity. Greenberg *et al.* (1979) showed that columns of high glucose consumption also had high rCBF, such that a functionally activated column consisted of a spatially coupled high rCMR and rCBF. These functional metabolic columns have also been noticed in the auditory cortex and prefrontal cortex (Kennedy et *al.*, 1978; Goldman-Rakic, 1984). In the ventral thalamus, somatosensory stimulation also gives rise to longitudinal bands of high metabolic activity (Juliano *et al.*, 1983b).

A reasonable question at this point is whether these columns, patches, bands and fields have any electrophysiological correlate. That the neurons in the cortex receiving specific thalamic afferents were arranged in functional columns with a particular stimulus specificity was first described by Mountcastle and Powell (1959). These functionally defined columns in the somatosensory cortex also arrange in longitudinal bands (Jones *et al.*, 1982). Even in the ventrobasal thalamus there are somatotopically and functionally defined longitudinal bands of neurons which increase their firing to specific stimuli (Jones and Friedman, 1982). Schoppmann and Stryker (1981) showed that in the visual cortex of the cat, the metabolic columns corresponded with electrophysiologically defined columns in which the neurons had orientation specificity for the stimulus used. This finding was consistent with the observation that metabolic label only occurred at cortical locations where the neurons possessed electrophysiologically defined functional properties (Whitsel and Juliano, 1984). However, the latter authors warn that in between the metabolic and stimulus active columns are neurons which by no means are silent (Whitsel and Juliano, 1984). Part of this inter-columnar activity could

originate from inhibitory interneurons. It is reasonable to assume that the cortical fields in man also are made up of numerous active columns and metabolically active bands dispersed over the active field.

From these observations in animals there are no objections to the cortical field activation hypothesis. Metabolic measurements are, however, of a different nature than extracellular recordings from single cortical or thalamic neurons. While the measurements of rCBF require a physiological steady state for 40-60 sec, measurements of the activity of a single neuron are done in the millisecond time-scale. However, it takes weeks, if not months, to map the electrophysiological activity of a population of neurons within a field. Whether the electrical and metabolic micro-structure changes in a cortical field in subjects or animals subjected to a consistent and specific stimulation is not known.

From electrophysiological mapping studies in the sensory-motor cortex it is evident, that within a cytoarchitectonic area a large and widely spread population of neurons is active with specific stimulus or motor-related activity. Georgopoulos and co-workers have demonstrated that neurons in the motor cortex generally are active with movements in many directions and that movements in a particular direction engage a large population of neurons. These neurons, however, fire with different frequencies. These observations led Georgopoulos to the hypothesis that all active neurons were coding for a movement in a particular direction in such a way that the final sum of the activity of movement directional sensitive neurons constituted a population vector determining the precise direction of movement (Georgopoulos *et al.*, 1982). The population vector is the vectorial sum of the individual neuronal contributions of action potentials. Similar observations have been made also for neurons in the parietal cortex monitoring the directions of reaching (Kalaska *et al.*, 1983) or directions in visual space (Motter *et al.*, 1987). The localization of an active neuronal population in the macaque seems to occupy an area of a little less than 100 mm^2. The neurons in a cortical area of the size of an active field can also compute other vectors, for example, of velocity of movement directions (Georgopoulos *et al.*, 1984).

Implications of the Cortical Field Activation Hypothesis and Neuronal Population Activation

The human studies provided evidence that a cerebral function is not localized to a certain cytoarchitectural area receiving input from a sensory

area and sending output to motor areas. Even the accomplishment of a rather simple sensory-motor task is a collaboration between a specific set of activated cortical fields and a multitude of localized subcortical neuronal populations, as exemplified in Fig. 6. In this sense there is no particular field or localized neuronal population which is responsible for discrimination of somatosensory information. This function is subserved by communications between the set of activated cortical fields and activated subcortical neuron populations, and this seems to be the general mode of processing information in the awake state. The size of cortical fields does not seem to correspond to a cytoarchitecturally defined area. Areas 9 and 10 of Brodmann, for example, presumably cover a large part of the superior frontal gyrus. Within this space several different fields have been described and activated in different types of brain work (Roland, 1985b).

It is tempting to assume that one cortical field receives information from other fields in the form of population vectors. These afferent patterns are dispersed over the entire field. The contribution of the field is the transformation of the afferent information into a new population vector. All types of cortical brain work, even storage and retrieval of stored information (Roland *et al.*, 1987, 1988, 1989) could be organized this way.

Since the information transformation is dispersed over the field, a small circumscribed lesion of part of the neurons in the field will only result in very modest noise added to the output population vector. Similarly, a random depletion of neurons within the field, for example as the result of age or certain diseases, will not in the beginning affect the information processing within the field to any great extent. The subhypotheses described here under the cortical field activation hypothesis are also in accordance with the uniformity in cortical microanatomy as described, for example, by Jones in this volume.

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DISCUSSION

WIESENDANGER

I have a short question about the precentral ipsilateral focus. You said you had a good reason and you would explain it.

ROLAND

This observation is consistent with Tanji's findings in which there was increased firing of a few ipsilateral neurons in MI. This present increase was also much less than the contralateral.

FREUND

These are very new data. Do you have a comparison of the active touch experiments with the passive touch situation? In particular, what would be different in the parietal lobe?

ROLAND

No, we haven't, but there is one advantage with this system, the Atlas system, and that is that we can subtract different functional activations. We have done that, and subtracted the rCBF of the motor sequence task from the somato-sensory discrimination task. Then we get differences in tasks showing post-central activation, some prefrontal activation, and some activation in the basal ganglia.

ITO

Concerning the sensory motor discrimination, I wonder what is the key factor which relates to the cerebrum. There can be discrimination, finger movement, matching of vision and tactile sensation and even learning in this process. What can the key factor be?

ROLAND

There is no visual information going into the brain, at least not from the outside. The subjects are blindfold during rest and test. There could be somatosensory information reaching the anterior lobe of the cerebellum on the contralateral side. It could also, of course, be motor commands reaching the cerebellum from the motor cortex. I don't think it could be learning. The reason is that since 1974 we have examined this task and observed all the different finger movements that they were doing during the task and recorded them. We could not see any change in the strategy or in the way in which the finger movements slid over the objects throughout a period of several days. This means that firstly we couldn't find any habituation with the tests, and secondly we couldn't see any motor learning effects in the test. Apparently subjects do the test very efficiently in a kind of semi-automatic way although the manipulation movements are very differentiated. (Roland 1977, Roland and Mertensen 1987).

INGVAR

I have just a very small question. Do these subjects talk, do they vocalize while they are doing the test?

ROLAND

They don't.

CREUTZFELDT

Can you tell us something about how linear is the relationship between the glucose consumption as measured with this method and the rCBF changes?

ROLAND

It is almost linear, up to blood flows of 100 ml/100 g/min. Above that most of the models don't apply any more, at least not for the oxygen consumption, and we don't know why this is.

DEECKE

Did the subjects make the exploration tasks with their right hands or

with their left hands? Wouldn't it be better to let them do the tasks with their left hand? If they are left-handed they should have a left-handed advantage for this kind of task because of right hemisphere preponderance.

ROLAND

We have checked that in about 50 normal volunteers and there is no difference between the right-hand and left-hand for this task, absolutely no difference.

DEECKE

We've just investigated blind people with their reading of tactile Braille language and they spontaneously prefer the left hand for this task.

ROLAND

I think these are totally different tests.

INGVAR

I had a small technical comment here, about this great Atlas technique where you standardize all the brains into one, shall we say, standard Swedish brain. How do you do it?

ROLAND

Not all brains are the same size, and of course the pixal size, when you reduce them all to a standard brain, will not be the same for all. The way you solve these problems is to use an extremely fine matrix that is so much finer than the resolution of our technique. Say, this region has a certain size here and has another size here. Now if you average all this, what you get is an average extent which is neither this nor that but something in between.

INGVAR

Now, the other technical point is about what we might call units. There must be a lower limit set by the technique. So when you say in absolute numbers that it is square millimeters here, this is just set by the technique, isn't it?

ROLAND

Yes. There is a lower limit. The spatial resolution of the technique at present for individual images is 7.8 millimeters, but my point was that even if you apply the constraints to the spatial resolutions, you still get the shapes extending in different directions.

LEVY

You're presenting the main difference in the rest and activation scan, but I have no idea what the variance of that was or what kind of change is a meaningful change. What differs from a random variation?

ROLAND

I could show you some significance images, as we call them, which are the mean divided by the standard deviation for that particular pixal so you get charts exactly like that. The regions I mentioned were those that were above two standard deviations. I didn't show you all the 15 slices of the standard deviation images, but they can easily be created by the Atlas software.

LEVY

One other question: since you had multiple regions through those scans, I will assume that these are standard deviations. Presumably many of these regions must have been correlated with each other, so they were not independent increases. It was hard for me to give a functional interpretation to many of the hot spots that you pointed to.

ROLAND

It's a good point, but the only way to solve the problem is to do a lot of independent tests and see if you get field increases in the same regions. You have to do that in the same individual. It's not possible to do more than 4 tests in the same individual. But that's the only way you can resolve this.

INGVAR

Just one final question. This beautiful study with the blood flow and the discrimination test, I don't want to be facetious at all, but were there any surprises in what you saw?

ROLAND

We were quite surprised that we were able, by the signal averaging obtained with the Atlas, to actually localize the changes in the ventral thalamic regions. We hadn't expected that. You probably know that the response of a detector in a positron camera depends on where you are in relation to the center of the crystal. By looking at the same structure in different people, you use different parts of this response curve and this is, I think, one of the reasons why you achieve higher and very accurate localization. You don't change the spatial resolution at all, but you work on this response curve and then you can increase the localization because the parts of the thalamus with insignificant changes in the individual scans are averaged out.

CEREBRAL PROCESSES THAT DISTINGUISH CONSCIOUS EXPERIENCE FROM UNCONSCIOUS MENTAL FUNCTIONS

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ABSTRACT — Conscious subjective experiences represent a phenomenological category independent of (that is, not directly describable by) associated, externally observable, physical-neural events. Subjective referral of sensory experiences, as to both spatial and temporal contents relative to their neural representations, provides objective examples of this principle.

A "time-on" theory is proposed to explain the difference between cerebral processes that mediate conscious experiences as opposed to those in unconscious mental functions. The theory states that the transition from an unconscious to a conscious mental function is determined, at least in part, by an *increase in duration* of the appropriate neural activities. Newer direct evidence for the theory is presented. This includes a study of (i) the cerebral initiation of a voluntary act, relative to appearance of conscious intention; and (ii) the behavioral detection without awareness, of stimuli, in the sensory thalamus, with durations not long enough to elicit subjective sensation. Some general implications of the theory are also presented.

Conscious subjective experience is what means most to us as human beings and is at the heart of the mind-brain problem. I believe it is important to articulate a few principles that should govern any investigations of the mind-brain relationship (see Libet, 1987a), before proceeding to some of our own experimental studies of the question.

Principle 1. Conscious subjective experience, awareness of some thing or some event, is directly accessible only to the individual having the experience, not to an external observer. Therefore, the only measurement of it that has primary validity requires an introspective report by the subject. The report may be verbal or non-verbal. The important point

is that the subject understands the question and can report his experience without limitations imposed by the observer in the form of certain tasks or expectations.

A corollary of this principle is that externally observable events, behavioral or physiological (e.g., EEGs, ERPs), are not valid primary indicators of a subjective experience, unless they are a part of the subject's introspective report appropriately elicited. It must be borne in mind that even cognitive and decision-making processes, complex and abstract problem solving, and purposeful successful behavioral responses to signals, can all proceed unconsciously/preconsciously, without awareness; evidence of their participation cannot, in itself, be taken to represent a conscious experience.

Principle 2. There are no *a priori* rules that describe the relationship between neural-brain events and subjective-mental events. The rules must be discovered and established by simultaneous observation of both phenomenological categories, the "physical" and the "subjective-mental". It also follows that even a complete knowledge of the neural-physical makeup and events would not, in itself, produce a description of any correlated subjective experience (e.g., Nagel, 1979).

Specific interesting illustrations of this general principle are apparent in the phenomena of subjective referral of sensory representations. Subjective referral or "projection" in the spatial dimension is already well known. For example, electrical stimulation of somatosensory cortex of postcentral gyrus in man elicits a sensory experience not located at the site of the stimulus but one subjectively referred to some bodily site contralateral to the side stimulated. Similarly, the subjective visual image we experience has a form and quality not directly evident in the pattern of neural activations associated with the experience. There is also the subjective "filling in" of neurological blind spots, or even of whole visual fields (as described by Baumgartner, this volume; see also Levy, this volume).

Subjective referral in the temporal dimension was only discovered more recently (Libet *et al.*, 1979). The experimental evidence for this phenomenon includes some that is basic to the ensuing part of this paper, and it will be presented briefly.

Neural delay. In the initial study we found that a substantial time period of neuronal stimulation in the cerebral somatosensory system is required in order for the subject to have a reportable sensory experience. The required duration of such activation varied with intensity (I) of the

cerebral stimulus; with a liminal I (below which no sensation could be elicited even with long stimulus trains) a substantial minimum train duration was required (Fig. 1) (Libet *et al.*, 1964; Libet, 1973). This minimum, termed the "utilization train-duration" or "U-TD", averaged about 500 msec. Similar U-TDs were observed regardless of pulse frequency (15/s to 120/s) and at all cerebral points in the specific sensory pathway (S-I cortex and its subcortex, ventrobasal thalamus and medial lemniscus).

On the other hand, a single pulse (at or near the absolute minimum I) could be sufficient when applied to skin, peripheral nerve or dorsal columns. In spite of this, we postulated that substantial times of activity were required to achieve cerebral "neuronal adequacy" for awareness following a single peripheral stimulus pulse, just as for cerebral stimuli. Such a single peripheral stimulus pulse elicits a series of event-related-potentials (ERPs) at the cerebral cortex, and the later components appear to represent necessary correlates for a sensory experience (Libet *et al.*, 1967, 1975). Several additional lines of evidence were developed in sup-

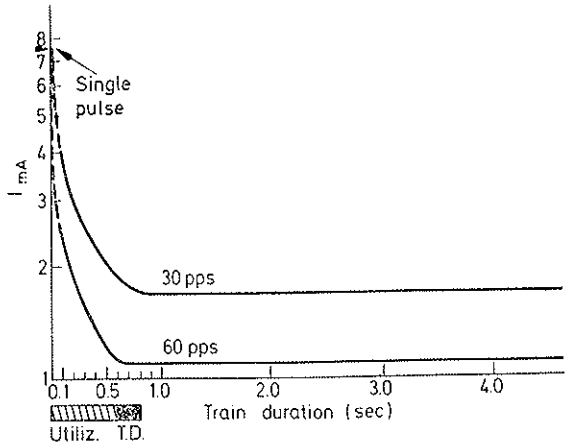

FIG. 1. Temporal requirement for stimulation of somatosensory (SI) cortex in human subjects. (The curves are diagrammatic representations of measurements in different individuals, which were not sufficient in each case to produce a full curve). Each point on a curve indicates the combination of intensity (I) and train duration (TD) for repetitive pulses that is just adequate to elicit a threshold conscious sensory experience. Separate curves shown for stimulation at 30 pps and 60 pps. At the liminal I (below which no sensation was elicited even with long TDs), a similar minimum TD of about 0.6 sec ± was required for either pulse frequency. Such values for this "utilization TD" have since been confirmed in many ambulatory subjects with electrodes chronically implanted over SI cortex and in ventrobasal thalamus. (From Libet, 1973).

port of this postulate (Libet, 1973, 1978, 1981, 1982), but these will not be reviewed here.

The concept of a "neuronal delay" of *up to* about 500 msec, before a *sensory experience* can appear in response to a sensory input, should not be confused with or deemed inconsistent with the *ability to discriminate* among much briefer time intervals present in certain pulsatile stimuli. For example, one can discriminate among vibratory stimuli at relatively higher frequencies applied to the skin, or appreciate the difference in pitch for sound waves differing in frequencies, all containing wavelengths with durations much shorter than our "neuronal delays". The question we are addressing in such instances is: *when* does one become *aware* of whatever temporal discrimination has been achieved.

Subjective referral backwards in time. If there is a substantial neuronal delay required before achieving a sensory experience or awareness, is there a corresponding delay in the *subjective* timing of the experience? In accordance with Principle 2 above, one could not answer this question solely from the neural knowledge available. In fact, an appropriate experimental test of this question indicated that there is no appreciable delay for the *subjective* timing of a normally arriving sensory input (Libet *et al.*, 1979)! Experiments utilizing reports of relative order of subjective timings for stimuli at skin, medial lemniscus and S-I cortex (Fig. 2) enabled us to conclude the following: (1) After a delayed achievement of neural adequacy for awareness, there is an automatic subjective referral of the experience backwards in time, to approximately the delivery time of the stimulus. (2) The initial cortical response (primary evoked potential at SI cortex) to the fast specific (lemniscal) projection sensory message, serves as the timing signal for this backward referral (Fig. 3). The experience would thus be subjectively antedated and would appear to the subject to occur without the actual substantial neural delay required for its production. Point 2 in these conclusions explains why the sensory experience elicited by a surface-cortical stimulus *is* subjectively delayed by a time roughly equal to the U-TD of the stimulus employed; this stimulus does not excite the normal ascending projection to SI cortex and so there is no subjective antedating. On the other hand, the experience elicited by a stimulus in medial lemniscus shows no subjective delay, relative to that for a single pulse stimulus to skin, even though medial lemniscus empirically required the same substantial duration of stimulus pulses as did SI cortex.

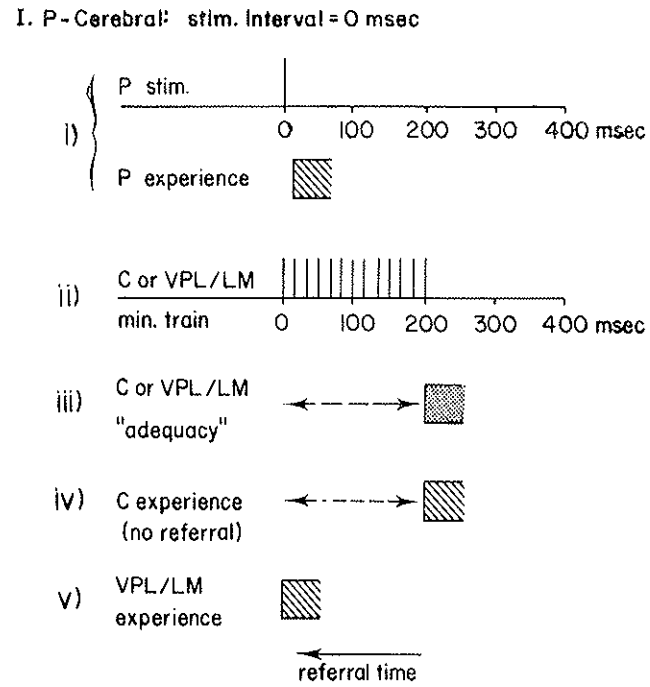

FIG. 2. Diagram of timing relationships for the two subjective experiences elicited, when a peripheral stimulus (P) is temporally coupled with a cerebral stimulus. The actual relationships were experimentally confirmed (Libet *et al.*, 1979).

P (see i) was a single, near-threshold pulse applied to skin of the hand ipsilateral to the cerebral stimulus; the latter thus produced a sensation referred to an area contralateral to that for P. Each cerebral stimulus (see ii) was a train of pulses, at 60 pps, with intensity (peak current) adjusted so that a min. TD of 200 msec was required to elicit any sensation. This means that "neuronal adequacy" for a reportable sensory experience (iii) was not achieved before 200 msec of stimulation had elapsed, whether stimulating at C (SI cortex) or in VPL/LM (n. ventroposterolateralis of thalamus or medial lemniscus).

The reported subjective timing for the C-elicited sensation (iv) was *delayed*, relative to that for P, by a time similar to that of the min. TD required, 200 msec in this case. However, subjective timing for the VPL-LM elicited sensation (v) was reported to be simultaneous with that for P; it was *not* delayed to the end of the min. TD as was the case for C. There was, therefore for VPL/LM elicited sensations, a subjective referral backwards in time, apparently to the time of the primary evoked potential response to the initial pulse in the stimulus train (From Libet *et al.*, 1979); see further in Fig. 3).

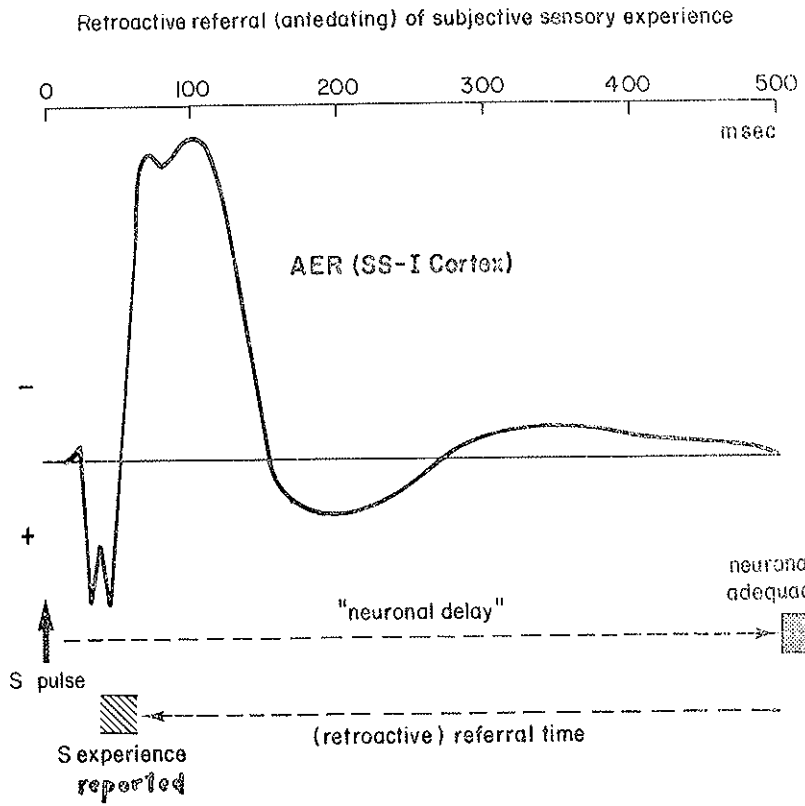

FIG. 3. Diagram of subjective referral of a sensory experience backward in time. The average evoked response (AER) recorded at SI cortex was evoked by pulses just suprathreshold for sensation (at about 1/sec, 256 averaged responses) delivered to skin of contralateral hand. Below the AER, the first line shows the approximate delay in achieving the state of neuronal adequacy that appears (on the basis of other evidence) to be necessary for eliciting the sensory experience. The second line shows the apparent retroactive referral of the subjective timing of the experience, from the time of neuronal adequacy backward to some time associated with the primary surface-positive component of the evoked potential. This would explain the subject's reporting the sensations elicited by skin and medial lemniscus as simultaneous, while a cortically elicited sensation is reported as delayed.

The primary component of AER is relatively highly localized to an area on the contralateral postcentral gyrus in these awake human subjects. The secondary or later components, especially those following the surface negative component after the initial 100 to 150 msec of the AER, are wider in distribution over the cortex and more variable in form even when recorded subdurally (see, for example, Libet *et al.*, 1975). It should be clear, therefore, that the present diagram is not meant to indicate that the state of neuronal adequacy for eliciting conscious sensation is restricted to neurons in primary SI cortex of postcentral gyrus; on the other hand, the primary component or "timing signal" for retroactive referral of the sensory experience would be a function more strictly of this SI cortical area. (The later components of the AER shown here are small compared to what could be obtained if the stimulus repetition rate were lower than 1/sec and if the subjects had been asked to perform some discriminatory task related to the stimuli). (From Libet *et al.*, 1979).

Subjective referral in space and in time both, interestingly, employ the same specific projection system to supply the signals utilized in the referrals, and both serve to "correct" (subjectively) the spatial and temporal distortions of the real stimuli introduced by their neuronal representations. It should also be realized that subjective referrals occur as "mental" functions; they are not apparent, as such, in the neural activities (Libet *et al.*, 1979; Libet, 1982), as also noted by Sherrington (1940) and Eccles (1979).

Conscious and Unconscious Mental Functions

It appeared to me more experimentally feasible to attempt to specify the *differences* between cerebral processes that mediate conscious vs. unconscious mental functions, rather than to attempt, at this stage of our knowledge, to specify the full panoply of cerebral processes which could account for the appearance of a conscious experience. The term "unconscious" is used here as a general operational one to cover all mental functions which are not reportable as introspective subjective experiences; it would include the more theoretical categories like subconscious, preconscious, etc., and is intended to cover a broad array of normal and abnormal mental processes, not limited to the usage in Freudian "repression", etc. Mental functions, whether conscious or unconscious, would apply to all those recognized as psychological in nature, including cognitive, conative (decision-making), learning and recalling, thinking (including complex, abstract and creative thought), etc. It is generally agreed that much if not most of such mental functions can proceed unconsciously, and there is no need to document this proposition here.

A "Time-on" Theory.

I have proposed this theory to explain the difference between cerebral processes mediating a conscious mental function and those for an unconscious one (Libet, 1965, 1973, 1981, 1982, 1985a; Libet *et al.*, 1983). The theory states that the transition, from an unconscious mental function or event to one that reaches awareness and is consciously-subjectively experienced, can be a function simply of a sufficient increase in duration (or "time-on") of appropriate neural activities. That is, appropriate neural activities whose duration is below some minimum substantial duration (in 100s of msec) could mediate a mental function that remains un-

conscious; but that when such activities persist for longer than that minimum time (as may be effected by influences from changes in attention, etc.), subjective awareness of the mental function can appear.

It should be clear that the theory does not exclude other important or even controlling distinctions between processes mediating conscious vs. unconscious mental functions. For example, the specific kinds of neural activity and/or specifically active sites in the brain *may* differ crucially. It is only proposed that the "time-on" factor is superimposed, as a critical requirement, upon any other differentiating factors. Indeed, one wants at present to avoid designing any specificity or mechanism into the theory other than the "time-on" factor *per se*.

Experimental Evidence on the Theory.

There are two basic propositions inherent in the theory, each of which is experimentally testable and falsifiable. (1) A minimum duration of appropriate neural activity, of up to about 500 msec depending on conditions, is required in order to elicit a conscious experience or awareness of an event. The available evidence already supports this proposition, as indicated above. (2) When appropriate neural activity has a duration briefer than that required for awareness, it may still mediate an unconscious mental function, without any subjective awareness of it. In addition to earlier indirect evidence (Libet, 1981, 1982), more recent studies have produced experimental evidence which directly supports this second proposition:

(a) *Initiation of a voluntary act.* The relevant experimental question here is: does measurable cerebral activity start before or after the appearance of conscious, subjective intention to perform a fully voluntary act? If cerebral activity begins first, by a significant time margin, that would constitute a direct demonstration of unconscious cerebral mediation of an important mental function, before the neural activity becomes sufficient for awareness of this intention; such a situation is predicted by the "time-on" theory.

The readiness-potential (RP) is a slow ERP (event-related-potential) whose onset precedes a "self-paced" movement by 800 msec or more. After its discovery by Kornhuber and Deecke (1965; Deecke *et al.*, 1976), we established that fully endogenous, spontaneous voluntary acts are also preceded by a type of RP with onset at about −550 msec (Libet *et al.*, 1982; Fig. 4). The onset of such "self-initiated" RPs was taken to be

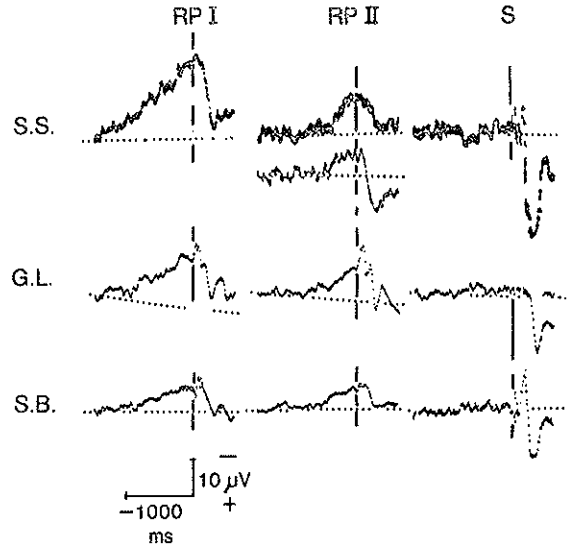

FIG. 4. Readiness potentials (RP) preceding self-initiated voluntary acts. Each horizontal row is the computer-averaged potential for 40 trials, recorded by a DC system with an active electrode on the scalp, either at the midline-vertex (C_z) for subject G.L. and S.B., or on the left side (contralateral to the performing right hand) approximately over the motor/premotor cortical area that controls the hand (C_3) for S.S. When every self-initiated quick flexion of the right hand (fingers or wrist) in the series of 40 trials was (reported as having been) subjectively experienced to originate spontaneously and with no preplanning by the subject, RPs labeled type II were found in association. When an awareness of a general intention or preplanning to act some time within the next second or so was reported to have occurred before some of the 40 acts in the series, type I RPs were recorded (Libet *et al.*, 1982). In the last column, labeled S, a near-threshold skin stimulus was applied in each of 40 trials at a randomized time unknown to the subject, with no motor act performed; the subject was asked to recall and report the time when he became aware of each stimulus in the same way he reported the time of awareness of wanting to move in the case of self-initiated motor acts. (No significant prepotential is seen before S stimuli, but a large P_{300} ERP follows S, indicating attention to and cognitive uncertainty for S here present).

The solid vertical line through each column represents 0 time, at which the electromyogram (EMG) of the activated muscle begins in the case of RP series, or at which the stimulus was actually delivered in the case of S series. The dashed horizontal line represents the DC baseline drift.

For subject S.S., the first RP (type I) was recorded before the instruction "to let the urge come on its own, spontaneously" was introduced; the second RP (type II) was obtained after giving this instruction in the same session as the first. (The lower tracing shows another such RP II for S.S. in a later session). For subjects G.L. and S.B., this instruction was given at the start of all sessions. Nevertheless, each of these subjects reported some experiences of loose preplanning in some of the 40-trial series; those series exhibited type I RPs rather than type II.

an indicator of the minimum advance starting time for specific cerebral processes leading to a voluntary act. Measurement of the timing of the associated subjective event, i.e., the time of appearance of the *awareness* of the intention or wish to act (W), was based on the subject's report (following each act) of the "clock-time" associated with the first such awareness in each trial (Libet *et al.*, 1983). (The control observations to indicate the accuracy of such reporting, and the analyses by myself and others of the validity of such reporting of the subjective timing of awareness, have been presented fully elsewhere, — see Libet *et al.*, 1983a; Libet, 1985a, b; 1987b, c; 1989).

The results of that investigation (Table 1, Fig. 5) led to the following experimental conclusions: (i) The cerebral processes that precede a voluntary motor act begin at least 350 msec *before* the subject is aware of his/her intention or wish (W) to "act-now". (ii) But this awareness (W) still appears about 150 to 200 msec before activation (EMG) of the muscles involved. This evidence thus demonstrates an observable but unconscious cerebral process associated with an initiation of at least the preparation to perform a freely voluntary act — something normally regarded as a

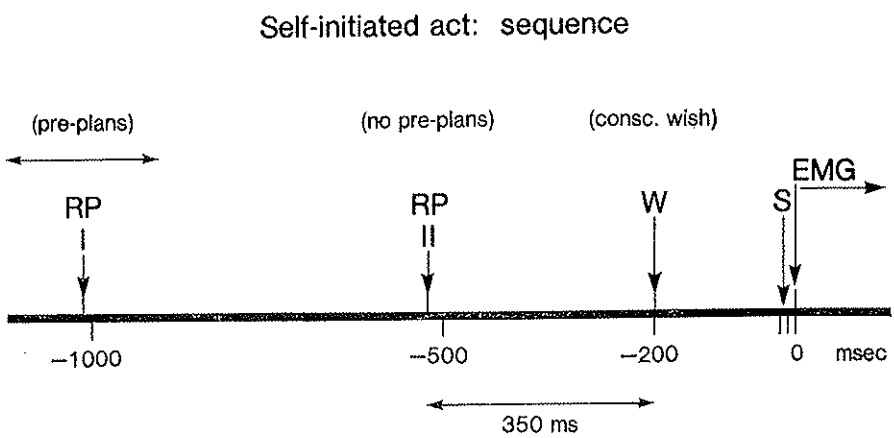

FIG. 5. Diagram of sequence of events, cerebral and subjective, that precede a fully self-initiated voluntary act. Relative to 0 time, signalled by the EMG of the suddenly activated muscle, the RP (an indicator of related cerebral neuronal activities) begins first — at about -1050 msec when some preplanning is reported (RP I) or about -550 msec with spontaneous acts lacking immediate preplanning (RP II). Subjective awareness of the wish to move (W) appears at about -200 msec, some 350 msec after onset even of RP II but well before the act (EMG). Subjective timings reported for awareness of the randomly delivered S(skin) stimulus averaged about -50 msec relative to actual delivery time.

TABLE 1 - Time of conscious intention (W, aware of wanting to move no) and time of onset of RP. Numbers given are grand averages found with 5 subjects for 20 series (of 40 acts each) that exhibited a type II RP (all acts experienced as spontaneous, with no pre-planning), and for 12 series with a type I RP (see text). Figures are msec, relative to time for muscle activation (recorded EMG as zero time for each act).

Type of RP	Awareness time, W	Awareness time, W, corrected for S *	Onset time of RP	(Onset of RP) *minus* (W)	(Onset of RP) *minus* (W, corrected for S)
II	−192	−169	− 535	−343	−366
I	−233	−170	−1025	−792	−855

* To "correct W for S", the subjects' errors in reporting awareness times for skin sensations (S) were subtracted from the W values (See Figs. 4, 5).

(Modified from Libet *et al.*, 1983b).

fundamental mental event. The evidence is also in accord with the proposal that the development of the associated subjective awareness of such an initiating intention requires a substantial period of neural activities. These conclusions depend on the assumption that the readiness-potential (RP) does represent cerebral processes that are actually involved in or meaningfully related to the initiation of the volitional preparation to "act-now". An alternative view of the significance of the RP has been proposed by Eccles (1985, and this volume) and also somewhat differently by Ringo (1985) and Stamm (1985).

This alternative view proposes that the recorded RP, as a component in the averaged recording of 40 trials in our experiments, represents random-like slow waves in cortical potentials which do not have a meaningful significance as initiators of a voluntary act. In this view, the actual initiating process, such as a conscious mental function, may "take advantage of" the propitious appearance of a suitable neuronal state developed by such slow changes; one would then expect the beginning portion of such a random slow wave to be recorded as a regular feature before each actual voluntary act and thus form the RP. Although this alternative view cannot be ruled out, it requires some extra *ad hoc* assumptions

and does not fit the overall evidence as well as the view we have proposed: (i) The recorded RP exhibits no identifiable change in contour at the time of appearance of W, the reported time of conscious intention to move; i.e., the RP appears to represent a continuous developing process, not an initial "irrelevant" phase upon which a delayed initiating event builds it into genuine volition. (ii) When the voluntary act is preceded by conscious pre-planning to act within the next second or two, the recorded RP begins much earlier (at −1.5 sec or earlier) (Libet *et al.*, 1982). This RP has a more ramp-like form but has a scalp distribution similar to the RP for the fully spontaneous act. Furthermore, the subject still reports a final conscious intention to "act now" at about the same −200 msec time as for the W report in a fully spontaneous voluntary act (Libet *et al.*, 1983a; Libet, 1985a). The initiating phase of RPs in acts with such pre-planning cannot easily be regarded as part of a random slow wave which, in any case, would now require a different wave length. To superimpose, on the pre-planned RP, a randomly appearing slow wave component (as an enabling mechanism for final initiation of the actual act) would require assumptions of timing, etc., that further complicate the interpretation of the observed evidence. (iii) Even if (despite the foregoing) one were to accept the alternative view (of Eccles and the others), there would be a limitation imposed upon *when* their specific (conscious) initiating process could trigger the voluntary act; this would mean that the time when a voluntary act could be initiated would be determined by the appearance of the preceding slow cortical wave, whether one chooses to regard this as a random event or as something more specifically meaningful to volition.

(b) *"Time-on" theory and sensory detection without awareness.* When stimulating ventrobasal thalamus (as well as SI cortex and medial lemniscus) in human subjects, we had found that a minimum train duration (TD) of pulses is required in order to elicit any reportable conscious sensation; with intensity level (peak current) near the absolutely liminal one, such minimum TDs averaged about −500 msec. With a TD below the required minimum, e.g., 300 msec when minimum was 400, subjects would report feeling no sensation. Although such a briefer stimulus train at the same intensity is inadequate for conscious sensation, it must clearly be exciting the same ascending axons that feed into the same cortical and other areas as does the longer train. The "time-on" theory would predict that such shorter lasting activations, even though they do not give rise to a reportable awareness, may be psychologically/mental-

ly detected and lead to meaningful behavioral responses in an unconscious manner.

We are now concluding a direct experimental study of this proposition (Libet, Pearl, Morledge, Gleason, Hosobuchi, and Barbaro, unpublished). The subjects were patients with permanent implantations of electrodes in some portion of ventrobasal thalamus for the therapeutic purpose of controlling certain kinds of intractable, intolerable pain. Patients were completely ambulatory, coming in from home for the studies. The completely internalized subcutaneous receiver coil, which fed the stimulus pulses to the intrathalamic electrode tips, received the input from an externally overlying coil connected to an external stimulator box whose controls were modified so as to be run from our controlled computer-programmed source. At near liminal intensities, with a pulse frequency of 72 per sec, we confirmed our previous finding that a minimum TD of about 400 to 500 msec was required in order to elicit a reportable conscious sensation, typically a kind of localized paresthesia or "tingling". Evidence for behavioral detection of the stimulus, with or without awareness, was obtained in a simple forced choice paradigm. For this, the subject observed two 1 sec-long lights which went on in succession (separated by a 1 sec interval); the stimulus was delivered in one or the other of these two light-on periods in a randomly distributed manner for the different trials. The subject was asked to choose which light (#1 or #2) might have included something different, even if he felt or was aware of no sensation at all, and even if he had no consciously definable basis for his choice. The pulse numbers in each stimulus were also randomly varied in different trials, between 0 and 55 pulses (i.e., between TDs of 0 and approximately 750 msec, thus including some stimuli of which the subject was aware).

Although the full statistical analysis is still in progress, it is already quite clearly shown that correct behavioral detection of these signals, at levels substantially and significantly greater than the 50% pure chance result, did in fact occur with stimulus durations too brief to produce any reportable conscious sensations. Some detection without awareness occurred with as few as 5 to 10 pulse stimuli (TDs of 70 to 140 msec) when sensory awareness required 29-36 pulses (TDs of 400 to 500 msec). Such results would provide direct evidence (i) that detection without awareness is possible. (This also provides a conclusive experimental distinction between the meaning of purely behavioral detection and subject reports of awareness. It should be noted that this behavioral detection without

awareness required some sort of cognitive and decision-making processes). (ii) They also show, in relation to the theory, that the duration ("time-on") of neural activations can determine whether such detection remains at unconscious levels or is accompanied by a conscious subjective sensory awareness of the neural input.

Some Implications of the "Time-on" Theory.

(i) *Cerebral representation.* If the transition from an unconscious to a conscious mental function could be dependent simply on a suitable increase in duration of certain neural activities, then both kinds of mental functions could be represented by activity in the same cerebral areas. Such a view would be in accord with the fact that the constituents and processes involved in both functions are basically similar, except for the awareness quality, and with the general view that a broadly distributed neural activity pattern probably mediates both types of function. Separate cerebral sites for conscious vs. unconscious functions would not be necessary, although this is not excluded (as noted above).

(ii) *"Filter" function.* The "time-on" requirement could serve as mechanism for the known condition that most inputs and cerebral activities do not reach awareness. This of course permits conscious-awareness to be uncluttered and to focus on one or a few specific issues at a time.

(iii) *Quick behavioral responses are initially unconscious.* Responses in reaction time (R.T.) tests, for example, can be made within less than 100 msec, depending on the complexity of the signal, etc. R.T.s even with the simplest signal (e.g., one loud sound or a visual flash) involve cognitive and conative processing. On our theory, all this would often occur before awareness of the signal could develop. There is much indirect and anecdotal evidence to support this view of the initially unconscious nature of quick reactions. However, when delayed awareness does appear, there would ordinarily be a subjective antedating of its timing (Libet *et al.*, 1979) — so that the subject believes he experienced the signal before reacting; for example, a racer may start within <100 msec after the starting gun, before he is consciously aware of the shot, but would later report having heard it before take-off.

(iv) *Unconscious mental functions proceed quickly*, since they would not require the fuller "time-on" needed for a conscious one. This feature is obviously advantageous not only for quick meaningful reactions to

signals but also in the ability to carry on creative, complex and intuitive thinking.

(v) *Permits modulation of a conscious experience.* It is well known that the *content* of the introspectively reportable experience of an event may be modified considerably in relation to the content of the actual signal, whether this be an emotionally laden sensory image or endogenous mental event (which may even be fully repressed, in Freud's terms). In order for this to happen, some delay between the initiating event and the appearance of the conscious experience of it is essential. The "time-on" theory provides a built-in basis for the appropriate delays. We have produced some direct experimental evidence for such modulatory actions on the awareness of a simple sensory signal from the skin; in this, an appropriate cortical stimulus was begun up to 200 msec or more after the skin pulse, but could either inhibit or enhance the sensory experience (Libet *et al.*, 1972; Libet, 1978, 1982).

(vi) *Conscious control and free choice of voluntary action.* As discussed above, an observable cerebral process (RP) regularly begins some 300 to 400 msec *before* the appearance of the conscious awareness of intention "to act now" (W). If a cerebral action unconsciously initiates (or, in the alternative view of Eccles and others, at least determines the available timing of) the process leading to performance of a voluntary act, that may raise a serious question about the role of conscious free choice or will in voluntary action. However, one must distinguish between the appearance of conscious intention (W) and that of a potential *conscious control* of the volitional outcome.

First, although the appearance of W is delayed well after the onset of the RP, W does appear 150 to 200 msec *before* the beginning of muscle action (as signified by the EMG). This allows for a substantial time during which some modulation of the volitional process could be developed, before the final "motor command" goes out from the motor cortex (at about −50 msec; see Deecke *et al.*, 1976; McCloskey *et al.*, 1983). A conscious "veto" of the process, resulting in no motor action at all, can be exerted *after* W, i.e., after the awareness of the wish or urge to act has appeared (Libet *et al.*, 1983b; Libet, 1985a). The reverse is also possible, namely that a "conscious trigger" is required (after the appearance of W) to enable the volitional process to proceed to the actual motor command (see Libet, 1985a, b, and Eccles, 1985), — although this would seem to add an unnecessary factor if the volitional process is already under way (Libet, 1985b).

I suggest that conscious control differs from W not only in its appearance after W but in its "nature". Conscious control does not constitute another awareness of something; it is rather a different phenomenon which may impose a change after an awareness of intention has already appeared. Even if one assumes that the "time-on" theory applies to all kinds of subjective awareness (each preceded by an unconscious initiating process), the theory would not necessarily apply to the phenomenon of conscious *control*. Conscious control is not a new awareness of something; it deals with a situation of which the subject has just become aware (W, in the present case). On this basis, the theory would not require that conscious control is also initiated unconsciously. Thus, the potentiality for a form of free choice (in the classical sense) is not excluded by the theory, even if the theory is generalized to all awarenesses. Indeed, the experimental observations provide an opportunity for the occurrence of free choice, but apparently in the form of control rather than initiation of an act (Libet, 1985a, b; 1987b, c).

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DISCUSSION

BROOKS

Did the intensity relate to the generation of the positive surface response?

LIBET

Yes it did, and with stronger intensity we got bigger positive secondary waves.

BROOKS

And a lower detection level?

LIBET

The positive wave began already to appear at the level where awareness came in.

INGVAR

I'm curious to know whether in these studies of, I presume, many hundreds of subjects, there are people who are slower than others.

LIBET

That's a very good point. When I said that the utilization train, the minimum train, was about 500 milliseconds, that was the average for all subjects. There were a few subjects as low as 200 milliseconds and there were some as long as 1000 milliseconds. They tended to clump around 500 milliseconds. Now we did not do a psychological study to see whether there is a correlation.

DESMEDT

You are stimulating the cortex, and you see a difference with a shorter

duration or a longer duration. Now I am saying that by stimulating with physically identical shocks, to the same finger for example, you get presumably the same input to the cortex, from one trial to the next, and you see a very big difference in the brain electrical response and in the conscious sense that are elicited, depending on the attention of the subject, whether he pays attention to this finger, whether he neglects the finger, whether he is involved in some other function.

LIBET

I don't see what the conflict is. I agree with the skin stimulus and the single pulse that the subject attends to; but the duration is for cortical stimulation, not out at the periphery.

DEECKE

I like your veto experiment very much and I am sorry that you didn't show a slide. If I am correct in remembering, there was first a readiness potential and then this was broken off by the veto function. I think this was very good. The clock I don't like so much, because I think this is a stimulus from the outer world. This discards the whole paradigm as being self-initiated. So it can be that there is just not the readiness potential but an expectancy wave in anticipation of this event.

LIBET

The subjects were reporting and it was fully spontaneous and just coming out of the blue. There was no expectancy experience by the subject. So as far as our evidence goes, it is that this prepotential, the readiness potential, is strictly involved with preparation to act or move, not with the expectancy of something going to happen.

ROLAND

I don't know if it's exactly relevant, but we found when people were attending to the tip of their index finger in preparation for a just detectable touch, then the blood flow in the contralateral somatosensory hand area increased by 25% as well as in the regions in the prefrontal cortex dealing with somatosensory analysis. So we took this as a kind of preparatory tuning of the cortex occurring in advance of any stimulus. It set up a basic tuning of neurons over vast areas in the cortex, long before any stimulus arrived.

LIBET

I don't see any conflict with that.

SINGER

I found it very interesting that you need a certain amount of time in order to get above the threshold of awareness, because one would think that you need to recruit a sufficient number of neurons to get above this threshold. Now, to your comments, Dr. Desmedt, one can see very easily how the same physical stimulus can produce a brief abortive response at the cortical level and in other instances very prolonged reverberating responses, and this depends very much on the state of the so-called arousal systems.

DESMEDT

This is not a question of arousal, because these stimuli are intermixed. We always have in the same series the control of other stimuli. So the task is of the same level; the subject has got the same level of arousal in these different runs. He has the same level of cognitive activities, but directed towards different targets. So I think you cannot say that there is a difference in arousal level that explains this difference. It's that the subject is focusing attention.

LEVY

I would like to ask about the clock judgements. It seems to me that what you are really asking these subjects is to specify the time at which they can say something like: I know that I am aware, rather than I am aware.

LIBET

We asked the subjects to associate the time of the clock with the first experience that they had that they wanted to move. You can say that they had to wait until they knew that they were aware and so on, but the first inkling that they had that they wanted to move they associated with the position of the clock. The subject knows that you want to know what he felt or what he was aware of. He gives the answer later. He does not give us the answer immediately because that would defeat the experiment. It would introduce other qualifications. So he has this experience and then after it's all over, he then reports what the clock time was.

GENERAL DISCUSSION

ECCLES

We have to concentrate on the experiments that we have been listening to this afternoon in relation to consciousness.

There was one experiment on this question that Ben Libet did, on the readiness potential. This involves Deecke as well. You have a readiness potential that goes on for at least a second. Now we dont't have to take this long time to make up our mind to get the movement going. What Libet finds out is that about 200 msec before the onset of the movement is the time when the subjects are first conscious of wishing to make the movement. With the readiness potential the subject is moving at random, out of the blue. But when does he know he is moving? That's what Libet has tried to analyze. And if so, what went on before W? We could ask is it pre-conscious or what is it?

I now go back to the recording of the readiness potential. You do it by taking say 700 traces for averaging. So I put up the hypothesis that there are all the time all kinds of slow waves going on in the cerebral cortex and these involve activities of neurons. And the subject, when he is cogitating to move or not to move, is subconsciously aware of the electrical situation in the part of the brain involved in the movement, the supplementary motor area. He is deciding to move in relationship to some wave form. It is possible that it's easier to initiate the movement during the rising negativity. The result is that when you add up these background waves, as long as there is some slight tendency for the subject to move when the wave is going negative, then you will get this part of the wave recorded before the authentic readiness potential, so the initial part of the negative potential depends on the method of recording. This hypothesis does involve being subconsciously aware of the brain activities in appropriate areas, but I think that this is true. How do we ever get any sensations or perceptions? It is because activities in the brain are recorded in the mind.

LIBET

First, there were 40 trials involved in our case and not several hundred,

but still Professor Eccles' point is valid in a sense. We have no proof of the inner workings of this machinery, but I think that if we adopt your viewpoint that the conscious initiation is waiting for the optimum negative wave to appear, then you're faced with additional *ad hoc* difficulties. That is, the consciousness would have to be monitoring the electrical activity to do this at the right time, and you would really then not even have free initiation of the voluntary act because you couldn't do it at any time you chose. It would have to wait until a peak of a slow wave appeared, whereas what we are proposing is, I think, less fraught with *ad hoc* assumptions.

ECCLES

It's the SMA which is triggering the movement, and this is true for the readiness potential. According to Deecke, SMA is the beginner and the largest performer in readiness potentials.

DEECKE

It is recorded over the supplementary motor areas. Over the frontal central mid-line, there is the earliest beginning of the readiness potential, and only later does it come over the motor cortex. What you just said here has already been measured. If you measure the cortical DC component with a DC amplifier, you find these fluctuations, and it could well be that some selection is made by the voluntary subject to move at these spots. For instance, we investigated the readiness potential on a single trial level and it was found that there is a certain proportion where it goes up, and a certain proportion where it goes down. Only the average makes it go negative. Goodman and Bauer in Vienna measured the spontaneous fluctuations of the cortical DC level and were measuring an inner psychological task. They found that the performance was better when the subject was on a negative slow wave than when he was on a positive slow wave.

MOUNTCASTLE

You have struck a memory chord with me. There is an old experiment by James Lacey, in which he showed that the preferential moment for emission of activities from the cortex leading to a conditioned response was the negative component of the EEG.

SINGER

There is a very similar example from the sensory systems. If one triggers the presentation of the sensory stimulus with the EEG that is recorded from the occipital cortex, there is a very clear dependence of the detection probability on the phase of the EEG. So stimuli presented during the negativity are much more likely to be perceived.

ECCLES

Thank you. So there is quite a bit of evidence on this. It doesn't eliminate free will. It just means that you tend to choose on a rising phase, subconsciously.

ANDERSEN

I must say that I have some difficulty with the slow waves because clearly what we have here is a composite activity of hundreds, in fact several thousands of cells. So if we reduce the number of cells we are observing by increasing our sensitivity of the recording, we are probably going to get less coherence, less DC shift, than you have with these very, very gross recordings. So I think we have to distinguish very much between the ensemble and the individual.

ECCLES

There is no point in talking about the individual cell with these experiments. Millions of cells are involved in these waves in the SMA and in the decision making. These cells are linked together, as it were, and the recordings by Per Roland in intentional states give us a feeling of this. He records the SMA when there is no movement, and millions of cells are involved in what he records.

ANDERSEN

But are you arguing then that, in order to make this simple movement that Ben Libet starts with, you have to recruit millions of pyramidal cells?

ECCLES

Of course.

ROLAND

I'd rather like to turn the discussion to include also what we heard this morning. Several of the speakers have been concerned with how long a time it takes to perceive something or how long it takes for a conscious perception. Professor Baumgartner stated that a percept is really clear around 40 milliseconds after the first activity appears in the visual cortex, and he argued that it was impossible for the prefrontal cortex to be involved. I don't think so. I think that the signals arrive in the prefrontal cortex around 35-40 milliseconds after they appear primarily in the visual cortex. I would also like to address a general question to the speakers: Exactly what is the role of the prefrontal cortex in awareness of percepts and stimuli? I think the neural basis of awareness and perceiving is a traffic of impulses going back and forth between the prefrontal cortex and the visual association cortex if there is visual perception going on, or between the auditory association cortex and other parts of the prefrontal cortex if auditory perception goes on, or between the somatosensory association cortex and still other parts of the prefrontal cortex when somatosensory perception goes on.

DESMEDT

In this question of the time it takes to make a conscious decision the somatosensory evoked potentials can help in answering. You know the time when signals get to the cortex — that's 20 milliseconds from the fingers. You know the time when the subject is taking the conscious decision about it when it is a target, and that is about 200 milliseconds, so it takes 180 milliseconds of cortical time. And if you take into account about 1 millisecond per synapse and the time it takes to travel along cortico-cortical fibres to involve not only the parietal (ipsilateral), but also the prefrontal regions, I think you have time for maybe 100 or 150 at most, steps in the sequence. This is why presumably you need to have so many parallel pathways involved in the sequence. But it's still quite a short time to reach consciousness, and I think it's much shorter than the 500 milliseconds of Libet's cortical stimulation.

GOLDMAN-RAKIC

I'd like to ask Per Roland a question. In 1985 you published a paper on the frontal lobe in which you said that you had many different tests which you gave your subjects, having in common some activation of a prefrontal cortical area which I think you called medial superior. It's not clear to me what really is the basic finding with respect to activation of prefrontal cortex.

ROLAND

That prefrontal cortex was clearly activated. It is further rostrally than the SMA on the prefrontal gyrus. This is an activation that we almost always see, no matter what tasks we tell the subjects to do, and we attribute that to the fact that the subjects get an instruction which they have to follow subsequently when the actual stimulus comes.

All kinds of detection, perception and discrimination, whether they be visual, auditory or somatosensory, engage multiple active fields in the prefrontal cortex. They are mainly located in the superior-lateral part of the prefrontal cortex. If there are any common sites — we don't know if there is an exact overlap because there are individual differences, but we suspect that in the anterior part of the mid-frontal gyrus there is a zone that is activated both in somatosensory and visual discrimination, but perhaps not in auditory. So the picture is complex, but the rule is that the prefrontal cortex is activated whenever there is perception, discrimination or detection.

GOLDMAN-RAKIC

I would like to ask Ben if in his task there is a delay between the subject's perception of when he first wishes to move and then his report, so that on top of the expression of conscious experience, you also have a memory component to the task. The subject is being asked to do a memory delayed response task. Isn't there a memory component to your test?

LIBET

There's always a memory component in any introspective report. It's unavoidable, but in subjects who don't have memory deficiencies a delay of a few seconds is normally not going to make any trouble.

GOLDMAN-RAKIC

It wasn't a criticism. It was merely to wonder whether there is some relationship between the conscious experience and the ability to hold information in mind during a delay, whether they are dissociable or not.

LIBET

As I say, it's not a delayed reaction time at all.

PARALLEL AND HIERARCHICAL PROCESSING IN THE MOTOR SYSTEM

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> There are undoubtedly animals that perform more forceful, more precise, even more delicate movements than those of the human being; human motor acts are, however, uncomparably superior to those of animals with respect to their richness and diversity.
>
> VON MONAKOW, 1911

Quite obviously, hierarchies can mean different things in the neuroscientific literature. Relatively loosely defined in neurology, the word acquired new, more stringent meaning in computer science and in its application to neuronal network models. In the first part, I will attempt to review the historical origin of the hierarchy concept as it emerged towards the end of the 19th century and how the concept was applied to clinical neurology and to anatomical neuronal structures. The latter field concerns mainly the issue of serial versus parallel processing. I will also briefly review newer ideas which arose from single unit studies in the cerebral cortex leading to the concept of nerve cell populations in "higher" brain structures encoding emergent complex features. In its extreme, this led to the now discredited notion of "pontifical" neurons or "grandmother" cells (Hubel, 1988). In a second part, I wish to summarize some anatomical and physiological features of sensory and motor cortical areas of primates that, I believe, reveal both hierarchical and parallel processing.

I. The Development of Ideas on Neuronal Hierarchies

Jackson's Doctrines and His Criteria for Hierarchical Classification (Jackson, 1932).

The concept of hierarchy as an organizational principle of the brain was introduced by Hughlings Jackson in the aftermath of Spencer's and Darwin's theories on evolution and dissolution in biology (Richards, 1987). The ideas were attractive for clinical neurology because in the process of "dissolution" or "taking to pieces" by "destroying lesions", when evolutionary new structures are damaged by disease, one can observe that the behavior is placed under the rule of the lower structures. In Jackson's words: "to undergo dissolution is to be reduced to a lower level of evolution". In its more naive form, it resulted in the still widely used concept of the "humunculus" made up of "upper motor neurons" that, like a keyboard, govern the lower motor neurons. If we want to avoid a simplistic and absurd cascade-like or "pyramidal" interpretation of hierarchy, we need clearly defined criteria for classifying hierarchical levels. Jackson's criteria are not sharply defined and are sometimes expressed in a vocabulary which needs interpretation. In essence and in Jackson's words *dissolution* meant:

— loss of the least organized or retention of the more organized,

— loss of the most complex or retention of the less complex,

— loss of the most voluntary or retention of the more automatic.

It may be necessary to briefly consider the meaning of these terms. The *automatization criterion* is perhaps the best known, but in my opinion also the most problematic one. What Jackson may have had in mind was the automaticity of breathing, stepping, chewing. Modern neurophysiological work indeed proved that these performances are organized, in their basic form, at a low level of the neuraxis. But what about the automatization of complex motor acts when we practice them and when they become habits? We don't know whether Jackson thought that with practice the control of such habits is delegated from higher to lower structures. I don't think that there is enough evidence to suggest that this is so; some evidence in fact pleads against this notion. For example, cells of the motor cortex will continue to discharge in relation to very simple elbow movements in overtrained monkeys (e.g., Conrad *et al.*, 1977).

At first sight, the criterion of *organization* is also surprising: why should high-level controls be the least organized? Presumably, what

Jackson had in mind concerned the degrees of freedom. Fixed action patterns would be the "best organized" ones, resulting in "machine-like behaviour" to use Sherrington's expression. The least organized movements would thus be those showing a high flexibility, or those that are the least preorganized.

And then the criterion of *complexity*. In Jackson's terminology, evolution from the lowest to the highest level means "... passage from the least complex to the most complex". Complexity is primarily a matter of the number of neural elements and connections. At a low level, anatomically speaking at the spinal cord segment, the neural network concerned with hand movements has much fewer elements than the cortical network dedicated to this task. Complexity is less well defined in functional terms. It has probably also to do with the degree of freedoms with which, for instance, hand movements can be performed. A complex movement disorder of the hand would be one in which the hand can be moved for one act, say greeting, but not for another, say writing. Complexity thus includes the context or the plan of the purposeful behavioral act in which the hand is used. Jackson was referring to this principle when talking of "re-representations" of movements in the cerebral cortex.

Interesting is also Jackson's proposition that "higher centres" are "*unifying centres*". Presumably, this refers to Jackson's view that "the cortex is organized in terms of synergies". A concatenation of activity in many muscles is needed for a purposeful act which might involve eye, head, trunk and hand movements. The detailed implementations, what Jackson calls the "local affairs", would be delegated to the lower control levels which are "... thereby raised to much higher power".

Jackson's ideas, centered on the concept of dissolution, had a strong and world-wide impact on clinical neurology. For example, the concept of dissolution ("*Abbau der Funktionen*") became also central in the work of von Monakow (1914). This happened at a time when many new discoveries on structural relationships in the brain were made thanks to the availability of new histological techniques. These allowed for the first time a more precise correlation of the clinical deficits with the site of brain lesions. This coincidence contributed much to the hierarchic conceptualization in the neurological sciences (for a stimulating critique cf. Kelso and Tuller, 1981).

Attempts to Identify the Anatomical Structures in a Serial Schema of Motor Control Processes.

Lesions within the precentral motor strip, i.e., in the primary motor cortex (MI), result in the well-known paretic deficits. This is in contrast to the complex apraxic disorders observed following lesions outside the Rolandic cortex. Recognizing the oversimplification, one may say that the former deficit is one of movement execution, the latter one of movement programming (for example, inability to perform properly sequenced movements without loss of muscular strength or of the ability to perform individual components of a sequence). Jackson conjectured that the highest level of movement organization occupies cortical areas in front of the Rolandic cortex, whereas movement execution would be the task of primary motor cortex being thus at a middle level of the hierarchy. Subsequently Campbell (1905), who constructed the first cytoarchitectonic map of the human cortex, was of the opinion that the highest level occupies what he termed the "*Intermediate Precentral Cortex*" which roughly corresponds to the ensemble of premotor areas. To quote him: "I am of the opinion that this particular stretch of cortex is specially designed for the execution of complex movements in which consciousness or volition takes an active part". To Liepmann (1920) goes the credit for having systematized the various forms of apraxias with the underlying cortical substrates.

At about the same time, von Monakow (1914), in his treatise on brain localization, in which he extensively deals with motor disorders including apraxias and aphasias, also addressed the problem of cortical localization of motor cortical centers. Here is my free translation of his summary:

"One can envisage that a purposeful behavioural act is produced in successive, partly overlapping steps:

1. If we aim towards a given target, we first construct a *mental image*, or *plan*, on how we will reach this target. This hypothetical stage cannot yet be correlated with any anatomical structure — it has probably no sharply defined localization in the cortex.

2. The next step is a translation of this general plan into instructions for elemental movements which are chained together. At this stage the *prefocal areas* are called into action via associational impulses coming from the various cortical areas. We can now identify these areas, but the situation is complex. The activity is not confined to one particular island of

cortex, rather it includes a number of disjunctive areas in various constellations. These areas extend far beyond the Rolandic cortex.

3. Now follows the *focal activity* within the Rolandic motor cortex. It is always a variable combination of activated foci which depends on the body part to be moved, but also on the purpose of the movement. It is only during this phase that we have well-localized, i.e., focal activity.

4. The last step then concerns *corticofugal transmission* from the motor cortex to the subcortical and spinal motor centers and the final translation of this impulse traffic into muscular activity".

Thus, it might be concluded from the above that, at the beginning of this century, the idea of a sequential processing for the initiation of voluntary, purposeful movements was established. Interestingly, one can already envisage a differentiation within the highest levels, with cortical association areas (frontal and parietal) being superior to premotor areas (the "intermediate precentral cortex" of Campbell or the "prefocal areas" of von Monakow). The former were held responsible for the general movement plan ("ideation of movements", "*Bewegungsentwurf*"), the latter for more detailed information ("the kinetic formula") which then would be transmitted to the executive zone of the motor cortex.

This anatomical schema of movement initiation has been revived in recent years as refined anatomical tracing methods became available allowing a more precise identification of the pathways connecting cortical association areas with the motor cortex. The cortico-subcortico-cortical circuits have been summarized in the well-known diagrams of Kemp and Powell (1971) and of Allen and Tsukahara (1974). These anatomical diagrams are widely used as reference for classifying brain areas in the framework of a hierarchical and serial organization of movement initiation (e.g., Rolls, 1983). An excellent recent treatment of this general proposition of movement initiation can be found in the review of Paillard (1982), from which I borrowed the updated diagram of Allen and Tsukahara (Fig. 1).

A serial ordering in the process of movement initiation was also conceived by Lashley (1951), but in a more abstract and non-anatomical sense. The key idea is that the central system has in store the basic building bricks of movements ("*expressive elements*"). Temporal ordering is achieved by a *syntax* of the act which Lashley describes as a "habitual order mode of relating the expressive element (in time)". The appropriate "syntax" is called into action by the *determining tendency* or *set* (Fig. 2).

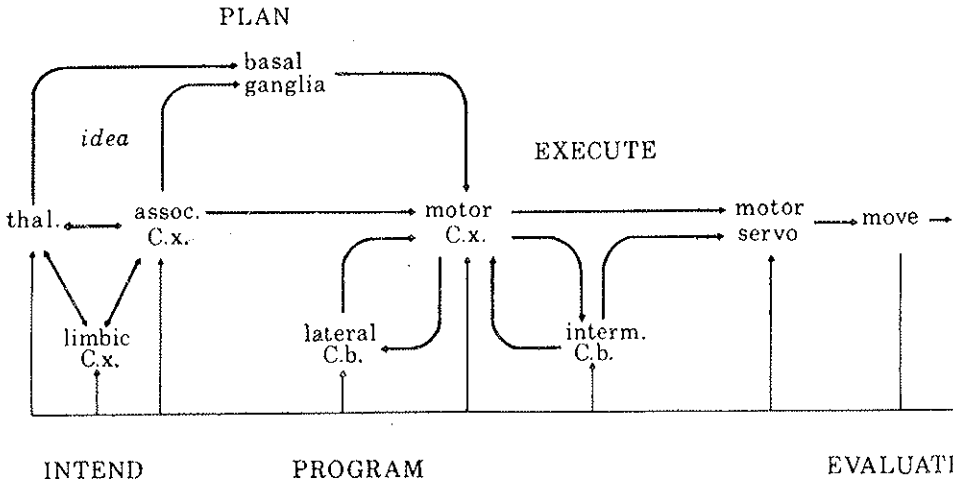

FIG. 1. Schematic representation of serial activation of brain structures in the course of movement initiation as proposed by Paillard. This is a revised and completed schema based on Allen and Tsukahara (1974). Note the association of anatomical structures to the phases of *Intention, Planning, Programming, Execution, Evaluation.* (From Paillard, 1982, with permission).

In Lashley's words: "This is the essential problem of serial order: the existence of *generalized schemata* of action which determine the sequence of specific acts...". Is there concrete evidence for the existence of "generalized schemata"? The question cannot be answered in physiological terms, but it is well known that the cerebellum has an important function in the correct timing of movements, perhaps also the supplementary motor cortex, as recently suggested by Deecke *et al.* (1985).

II. HIERARCHIC LEVELS OF CORTICAL AREAS

Multiplicity of Sensory Cortical Areas.

Recent detailed investigations of cortical sensory areas revealed a complexity of subareas for each modality that are richly interconnected. For example, "twenty areas are candidates for being largely or exclusively visual in function; 11 of these are demonstrably visual and have been identified with a reasonable degree of confidence" (Van Essen, 1985). Some of these areas have a full representation of the visual field (Hubel, 1987).

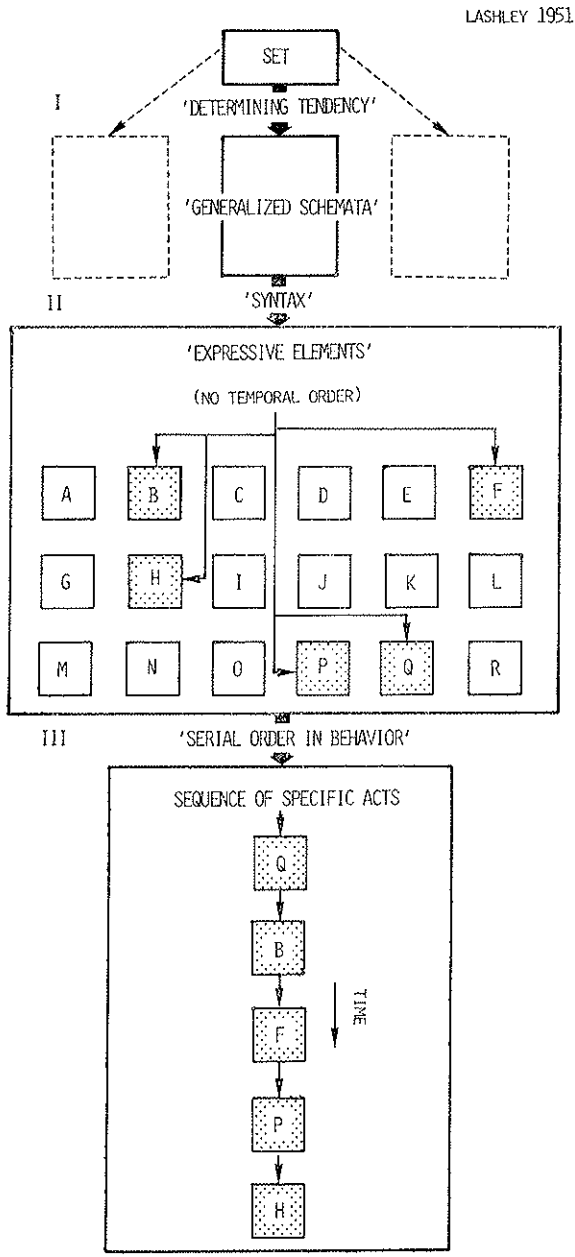

FIG. 2. Schematic representation of Lashley's ideas on *Serial Order in Behavior* (1951).

Most important in the current context is the observation that typically these visual areas have the tendency to be reciprocally interconnected. Interestingly, within an interconnecting pair of fiber systems, the terminations are often asymmetric. This is shown schematically in Fig. 3, taken from the work of Maunsell and van Essen (1983). It was proposed that the asymmetric distributions of cells of origin and of terminals reveals forward and feedback projections. Layer IV in the cortex is typically the

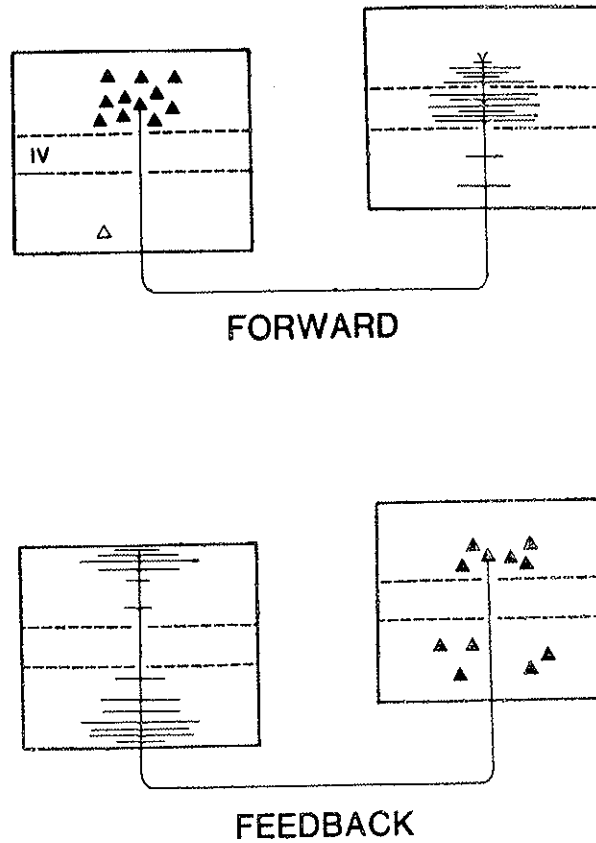

FIG. 3. Differential laminar distribution of neuronal cell bodies and terminals in feedforward and feedback pathways of visual cortical areas (Maunsell and Van Essen, 1983, with permission). According to this scheme and the anatomical results of Primrose and Strick (1985) in motor cortical areas, the primary motor cortex would have a feedforward projection to secondary (premotor) areas which, in turn, project back to the primary motor cortex.

recipient of specific ascending fiber systems. Therefore, the corticocortical fibers terminating in layer IV are considered to be also "ascending", i.e., feedforward, the target area becoming thus hierachically superior to the donor area. This hierarchic scheme, based on anatomical data, is still hypothetical. Some physiological properties are, however, in line with the hierarchical hypothesis in that receptive fields become larger and more complex in higher areas (Van Essen, 1985).

A hierarchic level may thus be defined by the ensemble of inputs and outputs which are common to a neuron population. In this respect, the visual areas are not homogeneous, rather it turns out that there are specifications in the cortical layers and in their intrinsic connectivity. The thalamic sources (from the magnocellular, parvocellular and interlaminar portions of the lateral geniculate nucleus) project to different strata in the visual area V1 and have separate cascaded projections within the cortex, thus determining the intra-areal hierarchic level. Again, this anatomical segregation appears to match a segregation of neurons with particular functional attributes. At least in a few situations, the orderly processing from thalamic nuclei to a cascade of intra-areal laminae appears to reflect the anatomical basis of functional transformations (leading to complex receptive field organizations, to orientation selectivity, to disparity selectivity, etc.). Even further transformations occur in visual areas outside the striate cortex with neuronal populations "recognizing" familiar objects and faces (Bruce *et al.*, 1981). The details of the circuits which lead to such transformations are, however, unknown or hypothetical and most likely depend on cooperative actions of distributed populations of neurons.

This recent combined anatomical and microelectrophysiological approach to reveal the step-by-step processing of visual information from the ascending inputs to the different layers of the visual cortex and the further area-to-area processing is still at its beginning, but nevertheless far ahead of the situation in motor cortical areas.

Sequential Processing in Other Cortical Areas.

In the *somatosensory system*, it was found that signals transmitted to area SI are further transmitted to SII and thence to insular and retroinsular areas (Friedman *et al.*, 1986). In accord with this, responses to cutaneous inputs were abolished in SII when SI was lesioned in the adult monkey (Pons *et al.*, 1988). In a brief note, Primrose and Strick (1985) reported on the pattern of connections in *motor cortical areas*. They also

found the reciprocal interconnections in motor areas to be asymmetrical with the primary motor cortex MI *feeding forward* to the premotor cortex, which in turn *feeds back* to MI. Given that the interpretation of the cortico-cortical connectivity, as revealed in visual areas, is correct and also applicable to motor areas, it would confirm that motor cortical areas too are hierarchically organized. Interestingly, the observed patterns of connections would be in line with the notion that the secondary somatosensory and motor areas are hierarchically superior to primary cortical areas. One has to realize that the hierarchization of cortical areas on the basis of cortico-cortical connections is an "ascending" one. In speculations about the hierarchic superior features of premotor areas, it was on the contrary assumed that the hierarchy is descending, i.e., that the hierarchically superior premotor areas "instruct" the motor cortex, being "*downstream*" to the former areas. I think that we touch here on a difficult, but crucial problem of defining hierarchic levels in sensory systems and in motor systems.

The problem of cortico-cortical relationships in the various motor areas clearly requires much more detailed investigation. Whatever we will learn in terms of hierarchic levels *between* motor cortical subareas, it is important to keep in mind the established fact that the connections are *not* unidirectional and that the simple unidirectional hierarchic view in the higher motor control centres does not apply.

Before returning to the motor cortical areas, it might be worthwhile to ask whether there are perhaps other criteria which may help to distinguish hierarchic levels of neuronal systems.

Emergence of Higher Properties by Convergence and Divergence.

Anatomically speaking, axonal branching and synaptic convergence on the somadendritic membranes is one of the most striking properties of all neuronal systems, sensory as well as motor. Intuitively, it seems obvious that such divergent and convergent connections are at the root of emergent features in the central nervous system. Emergence is, by definition, more than summation: Accordingly, it is hardly possible to explain emergent complex neuronal features by analyzing features of "lower" neurons converging to the complex neuron. The best-known complex and emergent encoding features of single neurons are those of the visual cortical areas alluded to above. They include features that contribute to stereopsis, color, form, movement, and even face perception. In recent years, much

progress has been achieved in unravelling the specific functions of visual areas, subserved by multiple afferent streams of visual information. Although there is clear evidence for a considerable *division of labor*, there are also many indications that visual processing in the various areas is not independent. Thus, there are areal interconnections providing opportunities for concurrent processing by convergence and divergence. The situation in visual areas has recently been reviewed by DeJoe and van Essen (1988), who came to the following conclusion, which might well be relevant also for the multiple motor cortical areas: "... one should not anticipate... a simple one-to-one relationship between a particular stream and a particular computational strategy. Rather, it seems likely that some strategies will be handled in parallel by more than one stream or will involve significant crossover between streams".

Emergent properties of sensory neurons by convergence find their counterpart in emergent features of projection neurons in motor centers by virtue of their divergent collateralization (Evarts, 1984). A focal excitation in the motor cortex inevitably will be widely distributed via collateral transmission to spinal as well as to supraspinal targets (Wiesendanger, 1986a).

Is There Evidence for Parallel Processing and for Division of Labor in Motor Cortical Areas?

The multiplicity of visual areas is paralleled by a multiplicity of motor areas in the frontal cortex, although classically only a few areas were identified: the primary motor cortex (MI), the premotor cortex (PMC), and the supplementary motor area (SMA). The two latter areas were also termed secondary motor areas (cf. Wiesendanger, 1981) as opposed to the primary motor cortex, considered to constitute the major control area of the motor apparatus. More recent hodological investigations, however, led to a more detailed parcellation of motor areas, a situation which might turn out to be more akin to that of visual areas (Wiesendanger and Wise, 1989). The motor areas, like the visual areas, are heavily interconnected, with MI not only receiving fibres from secondary areas, but also projecting to these areas as mentioned above. A somatotopic organization, clearly demonstrable with microstimulation in MI, is also maintained in the SMA (Mitz and Wise, 1987), although the topological efferent microzones appear to be more intermingled in the SMA (Macpherson *et al.*, 1982; Hummelsheim *et al.*, 1986). The

PMC, at least in its posterior portion near the arcuate sulcus, contains also corticospinal neurones, and microstimulation effects may be obtained, usually with higher thresholds than in MI. There is also evidence for somatotopy in the cortico-cortical connections between primary and secondary motor areas (Muakkassa and Strick, 1979), although these relations are presumably not organized in a 1:1 fashion, allowing for convergence and divergence.

Single unit recordings in somatotopically appropriate locations of MI in trained monkeys revealed cellular activity which was usually tightly related with the motor task. This work has been well reviewed (e.g., Fetz, 1981; Evarts *et al.*, 1984; Hepp-Reymond, 1988), and it may suffice here to recall that the technique of spike-triggered averaging (Fetz and Cheney, 1987; Lemon *et al.*, 1986) clearly demonstrates the direct transmission to sets of motoneurons. Moreover, it was shown that the activity of MI neurons may encode specific parameters of the performed movement, such as movement direction (Georgopoulos, 1986). It is, however, equally important to note that activity changes in MI have often been reported to occur also in the preparatory period "while the monkey waits" (Evarts and Tanji, 1974; Lecas *et al.*, 1986).

The emphasis of current reports on *secondary motor areas* concerns observations of relatively complex relationships of cellular activity with movements. Particularly revealing examples are those from the SMA reported by Tanji and coworkers (Tanji and Kurata, 1983) which all indicate that many neurons encode aspects of movement preparation rather than of the movement per se, such as cue signals or preparatory set. Most recently, Tanji *et al.* (1988) reported on SMA cells which had specific relationships with contralateral, ipsilateral or bilateral finger movements. Such neurons discharged, for example, exclusively in association with bilateral finger movements, but not when the same movements were performed either with the right or with the left hand. This type of neurons therefore appear to encode higher order commands, as for instance, in a coordinated bimanual task. Pointing in the same direction are recent results reported by Mann *et al.* (1988), who discovered SMA neurons covarying effector-independently with either goal-directed saccades or with goal-directed arm movements.

Gentilucci *et al.* (1988) and Rizzolatti *et al.* (1988) recorded from PMC neurons from monkeys performing natural behavioral acts and also found relations between the neuronal activity and the complex movement sequence. Such neurons were classified descriptively as "bringing-

to-the-mouth-neurons", "grasping-with-the-hand-neurons", "precision-grip-neurons", etc., the interpretation being that "... all together these neurons form a vocabulary where proximal and distal movements necessary for reaching, grasping, holding and bringing food to the mouth are represented".

In our own investigations on SMA neurons from monkeys performing arm movements in a choice-reaction paradigm (Wiesendanger *et al.*, 1987; Hyland *et al.*, in press), we could confirm the presence of neurons with activity changes during the waiting period (interval between warning signal and go signal). This activity may have been associated with various aspects of preparation, including postural preparation as suggested by concomitant electromyographic changes in some of the proximal muscles. However, we were struck by the surprisingly large population of SMA neurons which had properties indistinguishable from those of MI neurons. Out of 431 task-related SMA neurons, 67% were classified as "short-lead neurons" because they displayed a burst of activity preceding movement onset, often with shifts towards longer response latencies to the go-signal as the reaction time increased, thus demonstrating a clear relation with the executed movement. These neurons may still transmit instructions to MI. However, we obtained no evidence for an earlier involvement of the SMA cells in the task when compared with a similar population of MI neurons recorded in the same animal under the same conditions, and the histograms of lead-times of MI and neurons were completely overlapping.

Taken together with the well-established facts that the SMA has direct connections with the spinal cord and that microstimulation effects were obtained from this area, we come to the conclusion that the parallel model of the SMA, as proposed long ago by Woolsey *et al.* (1952) still holds. Of course, this does in no way exclude the hierarchical model as it emerged particularly from neurological studies on the SMA of the human brain (see Wiesendanger, 1986b), and from single unit recordings in performing monkeys as briefly discussed above.

Assuming that at least in part there is parallel processing in the various subfields of motor cortical areas, the question naturally arises whether there is a division of labor among these fields. The search for area-specific attributes is lagging far behind that in visual cortical areas. The PMC has a rich supply from teleceptive (Godschalk *et al.*, 1981; Weinrich *et al.*, 1984) as well as somatosensory afferent sources (Rizzolatti *et al.*, 1981). It was therefore suggested that the PMC might be

"specialized" for sensory, and especially visually guided movements (see Wise, 1984). On the other hand, clinical observations of patients with SMA lesions suggested that the SMA might be specialized for self-initiated movements (cf. review by Goldberg, 1985). However, recent single unit studies, in which the involvement of PMC and SMA neurons was compared, hardly supported this notion (Okano and Tanji, 1987). Our own studies revealed a preponderance of proprioceptive inputs to single neurons of the SMA whereas the PMC neurons were more often responding to light cutaneous stimuli (Hummelsheim *et al.*, 1988). The reported difficulty of monkeys with SMA lesions to perform a self-paced goal-directed movement in the dark (Passingham, 1987), together with the demonstration of proprioceptive inputs to the SMA, may be taken to suggest that the SMA is important for movements guided by proprioceptive signals. It is also noteworthy that the SMA is an important target of basal ganglia outflow via thalamus (Schell and Strick, 1984; Wiesendanger and Wiesendanger, 1985) whereas the PMC appears to be more dominated by cerebellar outflow (Schell and Strick, 1984).

The functional role of two further motor regions in the cingulate sulcus that are occupied by corticospinal neurons, is virtually unknown. As suggested by Hutchins *et al.* (1988), their proximity to the cingulate cortex and thus to the limbic system points to a role in transmitting signals from the limbic system to the spinal cord via their corticospinal projections. Evidently, present knowledge about areal specializations is still scarce, but so far not incompatible with the concept of division of labor.

Concluding Remarks

The problem was posed whether hierarchic organization, a cornerstone in neurological thinking, holds for those brain centers involved in movement control. Not long ago, the question was hardly asked and the model of hierarchic organization became well established in the 100 years of modern neurology. I have attempted to briefly sketch the story about hierarchies in the brain which had its root in theories of evolution and in the concept of "dissolution". I believe that if hierarchies are seen mainly as levels of increasing complexity and of increasing abstraction of the sensory representation and of the motor commands, then the principle of hierarchical organization might still be a fruitful concept. As it became apparent that populations of single cortical neurons may be specialized

to extract relatively complex features of the visually perceived world, time has come to search for similar complex and abstract features of "motor commands" (a term used for lack of a better one). A few insights have been gained in recent years, and were briefly discussed above, which point in this direction, such as the population coding of movement direction, independently of how and with which effectors the goal is reached. Such neuronal codes would clearly represent higher level commands with higher information content, as compared to the lower level motoneuronal commands.

On the other hand, it was precisely the single unit approach to investigate the functional attributes of cortical cells, together with the explosion of new anatomical knowledge about cortico-cortical connectivity, which led to the somewhat different view of "parallel distributed processing", which was first clearly expounded by Mountcastle (e.g., Edelman and Mountcastle, 1978) on the basis of his extensive work on the "modular construction" in the somatosensory and associational cortical areas. It is rather obvious that perception or movement plans are not encoded in single sets of neurons but in widely distributed multiple sets, each encoding different aspects.

Progress in unravelling the "language" of cortical cells in motor areas has been much slower than in the visual areas. But I wish to emphasize that more and more evidence is accumulating which indicates that a similar modular organization exists in these motor fields as in sensory fields, that a number of subfields address directly the spinal cord, and that there are massive reciprocal cortical interconnections among the fields. There is thus ground to believe that within the cortical motor areas much of the processing occurs in parallel as well as serially.

Theoretical approaches in studies of neural networks has become very popular. Provided that they rely on reasonably realistic anatomy and physiology, they may hopefully provide some impetus and help for understanding at least the basic principles of how the cerebral cortex is organizing and controlling movements (see for example Kawato *et al.*, 1987).

If the tenet today is that multiple cortical areas have developed to allow for division of labor, it might be appropriate to remember that it was Spencer (cf. Richards, 1987) who proposed, more than 100 years ago, that division of labor is a leading organizational principle in brain evolution!

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DISCUSSION

ZEKI

I have to say that I am surprised to hear that Jackson was plugging the idea of parallel pathways, because I don't think he was. I think Jackson made tremendous contributions which are recognized by visual people, such as the idea of the representation of movement as opposed to body parts, but the idea of parallel pathways is not a part of Jackson's work. It was very strictly a question of hierarchies.

I would like to question your last quotation of streams. I think you have to be quite careful about the word "stream". Stream as latterly employed in the visual system (and I think your quote was from the visual system), seems to include two isolated and serially organized areas starting in V1. One of them goes up to the parietal cortex and the other to the inferior temporal cortex. I think everything about the anatomy and the physiology suggests that you don't have these isolated streams.

WIESENDANGER

Well, you may be quite right, that the situation is different, but not totally different because you have all the incoming streams with the loops through the basal ganglia and the striatal nuclei which are separated and seem to implicate different territories in the thalamus and also in the cortex.

ROLAND

I would like to take you up on one of your last comments. You said set cells are found everywhere in the cortex; I suppose you meant the prefrontal cortex. I agree that set cells are a very poor description of the behaviour of a cell because it doesn't tell us exactly what the cell is doing. Maybe a suggestion could come from the work of Georgopoulos, who in the primary motor cortex found the population vector coding of direct goal movements, movements directed to a specific goal. Has anybody to your knowledge, and have you by your own studies found any general population vector coding in the SMA, because that I think would give us a hint of what the SMA is really doing.

WIESENDANGER

I haven't done it, and I think nobody else so far has done it. I agree that this approach that Georgopoulos has taken is very valuable.

JONES

I want to revert to something that Semir Zeki raised, and that's the question of applying principles which are emerging from the visual cortex organization. It's very tempting, I think, in view of the clearcut streaming and integration and segregation and all of these various principles that Semir raised yesterday, to try to impose these on other areas of the cortex. Now I think probably these principles are going to be present there, but not necessarily in terms of areal to areal sequential processing integration.

It's not yet clear to me that many of these areas which are being described in the motor and pre-motor areas are necessarily entities in their own right, as opposed to subdivisions of some wider entity, and I think this has to yet be analyzed. If you look at the data that have been used to identify these separate subdivisions, they depend very much on indirect arguments, principally anatomical. The reason for saying this is something which you mentioned in your answer to one of the previous questions, and that is, that coming into these territories there are major afferent streams which are really coming from separate territories which are segregated from one another. It's clear that there are portions of the motor, pre-motor area which are dominated by cerebellum and there are other territories which are dominated by basal ganglia. There really isn't any convergence of those two, either at thalamic or at cortical levels. Any convergence that occurs has to be by cortico-cortical arrangement. So it's possible, you see, that you have wide territories, one cerebellum, one basal ganglia only, with functional subdivisions within that and it's in those that we may have to look for parallels to the visual system.

ZEKI

I agree very much with what Ted Jones is saying, but I still have misgivings. For example there are in the somatosensory cortex regions where there are one-way connections. So that is different. The problem of convergence is very similar in the visual cortex to what it is in the motor cortex, but I am objecting that you force all your thinking into a sort of mould there. You say stream and you think the problem is solved, but it isn't. The anatomy is showing us that there are multiple levels at which these areas are connected with each other.

DEECKE

Our data suggest, I think very clearly, that the SMA is upstream in the temporal chain prior to voluntary movement. I think it's a nice term to use, upstream. We found out only recently that especially the SMA is active when it comes to bimanual coordination. When you have movements of both hands and they have to be coordinated in the temporal manner, we find the highest activation over the frontal central mid-line, including the SMA.

WIESENDANGER

I accept the one argument that you are recording in man with all the advantages, and also the disadvantages that you can't really localize the source of your potentials. I think that's one difficulty. But I stress that the human brain is not the same as the monkey brain.

LIBET

My point really follows up on what's just been said, but I wanted to make the additional caution about the monkey. In order to be induced to perform the act, the monkey is given a reward at the end of it. So the paradigm that you usually worked with is that the monkey is supposed to delay his response after a certain signal in which he is presumably planning to act and then he is rewarded. But the fact is that he learns what the process is and he almost instantly responds or acts at the end of the proper delay, so it becomes more like a delayed reaction time experiment than a really voluntary self-paced movement.

WIESENDANGER

Don't you think that if somebody has to do this movement 200 times he comes to a sort of rhythm which might be very similar to what the monkey is doing?

LIBET

I agree. We used only 40 trials and we made each one independent of the other so that the subjects did not get into that routine.

GOLDMAN-RAKIC

I thought that it was very interesting that Wise found that lead time preceded motor cortex, and you say that in SMA the lead time did not precede that of the motor cortex. Could it be that you are looking in the wrong part of the SMA for the particular motor act?

DESMEDT

When you see the histograms of large numbers of units, some of them preceding the motor cortex and some not, as in the Wise histograms, these are monkeys which are perhaps overtrained and do not do things so quickly or efficiently as humans to whom you give an instruction and they just do it. So by pooling so many units, are you not blurring any relationship that could be present? In other words would it not be nice to put the monkey separately where you have a very big, or very clear antecedent activity, in SMA for example, and try to focus on the reason why these differences occur?

WIESENDANGER

That is precisely what I said before. We did that, having smaller subgroups, and nevertheless we didn't find that.

ECCLES

I'll just ask Mario Wiesendanger one question. Why didn't you mention the work of Roland published in 1980, where he very clearly showed that in the movement task, when the subject was not moving but only thinking of the movements, the SMA came up and not the motor cortex?

WIESENDANGER

I am glad you bring that up because I know I should have mentioned all this work which I really do admire. The cerebral blood flow work has been of tremendous influence. When you just mentally prepare, you have something which may include SMA, and probably also a further area.

ROLAND

We did actually do electrical recordings from the human SMA in Bordeaux.

The activation of the SMA in individual patients was found to give characteristic responses preceding the motor cortex. So there is electrophysiological confirmation that this blood flow really covered the SMA and this was done by a statistical system, so I think there can be no discussion whatsoever that we could have been outside the SMA with our blood flow studies, because it was evaluated with three independent methods.

BAUMGARTNER

Are there any efforts to define within the motor domain some kind of motor modalities different from these self-induced and reaction type movements? For example, I could conceive that space controlled movement is controlled by the input from sensory systems, by the input from acoustics also. Are there any ideas about it?

WIESENDANGER

Very generally speaking, we have to learn the rules by which some types of movement are performed, be it a grasping movement or a bimanual movement. Then we could try to see whether we have some sort of encoding in cells which would correspond to these rules, but that's a very general answer.

CREUTZFELDT

It appears that also the motor areas are organized in a parallel manner. All the descending paths go directly or indirectly to the spinal motor control systems, though not directly to the motor neurons. The question is, what the supplementary motor area is actually contributing to this cooperative movement control to which many areas contribute? Neurologists don't usually come out with very clear statements. After isolated lesions or surgical removal, mutism is described, and lack of movement, but these defects wear off after a while.

DEECKE

Maybe I can answer this because we went through 30,000 CT scans and picked out patients who had unilateral lesions of the SMA and we found 16 with whom we made experiments. First we tried only simple movements and we found no difference. They could perform these very well, but with complicated movements, especially with bimanual finger tapping, they had real

trouble in the sense that we call a motor disrhythmia. They are unable to make different rhythms with different hands. They always fall back into simultaneity.

POECK

A short word of caution. These two examples that you gave I would not have chosen from a clinical point of view because anterior cerebral artery infarction involves more than SMA, and the degree of damage to SMA that you have is difficult to define on CT scan.

SINGER

It appears to me that you run into problems similar to those we ran into trying to analyze sensory systems. I guess that the problems of how movements, the sequential programmes, are generated are by no means simpler than the problem of invariant pattern recognition. Now we got completely stuck when we tried to understand from single unit recording what these neurons were actually doing in the perceptual context. The real new development in our field came when there was a large theoretical background emerging from the basic problem of pattern recognition. What operations do you have to analyze? I miss in the field of motor control this theoretical overlay that would make precise predictions of what sort of coding you might be finding for bundles of neurons.

ZEKI

I'm going to take issue with Wolf Singer. You are of course quite right in what you say, but the visual people have not been so great, because where is the theory that has been applied, except for colour vision which is rather special? Because you were talking about pattern, where has the theory been applied to pattern recognition in the form of specific cells and that has given you a good answer in terms of pattern invariants? Where is it?

Actually, I want to praise the motor people because Jackson pointed out in 1870 that movement and movement alone can be represented; and we visual people until the past five or six years have been blindly going around with the idea that it is the visual field that's represented in the cortex. That's the most absurd notion. It is an activity that is represented in the cortex.

SENSORY CONTROL OF HAND MOVEMENTS AND THE ACQUISITION OF MOTOR SKILLS

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The refinement in the use of the hand as a sense organ and for skillful manipulation has played a major role in human development. Although manual activities seem to be easily accessible, it is astonishing how little is known about the principles of neural control underlying the natural use of the hand. This is mainly due to technical limitations in the recording of unrestricted movements. Only recently has it become possible to record human motor behaviour in an almost unrestricted way. This article will concentrate on some experiments on sensory-motor processes during the performance of natural hand and finger movements. It will focus on the sensory control of such movements and on its role in the acquisition of motor skills.

Visual Control of Hand Movements.

For the visual system Julesz *et al.* [8] forwarded a hypothesis that there are two major categories in the processing of sensory information: focal and preattentive vision. Focal vision implies the foveal analysis of detail, whereas preattentive vision allows the immediate recognition of a picture at one glance. It is not known whether these two different sensory control modes are linked to different motor behaviours. Regarding eye-hand interaction and the visual control of hand movements, the eye seems well equipped to match its velocity to that of the moving hand, in order to provide precise sensory control. It has, however, been shown that

ocular pursuit is limited to a narrow frequency range, so that hand movements faster than 2 Hz cannot be followed by the eye (Leist *et al.* [11]; Mather and Lackner [12]; Van Noorden and Mackensen [14]).

Fig. 1 shows an experiment in which the subject pursued the tip of a pointer during self-paced arm-hand movements, and drove the lever back and forth at increasing frequencies until he had reached the limit of his ability. At low frequencies the eyes pursued the target smoothly, but with faster arm movements the ocular pursuit became smaller, saccades became larger, and at rates above 2 Hz the eyes stopped moving entirely, although the hand and arm continued to move sinusoidally up to about 5 Hz. There were only minor differences in amplitude of the hand-arm movement when the eye stopped tracking and became fixated. The limits of ocular pursuit cannot be due to mechanical constraints because the vestibulo-ocular reflex is capable of driving the eyes at frequencies above 4 Hz and the saccadic system is capable of driving the eyes even faster (Atkins and Bender [1]). It has been proposed (Leist *et al.* [11]) that the limitation of the pursuit mechanism reflects the temporal demands for the central processing of detailed visual information. The processing time for preattentive sensory control is shorter so that it can remain operative during faster motor performances. For eye-hand interaction this implies that the precise foveal information about the moving hand can only be provided by ocular pursuit. Since visually induced pursuit eye movements are rate limited, many natural manual skills that are performed at higher frequencies cannot be pursued visually so that they must employ a non-foveal visual control mode. When the hand moves faster, the eye

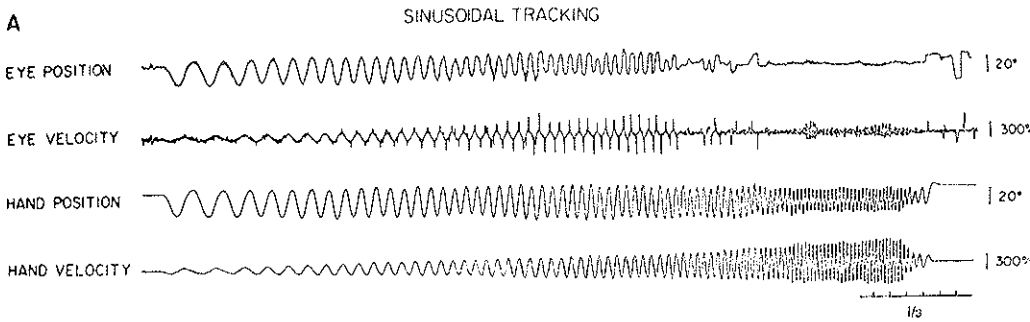

FIG. 1. Ocular pursuit (top two traces) of a target moved sinusoidally by the hand (bottom two traces). Modified from Leist *et al.*, 1987.

monitors the ongoing manual activities while fixated, so that motion is perceived largely via the retinal periphery. Such movements are not performed blind but are monitored by the motion-sensitive parafoveal retina. This is the case in everyday activities like handwriting where the eye is fixated while a word is written. The sensory control is nevertheless precise enough to enable the writer to keep to the lines. Such sensory monitoring obviously represents a preattentive control mode. It is important for the further consideration of sensory-motor processing that the change in strategy of sensory control apparently associated with the different types of eye movements makes it possible to draw inferences about the sensory control mode of manual activities from eye movement recordings.

The Temporal Properties of Natural Hand and Finger Movements.

It is not possible to extrapolate from the properties of ocular pursuit on eye-hand interaction before knowing more about the temporal properties of natural hand and finger movements. Kunesch *et al.* [9] have examined a wide range of unrestricted natural manual activities by means of an opto-electronic two-camera system utilizing light-emitting diodes. A set of seven natural hand movements was recorded from 20 healthy volunteers. Fig. 2 shows movement trajectories for the scanning thumb and index finger during exploration of a cube. It appears that movement trajectories are restricted to a narrow work space, and that the same path was never repeated. The temporal profile of the movement along the longitudinal direction of the scanning fingers is shown below, and reveals the typical repetitive sinusoidal movement pattern. Spectral analysis revealed distinct frequency peaks ranging from 0.78 to 1.56 Hz for those tasks employing object exploration, and a similar frequency range for those employing recognition of surface texture. As shown in fig. 3, pencil shading, handwriting and fast repetitive tapping movements, which were taken as examples of learned automized motor tasks are not exploratory in nature, are usually performed at peak frequencies between 4 and 7 Hz.

To our surprise this selection of natural hand movements performed by 20 volunteers did not show a broad frequency distribution across the frequency range, but did show a clear bimodal distribution with two narrow frequency groups. Although manual activities can be deliberately performed at any possible frequency, their natural performance falls into these two distinct groups. The low frequency peak between 1 and 2 Hz comprised those finger movements that were performed during tactile

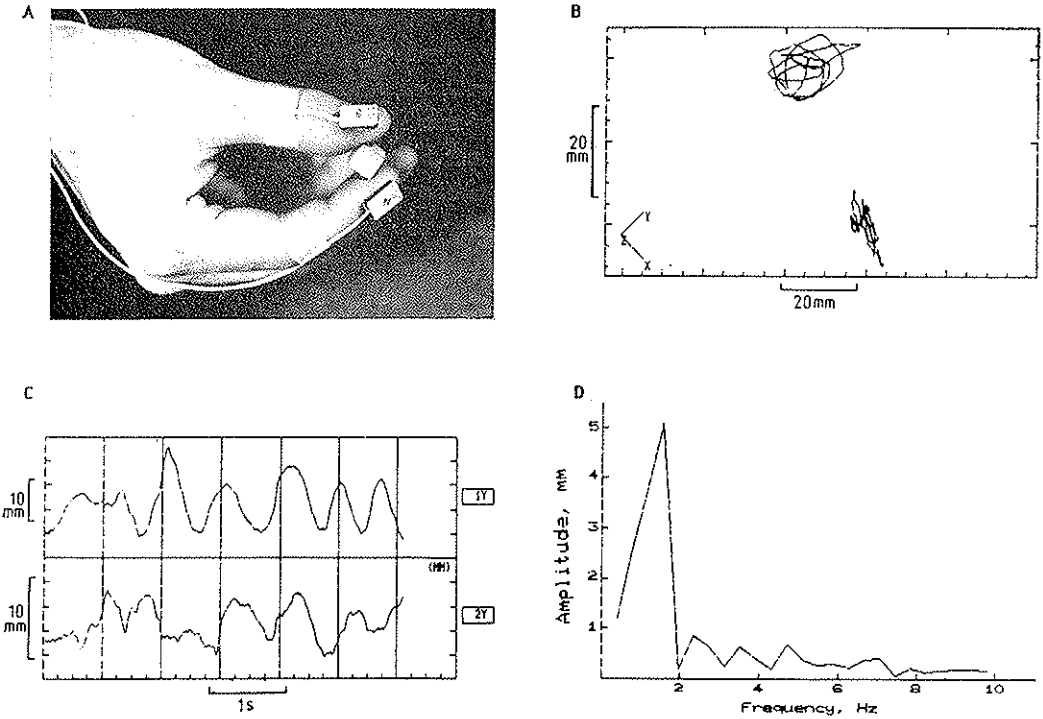

FIG. 2. LED placement at the fingers is shown in A, the spatial trajectories during exploration of a cube as viewed from the front in B, the the temporal profile of the movements in the longitudinal direction of the thumb and index finger in C, and their spectral distribution in D. (From Kunesch *et al.*, 1989).

exploration tasks. They correspond to the intrinsic hand movements as defined by Elliott and Conolly [3], whereas the extrinsic movements represented by the higher frequency peak have different behavioural goals. In contrast to the exploratory finger movements clustered in the low frequency range, these were movements of the hand or of a prehended object as a whole.

Evidence has been provided (Kunesch *et al.* [9]) that the restriction of tactile exploratory finger movements to the low frequency range below 2 Hz is due to the time required for sensory processing. Recordings from single mechanoreceptive afferents and calculations of their receptor densities indicated that the digital scan velocities have to match the

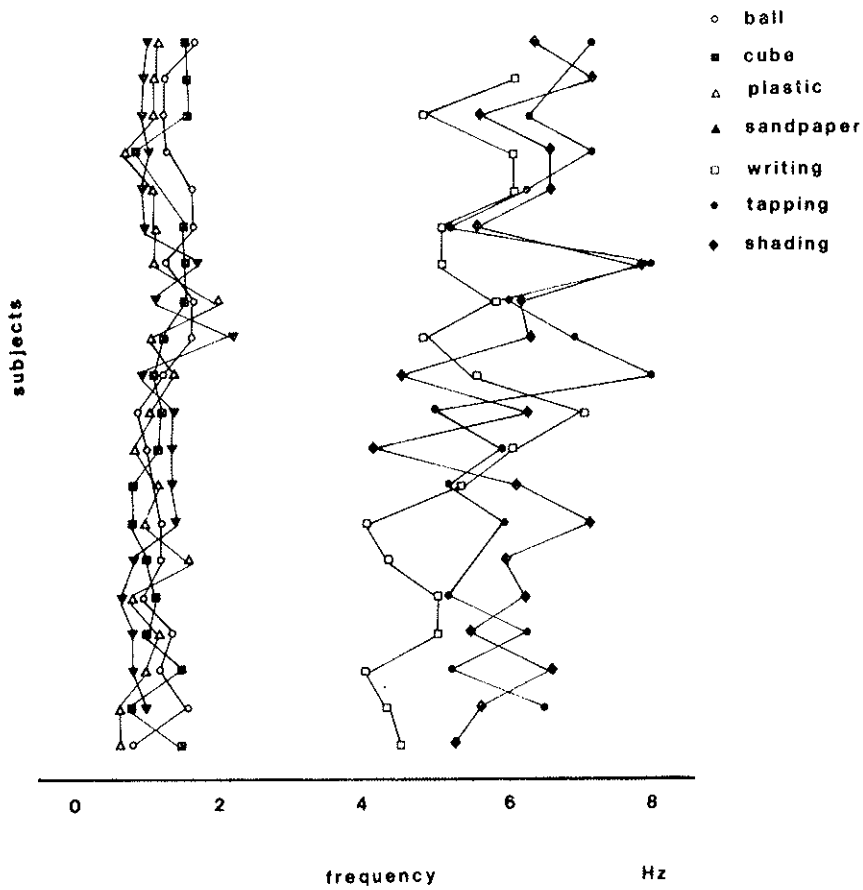

FIG. 3. Distribution of the peak frequencies at which finger movements are performed during four tactual exploratory tasks (left) and of hand movements during execution of three manual skills (right). The data were obtained from 20 normal subjects (ordinate). (From Kunesch *et al.*, 1989).

temporal demands imposed by the sequential sampling process from the skin mechanoreceptors. When the neural transform of tangential velocity between finger and object exceeds a certain limit, the temporal resolution of successive receptor hits cannot be accomplished by the central demodulator neurones.

The Relation Between Characteristic Movement Frequency and Sensory Control Mode.

The frequency similarity of the limits of exploratory finger and pursuit eye movements is striking. Both movements can be performed faster, but when engaged in visual pursuit or active touch they keep below 2 Hz, suggesting that this confinement is sensory in nature. Exploratory finger movements, which are conceived for the collection and focal processing of sensory information, fall into the same low frequency class as hand movements requiring visual guidance, i.e., ocular pursuit. What is different between these two types of manual activities is the nature of sensory-motor interaction. In one case, the moving hand is subject to visual guidance, in the other the hand movements generate, select and shape somatosensory input. Irrespective of that relational frame, the temporal characteristics of these movements are determined by the focal type of sensory processing that is involved. We would like to propose, for the sake of clarity and brevity, the term type I movements for the low frequency group and type II for the higher frequency group. This classification is solely and clearly defined by the frequency characteristics and applies only for serial manipulative movements. The functional implication of this classification is that the two frequency classes are determined by and indicative of the type of sensory processing associated with either class. We conclude from our data on hand movement recordings that the concept of foveal and preattentive vision (Julesz [8]) can also be applied for the somatosensory modality and that the temporal movement characteristics reflect the two types of sensory processing.

Implications of the Temporal Organisation of Hand Movements for Skill Acquisition.

It is well known that movements, before they are learned, must be performed slowly. Since these movements are not yet predictive, they obviously depend totally on precise sensory guidance. As soon as they are learned they become faster. This applies in the acquisition of manual skills such as handwriting, typing, playing musical instruments and various other skills. A child will start writing at frequencies well below 2 Hz, allowing for ocular and head pursuit. In other cases each finger movement has to be guided by a saccade identifying the target and directing the finger movement. This is the case before typing or playing a key-

board instrument is learned. Fig. 4 shows an example in which a beginner types the sentence shown at the top. Again this movement is recorded by the opto-electronic system and the movement of the digits II to V is recorded from top to bottom for the right (upper part) and the left hand (lower part). Figure 5 shows a similar recording but this time performed by a well trained typist. In addition to the difference in the speed of performance, a new aspect of motor learning emanates from a comparison of the two figures. The movement patterns used by the trained typist are differently organized as compared to those used by the beginner. Whereas the latter uses a single-finger key hitting strategy, the trained typist uses a rhythmic movement of all fingers, and the one finger that hits a key at a given time cannot be distinguished from the movement record on the basis of a particularly large amplitude. As revealed by other experiments

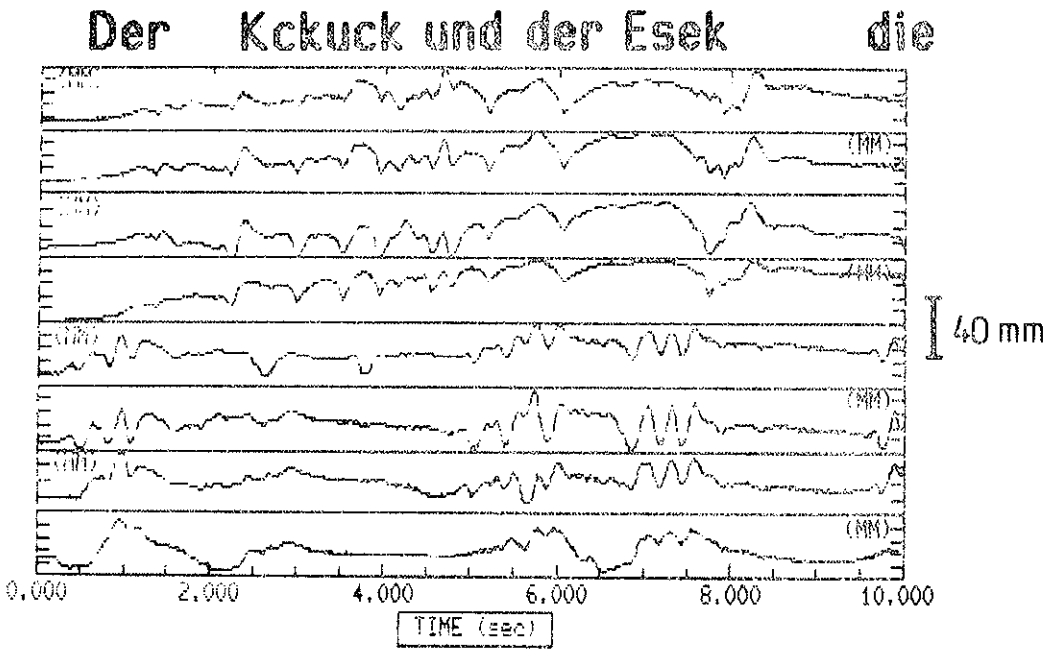

FIG. 4. Vertical typing movements of the four ulnar digits of the right (upper) and the left hand (lower) during typing of the sentence shown at the top. Performance of an unskilled subject. The sentence contains 2 typing errors. It should be: Der Kuckuck und der Esel (the cuckoo and the donkey).

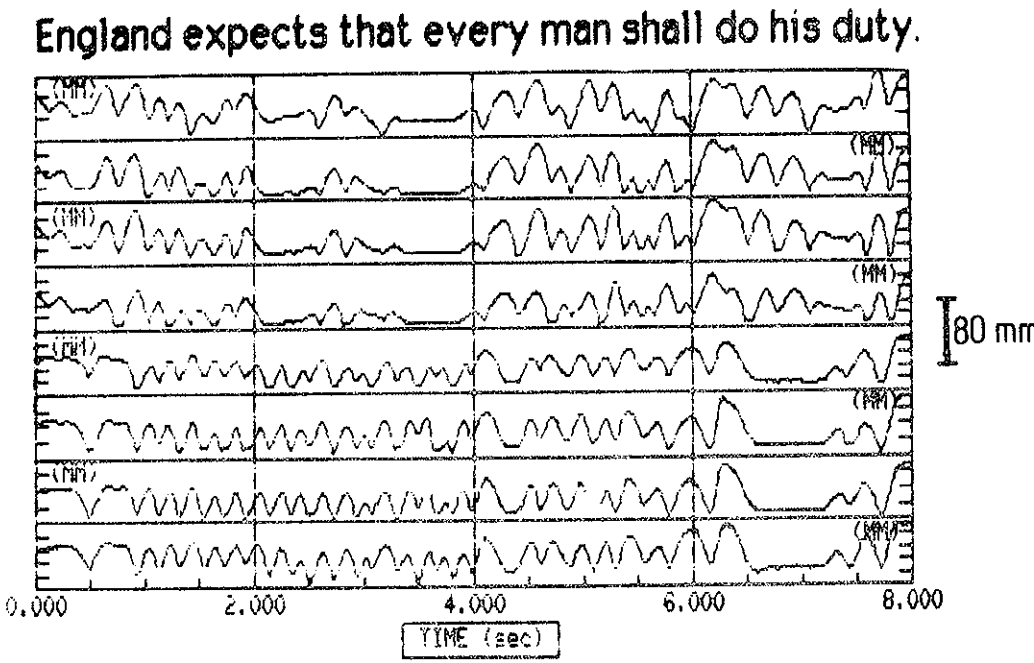

FIG. 5. Vertical typing movements of the four ulnar digits of the right (upper) and the left hand (lower) during typing of the sentence shown at the top. Performance of a skilled typist. (From Kunesch *et al.*, 1989).

in our laboratory, this strategy is strikingly similar to that used by skilled pianists.

Frequency analysis of such typing records shows that they lie within the same narrow frequency range as has been shown for pencil-shading, handwriting and fast tapping. The mean frequency which we measured in six secretaries scattered little around the mean value of 5.5 Hz.

On the basis of the evidence presented, we propose the hypothesis that type II movements engage different sensory control processes before and after they are learned. For unlearned movements it is not possible to plan trajectories on the basis of prediction. They must rely totally on high acuity guidance so that these movements must be executed at low frequencies. When learned, the movement trajectories are largely predicted. They are not performed open-loop as assumed in the old ballistic concept, but are monitored by preattentive sensory control

mechanisms. This applies for all manipulative movements except for those exploratory movements that collect somatosensory input for focal processing or which require visual guidance. The finger movements themselves are automized and preattentive control would be sufficient for their performance. Consequently, the temporal restraints are the same no matter whether it is the sensory-motor or the motor-sensory aspect that brings focal sensory processing into play. For this reason terms like sensory guidance (focal) versus sensory monitoring as general terms to be used instead of type I/II movements would not be adequate because they do not take into account the motor-sensory aspect.

A consistent feature of all the manipulative movements that we studied was their intermittent serial nature. They represent series of rather sinusoidal movement repetitions. The regularity of their performance is reflected by the shape and amplitude of the spectral peak in the power spectrum. As illustrated by figures 4 and 5, the rhythmicity of a type II movement is established only when it is learned. Skill acquisition of type II movements is associated not only with higher frequencies, but also with increasing regularity of movement. Highly sophisticated manual skills thus exhibit a rhythmic organization similar to that of many other automized motor behaviours such as breathing, chewing, locomotion, speaking and many others.

One intriguing feature of the type II movements is the fact that they fall into a surprisingly narrow frequency range close to that of physiological tremor. Lamarre *et al.* [10] have shown that the inferior olive neurones discharge rhythmically in the 8-12 Hz range. In their feline tremor model they assumed that this rhythmicity is related to physiological tremor and showed that both rhythmicities can be altered by the injection of harmaline or barbiturates. From human data, evidence for the assumption that the inferior olive and/or other intrinsic oscillators may have an attractor function, not only for tremor but also for the entrainment of movements at preferred frequencies, comes from observations on patients with basal ganglia or cerebellar nuclear dysfunction. They invariably show abnormally slow tremor rates and concomitant slowing of type II movements along with difficulties in carrying out such skills.

Are the Two Types of Manipulative Behaviour Processed in Different Neuronal Circuitries?

The evidence presented so far is compatible with the hypothesis that distinct sensory control models are associated with different temporal characteristics of hand movements. It is not known whether the two modes of sensory-motor behaviour are processed in different neural circuitries. For the visual system, it has been shown that certain stimulus features such as form, colour and motion are processed along separate neuronal networks (Ungerleider and Mishkin [16]; Hubel and Livingstone [7]). It is unknown how these different sensory analyzers are linked to the motor system.

Brooks [2] has shown that during learning experiments in monkeys two phases were defined by shortening of reaction times, with abrupt consolidation that coincided with the abrupt association of behavioural and motor skills. Gemba and Sakasi [5] recorded cortical potentials in prefrontal, premotor and prestriate areas, and demonstrated that visuomotor associations were formed in the first phase of learning, whereas in a subsequent second phase of motor learning cerebello-thalamo-cortical potentials were established in primary motor cortex. This was taken as indicating the activity of cerebro-cerebellar programming. Roland and Seitz [15] have shown that the primary sensory-motor areas become strongly activated in the early phase of motor learning. During performance after skill acquisition, metabolic activity increase was shifted towards premotor cortex.

Parietal cortex is involved in the elaboration of highly processed sensory information and in the command functions for motor behaviour in extrapersonal space (Mountcastle *et al.* [13]). Posterior parietal cortex has strong projections to premotor cortex, but also to brainstem and cerebellum (Glickstein *et al.* [6], allowing the distribution of sensory information into different motor circuits depending on the demands of the task. The severe disturbances of type I movements (tactile apraxia, visuomotor ataxia) in patients with lesions in that area indicate the functional significance of posterior parietal cortex in the elaboration of movements that are conceived for the selection and shaping of sensory input or that depend on visual guidance (Freund [4]). The evidence available so far is insufficient to answer the question whether distinct sensory-motor behaviours are processed in different neural circuitries. But the functional dichotomy of manipulative hand movement may serve as a useful model to further explore this question.

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DISCUSSION

MOUNTCASTLE

I found your presentation extraordinarily interesting, and I want to address just one aspect of it that interests me — the question of the fast oscillatory movements and whether they might be under tactile afferent control. For example, this summer I did an experiment on myself in blocking the nerve in my middle finger. It was blocked too long; it had a degeneration that lasted all summer. I have found great difficulty in typing. The question is, how important is the tactile feedback in regulating the fast oscillatory movements?

FREUND

It was an old observation that if somebody is deafferented, he is able to drive his old car because the patterns are learnt and he uses prediction, but when he gets a new car he can't learn to drive it.

MOUNTCASTLE

I've found my error rate on that finger to rise almost to 100 in trying to type rapidly with an anaesthetic finger tip. It's only the cutaneous afferents that are blocked. There is no block of the muscle afferents from the short muscles of the hand.

FREUND

I think the cutaneous afferents must play an important role. We had a few patients who had medial nerve difficulty and had similar problems but no weakness at all, and they were severely hampered in their musical performance.

ECCLES

I spent years demonstrating and analyzing the key role of pad tapping on the cerebellum of cats. These human disabilities demonstrate cerebellar dysfunction.

MOUNTCASTLE

Just one additional question. You surely are dealing with the slowly adapting afferents, aren't you, with the afferents from the finger tip?

FREUND

Yes certainly, they are very heavily involved.

JEANNEROD

I was struck by the difference between the low-frequency movements, typically at 2 Hz and the high-frequency movements at up to 6 to 8 Hz. One could agree that the slow movements are slow because they are feedback controlled. They are so-called closed-loop movements and the other ones are fast because they are open-loop movements. But then that doesn't fit the typical feedback time, which is something which would allow movements up to 4 or 5 Hz, the 200 milliseconds typical feedback time. So how do you explain the fact that those movements are slower than they could be?

FREUND

This is a question which discloses that I didn't state very clearly the concept which I have. You know the old classification of movements into ballistic open loop and random movements. However this cannot cover this broad range of possible performances. There are different types of sensory control. The Type 1 movements are certainly under what I would like to call focal sensory information processing, and Type 2 is preattentive. For example, take handwriting: your eye is fixated and you do a continuous movement with the hand while the eye is fixated. The eye jumps from word to word or does a saccadic sequence and this is a continuous movement which is monitored from the fovea and peripheral retina. This is certainly not done blind. These are rapid movements, but if you have lines on your paper, you can keep to the lines much better than if you close your eyes. So I'm sure there is some sensory information processing as Dr. Mountcastle says for the tapping and during all these rapid movements. There must be a feedback, so that simultaneous prediction and real feedback are both involved.

JEANNEROD

Wouldn't that fit into the instructions that you give to the subjects?

FREUND

You give instructions to do it slower and they can do it. They can never do the Type 2 faster.

MOUNTCASTLE

The idea of the pre-attentive control from the pyramidal and extra-pyramidal regions fits beautifully with the effect of directed attention upon the excitability of the parietal visual control system, where with directed attention of the focal portion of the field, there is an increase and not a decrease of receptive field size of the visual neurons in the parietal lobe by a factor of 3 to 4.

FREUND

May I ask you, would you find the term pre-attentive adequate?

MOUNTCASTLE

I think it's correct.

SINGER

In vision, Julesz uses the term pre-attentive for the pop-out effects which have short latency. They are usually interpreted as parallel processes while the others that require focused attention are considered to be serial processes. Maybe you find a homology there between some parallel processing and some serial because in the visual system clearly these two can be addressed as such.

ITO

Can I go to the problem of the cerebellum? The involvement of the cerebellum has been extensively studied in connection with locomotion and stepping. It has been clear that this is beautifully modulated in connection with the rhythm, but this modulation is due to mossy fibre input but never to climbing fibre input. Climbing fibres fire only when the animal makes a sudden unexpected error in locomotion by transforming the feedback model into feedhold model. So your observation in the cerebral patients which actually reduce the frequency of finger responses seems to fit quite well.

DESMEDT

I am fascinated by this story of the richness of input that you require to elaborate the programmes as you are doing in active touch. In addition to this, I think one should mention that you have a fast long loop from extroreceptive input from fingers that goes to the motor cortex and back to the motor neuron. We have for example recorded single motor units whose threshold was definitely decreased. That means you have for the same kind of innervation a higher frequency of discharge at the moment fingers were touching a target. So the extroreceptive contact is going to reinforce the precision grip at this stage. I think what Hans Freund is talking about is vastly different in having longer delays and more elaboration of a more complex input in order to guide these movements.

BROOKS

I wanted to connect with what Masao Ito and Hans Freund said because if you produce a temporary cerebellum patient by deactivating the cerebellum, or at least the dentate nucleus in the monkey, you abolish the ability to produce a learnt movement.

ECCLES

One of the factors in movement that has been left out of discussion so far are the Ia afferents from muscles. They go up very fast to the thalamus and to area 2 of the cortex and then can loop through to area 4. That fast Ia pathway has to be taken into account in all of the movements that are going on because within 30 milliseconds the information of the muscle contraction has got to the motor cortex. It's unconscious, but it has to be considered in motor control.

FREUND

That's a very interesting point. So far we were sure, with the scan, where in that loop we had a lesion, but now with the 1.2 mm cuts in the MR, we may be better if not good enough in determining the boundaries of the region, whether it is really only post-central or is pre-central as well. We have a second tool which we can use, which is magnetic stimulation of the motor cortex which is very sensitive to small damage. So if you have an intact potential after magnetic stimulation in the parietal lesion where you

think the post-central gyrus is affected, you would be more sure that the pre-central gyrus is undamaged and then such types of experiments can be done on a safer basis.

POECK

A Parkinsonian patient has a slower finger movement and he has a slower rate of tremor. If either by exercise or by certain drugs, his speed of finger movement increases, does the tremor rate increase at the same time?

FREUD

That's indeed the case.

INGVAR

I have a comment just from the clinical point of view to this fascinating paper. I would like to ask you about other forms of tremor, for example the hereditary tremor and the tremors you find in chronic intoxications. Do they produce a certain pattern in your records?

FREUND

Yes. If they are of large amplitude and therefore disturbing for the patient, they are slower. There are some cases where essential tremor may be of rather large amplitude and persist at rates around 6 or 7 Hz, but all the others go down. Our best model for the time being is the tremor in Wilson's disease, which shows you how fantastically reversible these tremors are. These people shake like this so that they are frequently sent to the psychiatrist first. Most of them are young, and 2 weeks after liver transplantation, the whole tremor has virtually disappeared. It's a very, very striking result. We now have a collective of liver transplanted patients whom we have recorded after liver transplant. It's amazing how this is reversible, and they had a longstanding disorder.

INGVAR

I might add another question. I didn't quite get your point on stutters.

Did you mean to say that you could identify waves of these frequencies in the vocalization?

FREUND

Yes, that's voice stuttering which is sometimes injected as you saw on the record. It's at the particular tremor frequency.

A HIERARCHICAL MODEL FOR VOLUNTARY GOAL-DIRECTED ACTIONS

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1. *Levels of Processing in Mechanisms for Voluntary Action.*

The aim of the present chapter is to discuss some of the issues related to the organization of voluntary actions, both in cognitive and in neurophysiological terms. The general idea will be that generating a goal-directed action implies coexistence of different modes of activation of neural structures, which will be conceptualized as levels of organization. At the beginning of this century, Woodworth had already made clear this distinction between the different degrees of what he called "intention". "When I voluntarily start to walk," he wrote, "my intention is not of alternately moving my legs in a certain manner; my will is directed toward reaching a certain place. I am unable to describe... what movements my arms or legs are going to make; but I am able to state what result I design to accomplish" (Woodworth, 1906, p. 375). The same notion that an action can be represented at different levels was also included in the classical physiological dichotomy between action planning (representation of the goal and the consequences of a given action), and programming (implementation of the detailed commands for achieving each stage of the planned action).

I felt that it could be interesting to explore the validity of this description of the processes underlying motor control under the light of more modern conceptions elaborated in the context of artificial intelligence, such as hierarchical control, parallel processing, and modular organization. These conceptions were heralded by the Marr's (1982) model of levels

of functioning, designed originally for information-processing devices. According to Marr, the top level of the representation is the level of the "computational theory", which defines the goal of the computation, its appropriateness, and the logic of the strategy by which it can be carried out. The intermediate level is that of the implementation of the computational theory into a representation of the input and output of the system and into an algorithm for transforming the input into output. The third level is the hardware implementation of the representation and of the algorithm. Another possible framework for conceptualizing these modes of activation is the Fodor's distinction between *peripheral* and *central* systems (Fodor, 1983). Although this author mostly used the peripheral and central metaphors in the domain of input processing (e.g., for explaining the comprehension of language), I will transpose his conception to the analysis of sensorimotor systems specialized for generating motor outputs. Paraphrasing Fodor, I will assume that peripheral (output) systems "constitute a family of modules: domain-specific computational systems characterized by informational encapsulation, high-speed, restricted access, neural specificity, ..." (p. 101). Modularity, one of the main characteristics assumed here for output systems, seems compatible with the notion, more familiar to neurophysiologists, of simultaneous processing of information in parallel motor pathways (for review, see Wiesendanger, 1989). By contrast, still in Fodor's conception, "central systems are, in important respects, unencapsulated, and ... it is primarily for this reason that they are not plausibly viewed as modular" (p. 103), with the corollary that they have low speed, less neural specificity and broad access to consciousness.

Similar models were also elaborated in a purely physiological context. Together with R. Schmid, we proposed some years ago such a model for explaining habituation of the vestibulo-ocular reflex. This model (Fig. 1) postulates that actions should be organized in three hierarchical levels (e.g., Schmid and Jeannerod, 1979). Accordingly, the upper level of control receives information from several sources: from the external world through the sensory channels, and from the lower levels of the motor system. One has to assume that this level also includes some *a priori* knowledge about the cognitive constraints which define the general context in which the action is taking place. The function of the upper level is to specify, in relatively broad terms, the goal to be achieved by the overall system. It therefore does not have to include the detailed specifications of the steps needed to achieve the goal. In so far as this level corresponds to the definition of a "central" system (in Fodor terms)

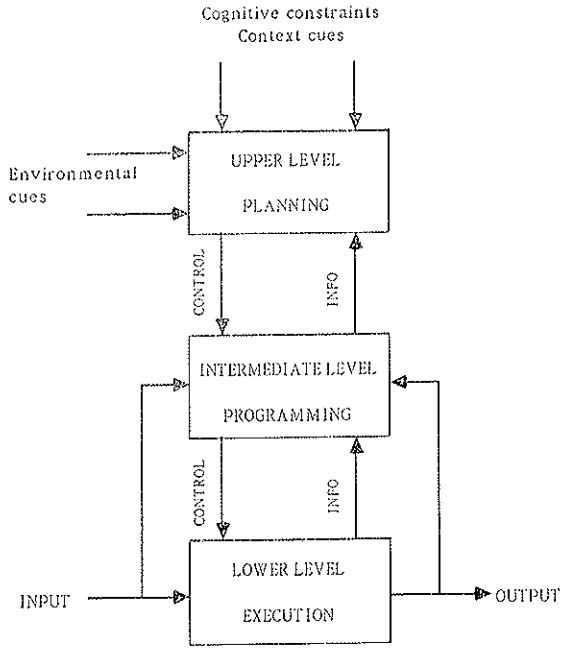

FIG. 1. A tentative hierarchical model for voluntary action (redrawn after Schmid and Jeannerod, 1979). The model implies that each level is controlled by those which are higher in the hierarchy. Although control is exerted in the top-down direction, the information concerning the state of the hierarchically lower levels flows in the opposite direction.

with a superordinate and supervisory role, it should be endowed with "central" properties, and it is for this reason that the representation it contains is assumed to be accessible and manipulable consciously.

The intermediate level controls the state of the lower level. It receives detailed information concerning both the stimuli for each subaction, and the corresponding responses produced by the lower level. In other words, it sets the best strategy to reach the final goal of the action, by implementing the global specifications made by the upper level. For achieving this function, the intermediate level must contain detailed specifications concerning kinematics and trajectory of the movements. Its representation of the action is a time-constrained, dynamic one, in that it changes and updates during ongoing movements. One of the main properties of the intermediate level is its modular nature: accordingly, it can be thought of as being split in as many modules as there are

movements to be performed in order to achieve the goal (see below). The modular organization has its own advantages and disadvantages because, as Johnson-Laird (1982) puts it, "we gain speed from parallel computation at the cost of insight as to how we perform" (p. 113). The specific disadvantage is that the fast and parallel processing performed at the intermediate level implies that it should not be accessible to consciousness.

Finally, the lower level is the execution level: it executes the strategy decided by the intermediate level to achieve the goal specified by the upper level.

2. *Awareness as a Specific Attribute to the Upper Level.*

One of the ways to assess the distinction between levels is to look for an attribute which would belong specifically to one of them, not to the others. The above concept of informational encapsulation allows making interesting predictions in this direction. It implies that peripheral (output) systems, because they are encapsulated, have only limited access to the mental representations that they are supposed to compute and implement. Awareness can therefore be looked at as a cue for dissociating processing levels in neural organization, according to the hypothesis that operations originating at the central level should be accessible consciously, whereas those originating at the peripheral level should not.

Indeed, there are many indications in the literature that awareness is not an undifferentiated attribute. The distinction between recognition and detection, which has been established in several experiments, implies a dissociation between explicit and implicit knowledge, and relies on the evidence of performance without awareness. However, demonstration of this dissociation requires situations where the overt, conscious process of recognition is impaired, and where the covert mechanisms of detection are still functional. I will take two examples from the neuropsychological literature, face and object recognition and blindsight.

It is commonly assumed that faces or objects are recognized by way of an overt identification process, whereby a given face can be named, shown, related to a given context, or a given object can be categorized and used. This process involves a large amount of conscious representation, with the possibility for the subject to remember, describe or verbalize the target object or face. A certain category of agnosic patients, following a cortical lesion, may become unable to achieve this conscious

recognition. It can be shown, however, that by using specific examination techniques, the lower level processes are preserved in these patients, with the consequence that discrimination (but not recognition) of the target stimulus remains possible. A good example of this is given by Volpe *et al.* (1979). They examined four patients with lesions of the right parietal lobe, without hemianopia. Pictures of objects appearing on a screen in front of the subjects were presented for a short duration. Presentation was either restricted to one object appearing in one of the two hemifields, or involved simultaneous appearance of two objects, one in each hemifield. All subjects named without difficulty the stimuli when presentation was limited to either hemifield. When two stimuli were presented simultaneously, those appearing in the left hemifield (contralateral to the lesion) could not be named, in fact they were even not seen. By contrast, when the subjects were asked, not to name, but to compare the two stimuli with each other (are they same or different?), they were quite accurate. This pathological condition thus offers the possibility of observing, under appropriate conditions, a dissociation between a conscious and a non-conscious mental system, whereby stimuli can be encoded and compared without being overtly identified. Even more striking is the dissociation demonstrated in one prosopagnosic patient by Bauer (1984). This patient was unable to match familiar faces with the corresponding names. However, the recording of his skin conductance (a variant of the "guilty knowledge test") during examination showed larger electrodermal responses on presentation of the correct names, suggesting that faces were indeed identified at the psychophysiological level, though they were not overtly identified. Similar results were also obtained in prosopagnosic patients by Tranel and Damasio (1985; see further references in Schacter, 1988).

Blindsight is another case of pathological dissociation between overt and covert mechanisms. Patients with lesions in their occipital lobes appear to be blind in the corresponding parts of their visual field, so that they cannot report any conscious experience from stimuli that arise from the blind area. Pöppel *et al.* (1973) were the first to suspect that residual visual capacities (relying on the spared subcortical visual pathways) might be demonstrated in these patients by using pure behavioural responses, instead of verbal responses. Indeed, they asked their subjects not to try to see stimuli that were presented within their scotomata, but rather to try to locate them by turning their eyes. Pöppel *et al.* recorded eye movements, the direction and amplitude of which were weakly but

definitely correlated with position of the targets. Because the subjects remained unaware of the stimuli, they subjectively experienced "guessing" rather than "seeing". This was a form of unconscious vision, later called "blindsight" by Weiskrantz and his colleagues (Sanders *et al.*, 1974; see also Perenin and Jeannerod, 1975, 1978), where subjects abandoned their usual, perceptual, mode of visual recognition, and used an alternative mode based on visuomotor responses. These results on "blind" orienting and reaching stress the fact that movements can be initiated and executed with reasonable accuracy without a direct conscious representation of the goal. The lesion artificially splits behavior into modular units (in this case a cognitive unit and a visuomotor unit) which normally cannot be dissociated (Jeannerod, 1981b).

The fact that in blindsight subjective experience is disconnected from information transfer and motor production mechanisms does not mean, however, that visuomotor channels make a simple direct transformation of visual input into motor output. Even though the upper level seems to be absent or deficient, the intermediate level still functions and some of its attributes can be tested. The work of Zihl and Werth (1984a and b) offers such a possibility. These authors have clearly shown that hemianopic subjects, even though they remain unaware of the final result of their movements, can be trained to improve performance. They examined two patients whom they required to direct their eyes where they guessed the targets had appeared. Patients first tended to make saccades of a rather constant amplitude without respect to target location. They were then informed that targets would appear at a different location each time, and that they should therefore shift their eyes by a corresponding amount. They were never informed, however, about the location of the target, nor about their localization performance. This "shaping" procedure, similar to that used in monkey training experiments, produced in the patients a clear and rapid improvement in performance (Zihl and Werth, 1984b).

Although dissociation between overt and covert modes of processing in the above examples clearly resulted from pathological condition, it may in fact reflect the existence of two levels of functioning in normal conditions. In the following paragraphs, I will attempt to demonstrate this fact experimentally and to show that the organisation of action can indeed be formalized in terms of a multilevel hierarchical model. Each level will be assigned definite functional properties, awareness being one of these properties. One of the postulates underlying this approach is

that the degree of awareness may be a cue for setting the limits between the Fodorian central and peripheral systems; in other words, that central processes are conscious and that peripheral processes are non-conscious. If the reverse also happened to be true (i.e., that conscious processes during generation of action pertain to central systems, and that non-conscious processes pertain to peripheral systems), then this might have important consequences for understanding the organisation of voluntary actions. The other advantage of these hypotheses is that they are open to empirical verification and can generate experiments designed specifically for probing each level.

3. *Probing the Upper Level.*

Experiments can be designed for probing the conscious aspects of the motor representation that pertains to the upper level. A number of psychophysical observations have revealed that visual images of objects seem to be represented as perceptual analogues which preserve the metric spatial properties of the represented objects. Shepard and Metzler first showed that represented three-dimensional shapes are mentally manipulated in the same way as if they were real 3-D objects; the time taken to mentally rotate such shapes increases linearly with the angle of rotation (Shepard and Metzler, 1971). Similarly, Kosslyn *et al.* (1978) showed that the time required to scan across visual mental images increases linearly with the distance to be scanned. These results suggest that processes underlying mental operations within visually represented space might be similar to those underlying actual operations within physical space. Support to this idea is provided by experimental data on reaction times. The concept that the length of time that precedes movement execution "often reflects the complexity of decisions required to select and prepare the necessary voluntary response" (Kerr, 1978, p. 55) is now widely admitted. Accordingly, in a recent experiment Georgopoulos and Massey (1987) requested subjects to perform reaching movements at various angles from a stimulus direction and found that reaction times of these movements increased linearly with the size of the angle. They proposed that this increase in reaction time was related to mentally rotating the movement vector until the angle of rotation corresponded to the size required. In both the Shepard and Metzler (1971) and the Georgopoulos and Massey (1987) experiments, the linear relationship between duration of the postulated mental rotation and the size of the

angle of rotation is remindful of the classical relation between movement time and task "difficulty" observed during execution of real movements (Fitts, 1954). This similarity suggests that both real and imagined motions might be governed by the same principles.

This hypothesis has at least one logical consequence, namely, that the time taken to reach objects located in physical space should be in one way or another related to the time taken to reach mentally the same objects represented on a spatial map. This relation, however, can be demonstrated only in a situation where physical and mental movement times are measured in the same subjects. This was attempted in a series of experiments performed in collaboration with J. Decety and C. Prablanc, where we compared movement times in subjects who were requested either to walk, or to imagine themselves walking, at previously inspected targets (Decety *et al.*, 1989).

The experiment was conducted on a running track in an outdoor stadium. Three white marks (30 cm by 20 cm) traced on the ground with white chalk were used as targets. Subject's starting position on the track was such that his/her distance from the targets could be either 5, 10 or 15 meters. Starting position was varied from trial to trial. At the beginning of each trial subjects were placed on the track. They were then allowed to look for 5 s. at one of the targets. After being blindfolded they were instructed to construct a mental representation of the track and the target. Finally, after another 5 s. delay, they were requested either to walk at a normal pace to the target and to stop when they thought they had reached its location (actual walking condition), or to imagine themselves walking to and stopping at, the target (mental walking condition). Walking time (in seconds) was measured in both the actual and the mental walking conditions. Subjects held an electronic stopwatch in their right hand. They switched the stopwatch on when they started to walk (actually or mentally) and off when they stopped. Walking time was read directly by the experimenter on the stopwatch. Subjects were given no information on their spatial or temporal errors.

Results showed that, in the actual walking condition, walking time varied across subjects, but that in each individual subject, it increased with the distance covered. In the mental walking condition, walking times were very close to those measured in the actual walking condition for the same subjects and for the corresponding targets. The similarity of the two distributions of walking times was confirmed statistically: the mean values of travel time for the actual and the mental walking

conditions were plotted against each other for each target. Intrasubject linear correlation coefficients ranged between $r=0.89$ and $r=0.99$.

The fact that walking time was invariant *across* actual and mental conditions, which confirms the above hypothesis, raises the interesting questions of whether this temporal invariance is related to the fact that the mechanism which is read to compute mental time is the same as the mechanism which is used for programming the actual movement. And if so, which parameter(s) of the motor representation are used during mental execution of the task?

One way to answer this question is to introduce an external constraint on the motor task. It was conjectured that such a constraint should not affect in the same way actual and mental performance, because the constraint would exert its effect only during execution of the actual movement. Therefore, and somewhat paradoxically, if the mechanisms used in the mental and the actual conditions were to be the same, the subjective representation of the movement should differ from its actual appearance. It was also conjectured that this difference might possibly affect the estimation of movement duration. The previous experiment was thus repeated in the same subjects in a condition involving an external constraint, namely, the subjects were requested to actually walk or to imagine themselves walking to the targets, while carrying a heavy load on their shoulders.

The same running track with the three targets was used. A 25 kg weight was placed on subjects' shoulders in a rucksack. Subjects were placed on the track and were instructed to look at one of the targets for 5 s. Then they were blindfolded and were requested either to walk and reach the target location (actual walking condition) or to imagine themselves walking to it (mental walking condition). Walking time was measured as in the previous experiment.

Walking times in the actual walking condition with the 25 kg load were not significantly different from those measured in the same subjects in the first experiment. By contrast, travel times in the mental walking condition with the load were significantly increased in all subjects and for all target distances. In addition, it may be worth noting that subjects spontaneously reported in the mental walking condition a strong sensation of effort which they felt to increase with the distance of targets.

The results of these two experiments seem to confirm the above hypotheses. First, the same amount of time was needed by the subjects to walk physically and mentally to the same targets, indicating that similar

mechanisms were at play in the two conditions. In addition, the systematic dissociation observed between physical and mental walking times when the subjects had to perform the same task with the load may reveal the way the upper level processed the goal of the action. If subjects walked physically with the load at the same speed as without the load, it is because they produced greater effort. When they performed mentally, however, they did not have to fight against the resistance caused by the load, and the extra-effort that they produced was read as an increase in duration of the action. This might have been the case because the upper level is normally incompletely informed of the detailed feedback from peripheral aspects of the movements which, as suggested by the hierarchical model, should be restricted to the intermediate level. If this speculation is true, it is therefore not surprising that no compensation for the effects of the load on the dynamics of the movements was effected at the upper level.

The upper level representation may thus be conceived as a representation of the final outcome of the action, encoding the respective relations of the body and the goal in the final, desired, position, but devoid of detailed specification on trajectories or dynamics. This representation might contain an estimate of the effort to be produced to reach the goal and of the energy needed.

4. *Probing the Intermediate Level: Evidence for Fast Processing.*

This section will be devoted to describing an experimental situation in normal subjects where upper and intermediate level motor processes can be clearly dissociated from each other. This situation is a variant of the so-called double-step paradigm, already widely used in the study of motor control. The basic premise of the paradigm is the following: if the target at which a subject is reaching is suddenly changed, the way the movement is reorganized in order to reach the new target should allow inference about the content of the structure which steers the movement. Specifically, knowing how the system reacts to the perturbation, what corrections can be made (e.g., alteration of the trajectory, of the kinematics) and how fast they are, should provide some insight as to how the motor program is organized. In keeping with the hierarchical model outlined above, the corrections generated by the perturbation should reflect primarily the activity of the intermediate level of motor control.

Typical experiments involving double steps have been reported by Pelisson *et al.* (1986). Subjects' task consisted in pointing at visual targets with their invisible right hand. The initial target steps were from midline to 20°, 30°, 40°, and 50°. The second steps were of a smaller amplitude (e.g., from 30° to 32°, or 40° to 44°) that is, sufficiently large to make possible pointing corrections clearly visible. The second steps, when present, were triggered at the maximum saccadic velocity, a procedure which turned out to be quite advantageous for the experiment: subjects were not aware of the target jumps and were never able to report the occurrence of a double-step. The results showed that the distributions of pointing positions for double-step trials were significantly shifted with respect to those of the corresponding single-step trials, indicating that the subjects corrected their hand trajectories in order to reach the final target positions. This result has important implications. If one assumes that final target position was not properly encoded until foveation occurred, then the hand had to wait until the saccade was completed, before corrections needed to reach the displaced target could be generated. Consequently, these corrections necessarily took place *after* the hand movement had begun.

One could hypothesize that corrections were in fact new movements resulting from reprogramming. Pelisson *et al.* (1986) clearly showed that this was not the case. Indeed, the durations of pointing movements toward displaced targets kept the same linear relationship with amplitude as for movements toward stationary targets. In other words, the increased duration on double-step trials reflected only the additional distance that the hand had to move, indicating that there was no reprogramming of movements to accommodate the second target displacement. Another argument as to this point was given by the kinematic analysis of the pointing movements. Indeed, if reprogramming occurred, it should become visible as a secondary movement and as a reacceleration of the trajectory. No such reaccelerations were seen for the double-step trial movements, which therefore, did not differ kinematically from the single-step trial movements.

Another example is provided by applying the same type of perturbation to prehension movements. In this case, the targets consisted in real tridimensional and graspable objects (dowels 10 cm high and 1.5 cm in diameter), which were placed on a concentric array at 35 cm from starting position of the hand. The dowels were made of transparent material, and were illuminated from below. In some trials the light

could be suddenly shifted at the onset of the reaching movement, from the initially illuminated dowel to another one located 10 degrees to the right or to the left (perturbed trials). The trajectories of the wrist, of the tip of the index finger and of the tip of the thumb were recorded. In addition, the kinematics of the wrist movement, as well as the distance between the two finger tips (the size of the finger grip) were monitored. Displacing the target by shifting the light from one dowel to another one produced a complex rearrangement of the wrist and finger trajectories, so that the fingers were finally placed in the correct position for an accurate grasp. This rearrangement was effected with only relatively small increase in total movement time (about 100 ms). Inspection of the wrist kinematics showed that, following the perturbation, the initial acceleration of the movement was stopped and that a secondary acceleration occurred in order to direct the hand at the new target position. Interestingly, the first peak in acceleration occurred earlier in the perturbed trials, such that it occurred at about 105 ms following movement onset in the perturbed trials, instead of about 130 ms in the unperturbed ones. This result means that in about 100 ms (that is in much less than one reaction time) the new object location influenced the kinematics of the ongoing movement in order to reorient it at the new target location. Finally, whereas the subjects were aware that the location of the target dowel had changed during the trial, they made an erroneous estimate of the time at which the change occurred: instead of seeing the change immediately after movement onset, they saw it near the end of the movement trajectory, when their hand was coming close to the target (Paulignan *et al.*, in press). As in the Pelisson *et al.* experiment, the early motor reaction to the perturbation was dissociated from its perception by the subject. In both experiments, the motor system was able to detect the perturbation and to correct the movement trajectory, even though the information it used was not consciously available.

There are other examples of fast corrections in ongoing complex movements. Abbs and Gracco (1984) have described rapid compensation of perturbations applied to articulators during speech, in an experiment in normal subjects where the lower lip was unexpectedly pulled down during production of the phoneme /ba/. They showed that lip closure was nevertheless achieved and that the phoneme was correctly pronounced in spite of the perturbation. Such a compensation, which implied that lip closure was performed by a larger lowering of the upper lip, was

effected within a delay compatible with the correct production of the phoneme. Indeed, EMG activity of the relevant oro-facial muscles was found to be modified as a consequence of the perturbation. Activation of the orbicularis oris superior, responsible for upper lip depression, occurred within 22-55 ms, which accounted for the close-to-normal lip closure. By contrast, activation of the o. oris inferior (the lower lip elevator), occurred several tens of milliseconds later.

Abbs and Gracco concluded that activation of these two independent muscles reflected two different compensatory mechanisms. They suggested that late activation of the lower lip elevator reflected reprogramming triggered by proprioceptive feedback, whereas early activation of the upper lip depressor reflected an open-loop adjustment, independent of sensory feedback in the usual sense, but nevertheless relying on proprioceptive signals generated by the ongoing movement. Such a conception clearly fits into the definition of feed-forward mechanisms given by Arbib (1981): "A strategy whereby a controller directly monitors disturbances to a system and immediately applies compensatory signals to the controlled system, rather than waiting for feedback on how the disturbances have affected the system" (p. 1466).

The above three experimental examples emphasize the rapidity of processing of information at the intermediate level. One possible explanation for this rapidity is that the representation of the action contained by this level would be a "dynamic" one, in the sense that it would map the ongoing movement by permanently monitoring the input stage. Accordingly, any change in target configuration, or any deviation of movement execution from the represented action, should trigger reorganisation of the commands sent to the execution level, in such a way that the goal would be reached in spite of the perturbation. One further assumption would be that the intermediate level representation contains several movement "formulae" (to use the Bernstein terminology, see Bernstein, 1967) for the same action, as seems to be required for dealing with the many degrees of freedom of most skeletal joints: the same action of grasping an object, for example, can be executed from different starting positions of the hand and may involve different combinations of joint torques. If, as it appears to be the case, the system were able to shift very rapidly from one formula to the other, then this mechanism would readily account for corrections in case of a perturbation. This view of the intermediate level functioning in fact may represent a solution to the classical problem of motor equivalence (see Abbs and Cole, 1987).

There are logical consequences to this property of the intermediate level being the seat of fast information processing, some of which are predicted by Fodor's definition of peripheral systems. It is partly because these systems are fast that their functioning is unconscious (1), and that the operations they control are mandatory. In other words, the corrections that were observed in response to perturbations in the above experiments could not but be executed.

5. *Probing the Intermediate Level: Evidence for Parallel Pathways.*

The second main set of properties attributed to intermediate level processes relates to their modular structure and their parallel functioning. The analysis of a simple action like grasping an object provides arguments for discussing these properties.

Formation of the finger grip during the action of grasping a visual object involves two main functional requirements, the fulfillment of which will determine the quality of the grasp. First, the grip must be adapted to the size, shape and use of the object to be grasped. Second, the relative timing of the finger movements must be coordinated with that of the other component of prehension by which the hand is transported to the spatial location of the object, so that closure of the finger grip occurs in tight synchrony with approach of the target object by the fingertips. Early or late closure of the finger grip will both result in inaccurate grasp, with the consequence of bumping and possibly breaking fragile objects.

Simple observation of prehension movements shows that finger posturing anticipates the real grasp and unfolds during transportation of the hand. The co-occurrence of these two components reflects co-activation of different visuomotor mechanisms. At the output level, movements of proximal and distal segments of the arm are respectively controlled by neural subsystems which differ widely in their mode of organisation (for references, see Jeannerod, 1988). At the input level,

(1) Another reason for the intermediate level processes being unconscious is explicitly stated by Fodor (1983). According to this author, it seems "plausible that the relative inaccessibility of lower levels of input analysis is at least in part a matter of how priorities are allocated in the transfer of representations from relatively short- to relatively long-term memory. The idea would be that only quite high-level representations are stored, earlier ones being discarded as soon as subsystems of the input analyser get the goodness out of them" (p. 58).

the same two components also reflect a duality in the organization of the visual system. Mechanisms which detect elemental visual features such as size, shape or texture (which represent intrinsic constituents of object identity) are different from those that detect orientation of objects, their distance with respect to the body, or their location in the frontal plane. It has been suggested that these different aspects of an object are matched by specific mechanisms which can be conceived as specialized input-output structures (visuomotor channels, Jeannerod, 1981a and b, Jeannerod and Biguer, 1982). Each visuomotor channel extracts a limited number of parameters from the visual world and produces the corresponding responses. This notion of parallel structures governing the two components of prehension is in fact complementary to the other notions of a single act and a unified percept. One can further speculate that visuomotor channels only represent selective pathways for the input-output information flow related to each component of prehension; but that the action as a whole belongs to a unique representation accounting for its integrated aspect, or in other words the coordination of its components. Accordingly, the musculo-skeletal segments related to the act of prehension, in addition to their differential involvement in independent channels, would also be constrained as a motor ensemble governed by a specific set of rules, hierarchically higher than those of the channels, and coordinating the activity of the channels in the time domain. Interactions between the two components of prehension have been conceptualized by Arbib (1981) in a model which stresses both separate activation of each component by specific visual pathways, and coordinated output. The notion of uniqueness of the representation is thus in theory not incompatible with that of parallel visuomotor channels. The above description of prehension is clearly relevant to the notion of modular organization and its corollary, informational encapsulation (Fodor, 1983, Marshall, 1984).

The same notion of parallel functioning of the intermediate level is illustrated by an observation of Marteniuk *et al.* (1987) in an experiment where reaching and grasping movements in different conditions of task constraint were compared. Subjects had to grasp a small disk placed at 40 cm from their body. After grasping the disk, they had to rapidly either throw it in a large container, or tightly fit it in a small box. The kinematics of the reaching part of the movements only (i.e., that part common to the two conditions, between onset of movement up to contact with the disk) were analysed. Movement time was found to be longer

for reaching movements executed prior to fitting than for reaching movements executed prior to throwing. In addition, although the movements in both conditions had the same value of maximum velocity, they differed in repartition of movement time into acceleration and deceleration. The lengthening in movement time in the fitting condition was due to a higher percentage of total movement time spent in the deceleration phase. These data can be interpreted as reflecting the parallel activation of two different sets of modules, one for reaching and grasping, the other one for throwing or fitting. Although the two modules operated in succession, some activation of the throwing or of the fitting module was already present during execution of the reaching part of the action, which affected the overall output of the system.

The model outlined in Figure 1 must therefore be modified to account for the notion of modular structure, by splitting the intermediate and the lower levels into several parallel pathways, each one supporting specialized programs for the different visuomotor channels (Fig. 2). The information contained in each of the modules remains encapsulated. The

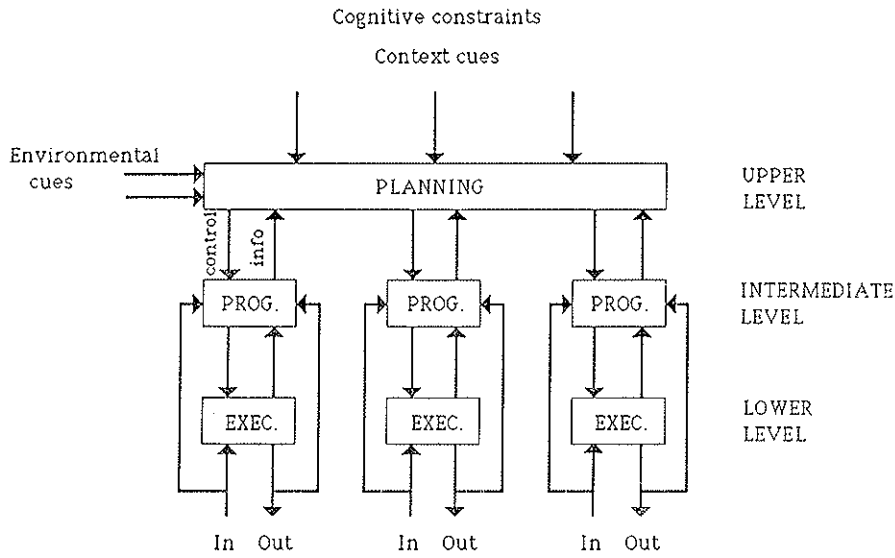

FIG. 2. The model outlined in Fig. 1 has been modified to account for the notion of modular structure of the intermediate level. The upper level plays the role of the Bernstein "ecphorator", by setting the goal and organizing the timing of the action sequence.

upper level controls all the modules and determines their relative timing according to the internal and environmental constraints that it has encoded for carrying out the action and achieving the goal. This timing, however, does not seem to rely on a strong sequential organization of the upper level. In the Marteniuk *et al.* experiment described above, for instance, the control exerted by the upper level appears to "leak" into the modules before they become fully activated. Similarly, in the production of speech, execution of earlier stages of the sequence can be affected by later stages (as revealed by occasional occurrence of spoonerisms). These examples suggest that the planning of the action might be organized globally rather than sequentially and that the rule of succession accounting for activation of the modules should be relatively weak.

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DISCUSSION

LIBET

I like the results, in the sense that you are showing a response, apparently, in which the subject is unaware when the target moves. I am not quite clear though how you could be sure he was not aware of the target moving. I like that idea, but how do you get that result?

JEANNEROD

In the experiment where the target step was triggered by the eye, the subjects were definitely not aware of the target jump, and we asked them systematically to press the switch whether they saw one target or two targets and they consistently pressed on one. That is, they always saw one target.

INGVAR

I should like to return for a moment to your slide about the performed walking up to a distance, and the imagined walking, and how these times coincided. My first question is, is there an upper limit where you cannot imagine walking?

JEANNEROD

What do you mean by upper limit?

INGVAR

Well, you can walk let's say 100 meters, in your case it was 5, 10, 15 meters. If you say 100 meters, is it possible to retain that in the timetable too?

JEANNEROD

I can't reply because we didn't do that experiment, but there is a classical experiment by Thompson which in fact was never replicated. He says that subjects can retain with relatively good accuracy target positions for

something like 8 or 10 seconds. Then if you put the target too far, the subject will take too long to get there as they often forget. So this is why we put our targets within the limits where the subject was able to remember, and in fact I didn't speak of the accuracy data but the subjects were very accurate.

INGVAR

My second comment is that there are experiments to show that in these simulated movements not only can you appreciate the time, but these movements are accompanied by autonomic changes. You know of the experiment in which swimmers imagine a 100 meter swim and this imagined swim was accompanied by an increase in the respiration that was further increased when they came closer to the goal of 100 meters. There is apparently another set of mechanisms which are activated during such imagined movements. If you walk 15 meters there is certainly an increase of your blood pressure and your pulse to some little extent. These imagined promenades, were they accompanied by heart actions?

JEANNEROD

In the weight-walking experiment done mentally the subject doesn't experience the weight against his movement. He is reading this as an increase in duration because if you produce more effort, you go further. So this indicates how poor is the upper level of computation. It just sets the target and a few specifications about timing and effort, but is not aware of what's happening downstream.

Now the subject always reported in this experiment experiencing a strong feeling of effort, in the same way as patients with paralyzed limbs. So it's another indication that goes with what you say. I mean, the autonomic system was probably involved.

INGVAR

A brief comment. I think that experiments of the type that I am going to show you on Sunday open up a completely new field which can be used clinically where you can ask patients to imagine things and to ideate them, motor ideation and speech ideation. We have some evidence, although not very systematic, that people with advanced organic dementia lack completely this capacity to imagine movements and words. This can be quantified and localized.

FREUND

You didn't talk about this but you have the data: how is the correlation between these corrective reaching movements or pointing movements and the corrective eye movements?

JEANNEROD

The eye movements correlate very well, as you know from the classical experiments, so we only recorded them. There were always corrections and those corrections were made before the hand was corrected, but that I think is more trivial, because one is very little aware of one's eye movements.

INGVAR

I was simply pointing out that sports medicine has demonstrated conclusively that the performance in certain sports like tennis and slalom, for example, can be improved significantly by simulation, by mental simulation.

ZEKI

What I wanted to ask was really in neurobiological terms; you see this as a huge distributed programme because it must involve the hippocampus and presumably also the visual cortex.

JEANNEROD

For the central systems there is little neural specification. I don't think we can put the plans or the goals of the movement in a single place, so we have to assume that it is a largely distributed and probably a sequentially organized network.

SINGER

Marc, I wonder whether you could speculate a little bit on the timer. I remember data from Shaw, who had measured the time that it took conductors to mentally rehearse their symphonies and they were better than 1% over performances that lasted over 40 min. This is a fantastic degree of precision in the representation of sequences and I wonder if one has any idea whatsoever of how this can be done.

JEANNEROD

I don't know. I think there are two levels of training. You can train the upper level by mental rehearsal, but also you have to train the intermediate level by making the movement and doing the thing faster and faster. But those are completely different types of training. I know that the sport people have realized that. They train themselves in two ways, either sitting in their bed and mentally rehearsing, or doing things with the game.

CREUTZFELDT

In this context another example of non-cortical or pre-attentive movements may be mentioned, and these are the express saccades of Fischer. They indicate that there are two levels, the subcortical and the cortical (or mental) level. The latter makes us more secure but slows us down, while the subcortical level has a more direct access line.

JEANNEROD

Now, I would be very careful in not putting the intermediate levels in the cortex. I don't think that conscious-unconscious overlaps with cortical and subcortical.

NEURAL CONTROL AS A MAJOR ASPECT OF HIGH-ORDER BRAIN FUNCTION

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"To control" is to regulate a mechanism for a purpose. Neural control is a function of the central nervous system which regulates a variety of mechanisms of the living body for the purpose of daily activities. It is obvious that neural control is a predominant aspect of autonomic and motor activity in which visceral and skeletomuscular mechanisms are regulated for the purpose of homeostasis and behavior. Neural control is an important theme of physiology which has successfully unveiled structural and functional counterparts of neural control in the central nervous system. In particular, the cerebellum is now regarded as an organ which adaptively controls various bodily mechanisms.

Much effort has been devoted toward the development of an effective means of controlling complex machine mechanisms. There are a number of common features in the control of the machine and the living body. Control theories extensively developed in recent years for machine control also indicate various applications to principles of neural control.

The theme of this article is to account for major problems in neural control on the basis of current knowledge of cerebellar function. Beginning with the neural control of reflexes, I attempt to generalize the idea of cerebellar adaptive mechanisms over a wide range of neural control problems, including voluntary movements. Eventually, a possibility will be raised that the cerebellar adaptive mechanisms can apply not only to bodily but also to mental mechanisms which generate and manipulate ideas and thoughts.

Feedback Control vs. Feedforward Control

Feedback is an element of essential importance in classic control systems (Fig. 1A). A feedforward system which lacks feedback is inevitably susceptible to external disturbances as well as to changes in internal parameters (Fig. 1B). Any malfunctioning of such a system would persist or worsen since there is no feedback to correct it. Nevertheless a feedforward system has the advantage of being free from a delay in operation due to feedback and also from any complications that the feedback may introduce into the dynamics of the system. In fact, neural control systems seem to prefer the feedforward mode to the feedback one, since in a living body, a feedback loop is not always available. Also, a feedforward system performs more quickly, with less loading of the central nervous system, than a feedback system. The importance of feedforward control in bodily functions has previously been pointed out by McKay (1966).

The above view applies to reflexes that serve as classic control systems of a living organism (Ito, 1974). A number of reflexes lack feedback, and even if a feedback loop is available, it may function only within a certain limited operational range. For example, visual feedback ceases to operate in a high frequency range of movement because of its relatively long loop time. To be an effective means of neural control, the functional drawbacks in the feedforward operation of a reflex, as mentioned above, must be removed by a neural device which replaces a feedback loop. Such a neural device would be composed of a comparator (COM in Fig. 1C) for detecting control errors through comparison of intended and executed controls, and an adaptor, which, based on the control error, acts to correct the performance of a feedforward controller (AD in Fig. 1C).

Similar consideration applies also to voluntary movements. One first performs a voluntary movement relying upon feedback from sensory organs, but after some practice one will perform the same movement without feedback, the movement being performed more quickly and more automatically with less conscious effort. Here, practice converts the mode of a voluntary movement from feedback to feedforward. This daily experience would suggest a design of a voluntary movement system where both a feedback and a feedforward controller act in parallel with each other (Fig. 2). Initially, the feedback controller would predominate, but it would then be taken over by the feedforward controller adapted during practice in the manner as shown in Fig. 1C.

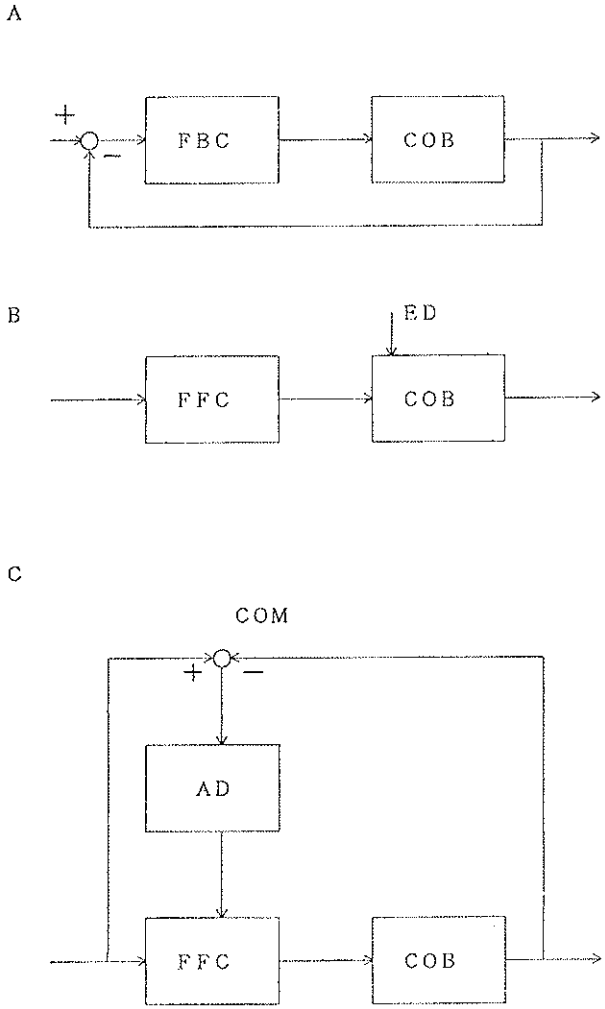

FIG. 1. Block diagrams for control system: A) feedback control system. B) feedforward control system. C) feedforward control system with an adaptive mechanism. FBC: feedback controller. COB: control object. FFC: feedforward controller. ED: external disturbance. AD: adaptive device. COM, comparator.

Adaptive Control of Reflexes

A reflex of the feedforward control mode requires an adaptive mechanism (COM+AD in Fig. 1C) to carry out its purposeful performance. Investigation of the vestibuloocular reflex, which is typically a feedforward control system, disclosed that a part of the cerebellum, the flocculus, provides this adaptive mechanism (see Ito, 1984). The flocculus receives vestibular signals as mossy fiber inputs, which are mediated by granule cells and their axons (parallel fibers) to Purkinje cells. The Purkinje cells of the flocculus, in turn, send inhibitory signals to the relay cells of the vestibuloocular reflex, the flocculus thus forming a sidepath to the vestibuloocular reflex arc (Fig. 3). The flocculus also receives retinal error signals through climbing fibers that monitor performance of the reflex when compensating for head movement. Climbing fiber signals induce synaptic plasticity called long-term depression (LTD) in those parallel fiber synapses which are mediating mossy fiber signals to the Purkinje cells approximately simultaneously with the climbing fiber signals (see Ito, 1989). If this happens, retinal error signals would lead to a modification of the signal transfer characteristics of the floccular sidepath, and as a consequence, dynamic characteristics of the whole vestibuloocular system would eventual-

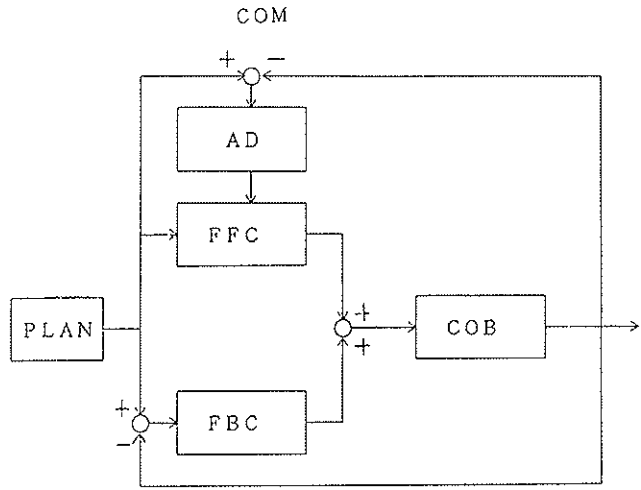

FIG. 2. Scheme for learning in voluntary movement control. Learning shifts the dominant mode of control from feedback to feedforward.

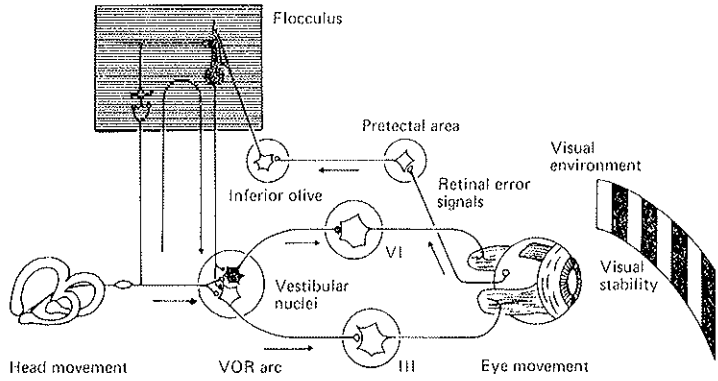

FIG. 3. Neuronal circuitry for flocculovestibuloocular system. III, VI, oculomotor and abducens cranial nuclei. Note that inhibitory neurons and their processes are filled in black, excitatory ones are left as hollow (Ito, 1984).

ly be modified toward minimization of retinal error signals. Thus, an adequate performance of the vestibuloocular reflex against external disturbances and changes of internal parameters would be secured in the manner shown in Fig. 1C.

Adaptive Mechanisms of Cerebellum

The functional feature of the flocculo-vestibuloocular system conforms to the principle of adaptive control, in which the system's operation is maintained as optimal by automatic adjustment of its parameters according to information obtained during the control operation. In particular, the function matches the scheme of a self-tuning regulator, a type of adaptive control system. During the course of evolution of vertebrate nervous systems, the cerebellum emerged in association with vestibular afferents and also with spinal ascending tracts (Larsell, 1934). The original role of the cerebellum seems to be to endow vestibular and spinal reflexes with the adaptability of a self-tuning regulator type of control system.

The above-assumed adaptive mechanism would emerge from the self-organizing capability of the cerebellar cortical networks as theoretically postulated (Marr, 1969; Albus, 1971; Fujita, 1982) and as experimentally evidenced (Ito *et al.*, 1982; Ekerot and Kano, 1985; Sakurai, 1987)

Therefore it would apply widely to the entire cerebellum. In each part of the cerebellum, a small area of the cortex (microzone, Oscarsson, 1976) is closely associated with a small cell group in the vestibular or cerebellar nuclei through Purkinje cell projections and common innervation by climbing fiber afferents arising from a small group of inferior olive neurons (Fig. 4). Collaterals of the mossy fiber afferents to the microzone supply the major excitatory inputs to the nuclear neurons. The cerebellar cortico-nuclear microcomplex shown in Fig. 4 may be viewed as a functional unit of the cerebellum, whose action is based upon the following three principles. First, the Purkinje cell signals are always inhibitory (Ito and Yoshida, 1964; Ito *et al.*, 1964) and so modify the major signal flow through the stem axons of mossy fibers and cerebellar or vestibular nuclear neurons. Second, climbing fiber signals represent errors of the control system in which a corticonuclear microcomplex is involved. Supportive evidence for this postulate has been obtained from studies of Purkinje cell signals related to the vestibuloocular reflex (Ghelarducci *et al.*, 1975), classically conditioned eyeblink reflex (Thompson, 1987), postural adjustment (Amat, 1983), locomotion (Matsukawa and Udo, 1985; Gellman *et al.*, 1985; Armstrong *et al.*, 1988), smooth pursuit eye movement (Stone and Lisberger, 1986), and voluntary arm movement (Gilbert and Thach, 1977; Wang *et al.*, 1987). Third, conjoint activation of a climbing fiber and parallel fibers converging onto a Purkinje cell induces LTD in transmission efficacy from the parallel fibers to the Purkinje cells (see Ito, 1989). In this way, signal flow through cerebellar or vestibular nuclear neurons is adjusted by error signals of climbing fibers through induction of LTD in a cortical microzone. Thus, a corticonuclear microcomplex would represent the neural device of Fig. 1C, if a comparator (COM) is provided by an error detector system which ends at the climbing fibers, and if a microzone constitutes an adaptor (AD) and a nuclear neuron group a feedforward controller (FFC).

Adaptive Control of Voluntary Movements

The exact mechanism of voluntary movement control is still unknown, but based on the above postulates of cerebellar-aided feedforward control, one may assume the following scheme for the implementation of arm trajectory formation. An arm trajectory to be generated would be conceived in cerebral association cortices, including the premotor area.

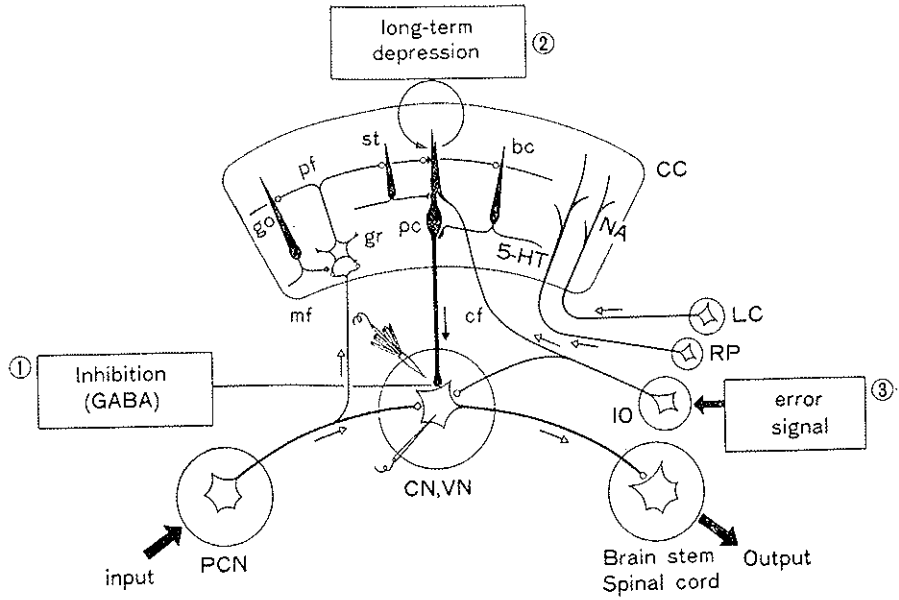

FIG. 4. Structure of a cerebellar corticonuclear microcomplex. CC: cerebellar cortical microzone. CN, VN: cerebellar and vestibular nuclei. PCN: precerebellar nuclei. IO: inferior olive. LC: locus coeruleus. RP: raphe nucleus. NA: noradrenaline. 5-HT: serotonin. mf: mossy fiber. cf: climbing fiber. pc: Purkinje cell. bc: baslet cell. st. stellate cell. gr: granule cell. go: Golgi cell. pf. parallel fiber. (1), (2), (3): major findings that suggest adaptive operation of the corticonuclear microcomplex.

It would then be fed to the executive area of the cerebral cortex (premotor and/or motor cortex), which would convert the planned trajectory into command signals. The motor command signals, in turn, would act upon the skeletomuscular system of the arm to produce the actual trajectory.

During the above processes, the executive cerebral area would initially function with the aid of feedback from the periphery. However, this executive cerebral area may be paralleled with a cerebellar corticonuclear microcomplex that acts as a feedforward system with an adaptive mechanism (COM+AD+FFC in Fig. 2). During practice, the dynamics of the cerebellar corticonuclear microcomplex would be adjusted so that it would eventually replace the action of the motor cortex. Thus, the voluntary movement control would be executed automatically with less conscious concern.

Concept of Models in Neural Control

The above-mentioned manner of operation may be interpreted in the following way. If the actual movement produced by the skeletomuscular system is equivalent to the planned trajectory given to the executive cerebral area, the latter must bear dynamic characteristics inversely equivalent to the dynamics of the skeletomuscular system. In other words, the motor cortex creates an inverse-dynamics of the skeletomuscular system through neural computation referring to sensory feedback. During practice, this inverse-dynamics would develop in the cerebellar sidepath, which then would replace the executive cerebral area (Fig. 5). The practice of voluntary movements would thus be viewed as a process in which an inverse-dynamics model of skeletomuscular system is developed within the cerebellum.

The inverse-dynamics model has been introduced in trajectory formation by a robot arm (Hollerbach, 1982). A computer simulation study using the scheme shown in Fig. 5 demonstrated a remarkable effect in practice on the smooth, efficient trajectory formation (Kawato *et al.*, 1987). It is extraordinary that practice for a trajectory could lead to an improved manner

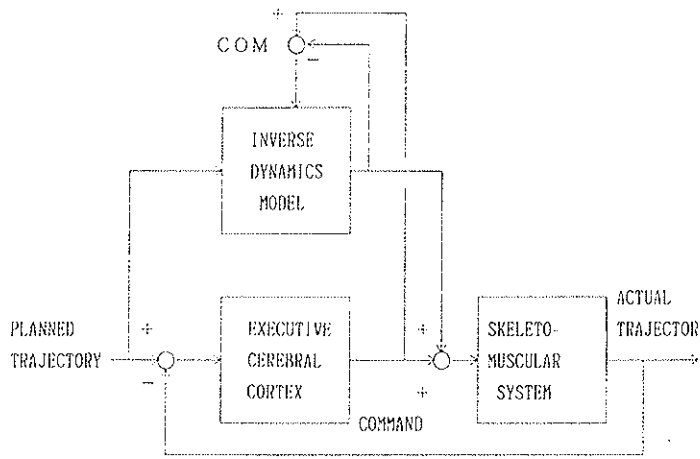

FIG 5. Block diagram showing neural control of voluntary arm trajectory formation with an inverse-dynamics model. Motor learning is assumed to take place by formation of an inverse-dynamics model of skeletomuscular system in a cerebellar corticonuclear microcomplex.

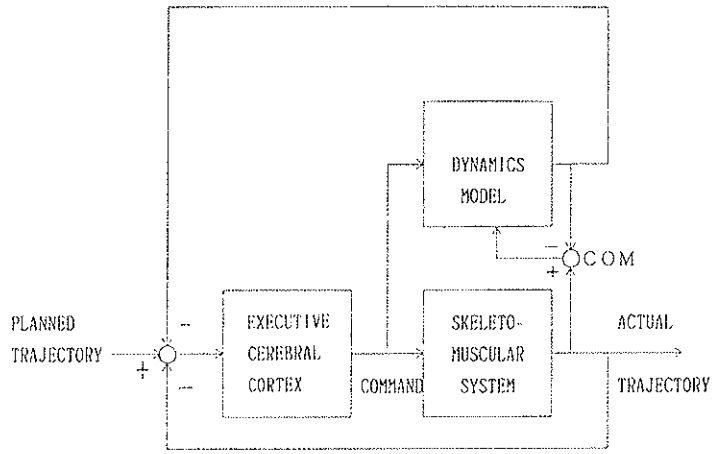

FIG. 6. Block diagram showing neural control of voluntary arm trajectory formation with a dynamics model. A dynamics model is assumed to be built in a cerebellar corticonuclear microcomplex.

of the formation of other trajectories as well, as one experiences during the practice of coordinated movement (e.g., sports).

Another scheme of voluntary movement control using a cerebellar dynamics model was suggested previously (Ito, 1970). If a cerebellar corticonuclear microcomplex represents the dynamics of the skeletomuscular system, an internal feedback loop would be formed through the cerebellum, which would then replace the feedback loop through the external world (Fig. 6). The cerebellar sidepath may be adjusted through comparisons of inputs to the motor cortex and outputs of the cerebellar corticonuclear microcomplex. The fact that the pyramidal cells of the motor cortex send signals to the paravermal cortex of the cerebellum and receive return signals would favor the dynamics model of Fig. 6.

The dynamics model of Fig. 6 replaces the skeletomuscular system so as to enable the motor cortex to perform without feedback from actual movement, while the inverse-dynamics model of Fig. 5 replaces the executive cerebral area so that the cerebral cortex may be omitted once the sequence has been learned. At present, there seems to be no particular reason to exclude either one of these two models. Further, it seems possible that the two models account for different stages of motor learning or for learning of different types of voluntary movements. In either

case, a model can be formulated in the manner of model-reference control, a type of adaptive control, within a cerebellar corticonuclear microcomplex.

Mental Control

In Fig. 5, it is assumed that an inverse-dynamics model which replaces the motor cortex can be formed by comparing outputs of the motor cortex and the model, without referring to the actual movements. Even when the skeletomuscular system is not activated, i.e., movement is not actually carried out, learning will proceed just by involving the motor cortex and a cerebellar corticonuclear microcomplex. This situation may apply to mental activity represented by image training of a gymnastics routine through which one acquires motor skill without practicing the actual movements. Supportive evidence is provided by non-invasive measurement in human subjects showing that the cerebellar activity is significantly enhanced during imagined tennis playing (Decety and Ingvar, 1989).

If Fig. 5 is modified so as to replace the motor cortex and skeletomuscular system with cerebral cortical areas that are irrelevant to movements (Fig. 7), it would represent adaptive control in mental activity such as mental arithmetic, silent reading, etc. In Fig. 7, the pathway for adapting a cerebellar model is assumed to run through the parvocellular red nucleus, inferior olive and eventually impinge onto a model, supplying a collateral to the dentate neurons. This postulated adaptation pathway may suggest that the well-known rubro-olivo-dentate triangle (for references, see Ito, 1984) serves as a pathway for internal learning.

Involvement of the cerebellum in mental activity has been suggested based on comparative anatomy that the most lateral parts of the cerebellum enlarged dramatically in the human brain, concomitantly with the enlargement of the cerebral association areas, and also on clinical evidence that lesion of these most lateral parts of the cerebellum causes no apparent motor disturbance (Leiner *et al.*, 1986; Dow, 1988). The observation that the activity of human cerebellum is enhanced during silent counting (Decety and Ingvar, 1989) conforms to the above view. Whether the view can be extended over a wide range of our mental activity, including language and cognitive functions, in terms of mental models proposed by Johnson-Laird (1983) is yet uncertain, but it is an interesting possibility for future exploration.

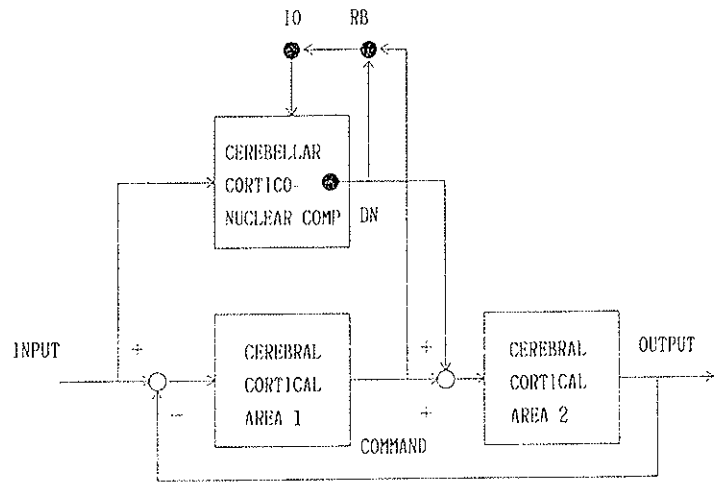

FIG. 7. Modification of Fig. 5 for mental control. IO: inferior olive. RB: parvocellular red nucleus. DN: dentate nucleus.

Control Augmentation vs. Stabilization Augmentation

Above considerations may lead to a general concept that the cerebellum is an organ specifically evolved for augmenting neural control, owing to its unique capability of adaptive control. This cerebellar action covers reflexes and compound reactions (such as posture and locomotion), both motor and autonomic, and further extends to voluntary motor control, and probably also to mental activity.

Stability is another important factor to be considered in the control of complex systems. It is to be noted that control augmentation and stabilization augmentation each require a separate device. If the cerebellum is devoted to control augmentation, there must be another brain region devoted to the augmentation of neural stabilization.

The basal ganglia consist of a massive neural structure lying deep in the interior of the cerebrum. This structure has vast connections with the brain stem and the cerebral cortex. Lesion of the basal ganglia leads to either akinesia, as seen in Parkinsonism, or hyperkinesia, as seen in chorea. These neurological symptoms suggest that a major role of the basal ganglia is to maintain stability of motor systems.

These considerations conjointly lead to a suggestion that, as the cerebellum is devoted to augmentation of neural control, the basal ganglia are specifically dedicated to augmentation of neural stabilization (Ito, 1986). This suggestion is useful in the efforts to uniquely define functional roles of the basal ganglia.

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DISCUSSION

SINGER

Dr. Ito, you showed beautiful evidence of how down-regulation of synaptic efficacy can be used to adjust reflexes. Now it has been a puzzle for a long time to people working in the field, that they only saw up-regulation and the question always was, can you continue a whole life by up-regulating things and the same question is now addressed here. Can you have down-regulation as the only available mechanism? I guess you cannot. Is there any evidence for a neuronal process or a resetting process by which you can also increase the gain of your synapses due to a reward signal?

ITO

On theoretical grounds, this is also a very necessary consideration. People have been assuming that the frequency of these climbing fibres and of the parallel fibres must be above a certain threshold to produce plasticity for long term depression. However if it's smaller, it will produce the opposite. So minus long term depression will occur and this theoretically accounts for the upward regulation. In the physiology there is also evidence that the stimulation of parallel fibre alone produces a certain amount of potentiation.

ROLAND

My questions are about what goes on in the Purkinje cell dendrites when an animal is learning something. You mentioned that calcium goes into the dendrite, and I think it is suggested at least that the receptor is an aspartate receptor which might open an NMDA receptor-type channel. Is that established or how does the calcium get into the dendrite first?

ITO

The climbing fibre has numerous synaptic junctions with dendrites, so it activates the dendritic membrane at the same time with very powerful excitation. Then the dendrites generally give a beautiful calcium-dependent spike by calcium flow into the dendrite.

ROLAND

But what is the channel involved?

ITO

This has not been shown very well, but certainly membrane calcium channels. Which type, we don't know yet.

ROLAND

But they are transmitter operated or are they not? They are just voltage.

ITO

Yes, that's right. That's the difference from hippocampus. So the transmitter causes a big depolarization, 20 millivolts or so, a big PSP.

WIESENDANGER

I have a question regarding your two models, the inverse dynamics and the dynamical model. I don't know which one you favour, one I know has been tried out on the computer. I think that both are compatible with the anatomy. However, I fear that the inverse dynamics model has no support from physiology insofar as the model would predict that the motor cortex is at rest when we have automatized the skill. I think there is absolutely no support for the concept that when learning is complete the motor cortex is not involved any more in the task. I would like to know your opinion and whether your original model, which I would like better in this respect, has been tested also on the computer; whether it's also smooth-running like the other one.

ITO

In the computer simulation model the two models are combined.

DESMEDT

In the model you are proposing for the teaching in the cerebellum, you are relying on the teacher and this is a highly symbolic and restrictive postulate.

I am wondering, if you are dealing with such a complex function, everyone would expect that this involves many cells acting in parallel, many circuits acting in parallel. I am wondering if there are enough cells in the inferior olive to do the job and whether the projection from single cells is sufficiently selective to do the job. I think you are investing so much in this small nucleus compared to the whole cerebellum that I am a bit uneasy about it. Maybe you have some answer to this question. I think it is a major question if you are investing it with the teacher function which is the essential function in the whole learning process.

ITO

Yes, certainly I understand your question. It's a teacher in the original model, but now I assume that it's in the final stage of an error detector system. So the inferior olive is the final stage, and before that there will be very complicated mechanisms that detect errors. That can be in the periphery or can be in the cerebral cortex. Number? If I divide the total number of Purkinje cells, it's 20 million in humans, by a factor of 10, 2 million.

FREUND

Along the same lines as the question from Mario Wiesendanger, how could you explain that you never, to my knowledge, after hemicerebellectomies see any following weakness? So if your model would work, I would expect that at least some sort of movements, skilled movements, highly trained movements would have major deficiencies also in terms of power.

ITO

I wish to assume that cerebellectomy may abolish the learning capability and abolish the models previously formed, so the cerebral cortex now has to operate through feedbacks. So it has to be slow, but it wouldn't produce any difficulties in terms of muscle forces.

MOUNTCASTLE

I would like to ask you, Ito, or others here who may know, whether there has ever been any disorder of cognitive functions described in patients with cerebellar disease, which I think your model would require?

ITO

One point maybe is that a recent review by Dow pays attention to the fact that when neurosurgeons destroyed the very, very lateral part of the dentate nucleus, there was no obvious motor disturbance. So they propose that this very lateral part of the dentate nucleus is involved in mental activities, and their further proposal is that as the major part of the cerebellum takes care of motor dexterity, this part may take care of mental dexterity, quick and smooth thinking.

BROOKS

My comment relates to Mario Wiesendanger's question about the motor cortex activity. After all, the dentate projects not only to the primary motor area but also to the premotor area, and the premotor area neurons mostly are not related directly to the details of the movement. I had assumed while you were talking that your inverse dynamics model was perhaps about a component in the premotor area. Your dynamics model would fit very well what happens in motor cortex. Has anybody ever undertaken an experiment where you could follow the development of motor or not motor related cells in premotor cortex during learning?

ANDERSEN

I wonder about one specific point. If the inferior olive is an essential element in the error detector, then one would like to preserve the specificity of the errors. How would you see the electrical coupling between the different inferior olive cells? Does that have a function in this regard or will it be something you do not want to have?

ITO

The real physiological meaning of electric coupling is not clear yet. However, concerning the function of the inferior olive I wish to propose one specific function, that is randomizing impulse frequencies. The error correction signals should not be rhythmic because then it will cause rhythmic movement. So it seems to be carefully randomized.

RAKIC

In looking at the three animals that I have experience with: mouse, monkey and humans, the pons increased tremendously in size. It's tiny in mouse and it's big in monkey, tremendous, but when you come to humans it's gigantic. It's millions and millions of neurons added in evolution in the pons, and input comes from the cortex but not from the motor cortex. The increase is from the so-called frontal pontine, parietal pontine, temporal pontine. What has this to do with the purpose or intention of movement and perhaps motivation? It's not from the motor or premotor cortex but from the other areas. So where is that in the model?

ITO

In the final model, the cerebellar complex can be inserted in any part of the cerebral cortex as providing for the inverse dynamics model, even in mental activity which is not immediately related to movement.

RAKIC

Everything is going from the cortex to the pons and then secondarily to the cerebellum, except area 17. Is there anybody who knows more about that?

ITO

In the monkey, not in lower mammals. The thinking about cerebellar function should be referred to where the cerebellar output goes, because it is a target to be modulated. Input to the cerebellum may come from anywhere. The cerebellum would collect the necessary information through the mossy fibres, but what it does do is related to the target. So we have to think of the areas to which the cerebellum is projecting, which are mostly the frontal part of the cerebrum.

ECCLES

Heinz Stephan has a study of all of the sizes of the cerebellar evolutionary processes from the primates up to man. He does this extremely well, showing you that, for example, the pontine nuclei go up extraordinarily, almost tenfold, in size index relative to prosimians. The inferior olive has a size index over 4. The nuclei of the cerebellum vary, but of course the dentate nucleus has a

size index over 4. This is exactly what you would expect in relation to the evolution of the cerebellar cortex.

INGVAR

I'd like to ask, is there any evidence at all that there is a hemispheric dominance in the cerebellum? That is to say, that one half of the cerebellum is more involved in, shall we say, more sophisticated type of control than the other one. Could it be that all control mechanisms are double?

ITO

The question is, is there any hemispheric dominance in the cerebellum? No.

GOLDMAN-RAKIC

I'd like to come back to the issue of cognition and cerebellum. I hate to contradict Pasko, but I'm not aware that the prefrontal areas project very much at all to the pons. Also the occipital may not. That's the first point. The second point is I thought my understanding of the evolutionary changes is that relative to the cerebral cortex the cerebellum gets smaller relative to the rest of the brain. I mean absolute size increases but not relative. The third point relative to the stabilization issue is that everything that we have learnt from the anatomical tracing studies in recent years suggests that the basal ganglia inputs back to the premotor cortex are separable and segregated from the cerebellar projections. There seems to be a kind of parallel circuitry. I'm wondering whether you are thinking about the convergence of these two massive inputs to the premotor cortex.

ITO

First, the involvement of prefrontal cortex. It may not be a very big projection to the cerebellum but there is also electrophysiological evidence by Sasaki in the monkey.

JEANNEROD

I would like to discuss the problem of sensory feedback in your models. I think that one has to be careful before assuming that sensory feedback is

no longer used after the dynamic model has been established. For instance, this is shown by denervation experiments in monkeys. It shows that the loss of sensory feedback may have very dramatic effects, at least for movements beyond a certain degree of complexity. Although the simple single joint movements may be preserved reasonably well, the multiple joint movements are absolutely impossible, even of learned movements, after the loss of sensory feedback. So I think one has to be careful about that.

Iro

I don't assume that the cerebellum model can replace the motor cortex completely, but there seem to be two feedback systems always connected in parallel. So the feed-hold part is always helping to reduce the load on the feedback system, but whenever its performance is inadequate, the feedback system has to come in to take over.

MOVEMENT-RELATED POTENTIALS AND COMPLEX ACTIONS: COORDINATING ROLE OF THE SUPPLEMENTARY MOTOR AREA

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INTRODUCTION

Historically, our knowledge of human brain functions and brain-behaviour relations was based either on clinical or neuropsychological assessment in patients having localized lesions, or on comparative research of animals to man. Conclusions in clinical research were indirect; the function of a brain area was hypothesized by studying the symptoms after its lesion. Localizationists have often been accused of making false assumptions in their attribution of a certain function to that brain area whose lesion destroys that function, as this area may only be a link in a complex functional chain. This point of argumentation can now be operationally defeated by more recent techniques that offer the possibility to directly investigate the relations between brain and behaviour in the intact human brain in action rather than relying on merely negative evidence obtained from destruction. From these studies we know that, for instance, the classical speech centers are really active when we are speaking, confirming the localizationists. One of the areas whose function is less well known is the supplementary motor area (SMA) on the mesial, fronto-central surface of the cortex between the hemispheres. In the last five years we have designed and conducted experiments that were aimed at elucidating the function of the SMA. As will be shown in this paper, the SMA is critically involved in the initiation and temporal organization of human volitional acts.

Methods

Brain activity was assessed by measuring changes of cortical steady (DC-) potentials, regional cerebral blood flow (rCBF), and neuromagnetic fields (magnetoencephalography, MEG) during behavioural tasks.

The electromagnetic techniques (EEG and MEG) measure neuronal activity with a high temporal resolution (limited only by the setup of the data acquisition system). Changes of magnetic fields are measured by superconducting quantum interference devices (SQUIDs). In order to investigate higher functions of the brain, shifts of the cortical DC-potential are averaged in a task-related way. Registration of the DC-EEG by scalp electrodes requires special techniques of electrode application and data acquisition (Lang *et al.*, 1988a,b; Bauer *et al.*, 1989). In some of our studies, radial current densities in the scalp have been calculated and mapped. Radial current densities have the advantage of being reference-free and of reducing effects of volume conduction (Hjorth, 1975; Nunez, 1981; Perrin *et al.*, 1987; Lindinger *et al.*, 1989).

Both in MEG as in EEG studies, methods of signal enhancement such as averaging are necessary. In the present experiments 48 to 128 trials per experimental condition have been averaged. The following electrode positions were used for EEG recordings (Spatial relations of electrodes to cortical gyri have been described by Homan *et al.*, 1987): F3/4 (rostral bank of the superior frontal gyrus), Fz, C3/4 (precentral gyrus, shoulder to wrist area), Cz, P3/4 (superior parietal lobule near intraparietal sulcus, superior to posterior portion of supramarginal gyrus), Pz, T3/4 (overlapping middle and superior temporal gyri), 01/2 (occipital lobe), Oz. In addition to the 10/20 system, FCz (midway between Fz and Cz), C1 (midway between Cz and C3), and C2 (midway between Cz and C4) were used for recordings.

Circulatory-metabolic methods such as PET (Positron Emission Computerized Tomography) and SPECT (Single Photon Emission Computerized Tomography) do not measure neuronal events directly but changes of blood flow and metabolism. Close relations of neuronal events to blood flow and metabolism are still controversially discussed. Temporal resolution of PET and SPECT is limited, 20 sec may be best at present. But these techniques offer the possibility to assess activation patterns in the whole brain with spatial resolutions as good as 4 to 6 mm.

Investigations in present studies apply the SPECT technique using 99^{m}-Tc-Hexamethyl-Propyleneamineoxime (99^{m}-Tc-HM-PAO). This tracer crosses the blood brain barrier with a high first pass extraction fraction and

is deposited in brain tissue within the first 2 min after intravenous injection. Deposition is mainly related to blood flow. Within about 2 hours, redistribution of the tracer was not measurable (Neirinckx *et al.*, 1987; Podreka *et al.*, 1987; Lang *et al.*, 1988d). Local radioactive count rates (gamma-ray) were measured by a dual head rotating scintillation (gamma) camera (for methods see Podreka *et al.*, 1987). Regions of interest (ROIs) were defined according to anatomical templates within five consecutive 21.9 mm thick transversal slices. For each ROI a relative local count rate (RI, regional index) was obtained by referring the tracer concentration within a region to the mean concentration as calculated across all regions.

Results and Discussion

1. *Volitional Actions*

There is physiological evidence enabling us to distinguish basically two ways by which movements are initiated in humans: Firstly, movements are initiated as responses to external cues. Of course, such reactions are also internally mediated before gaining access to the motor system. Secondly, humans perform self-initiated actions, i.e., movements without any external cues (endogenous actions). Self-initiated movements will be subdivided into those which are intended, which means that initiation and execution of these particular movements are closely directed towards the achievement of a goal, and those which are non-intended per se (although they may be part of an action which is intended as a whole). Two examples may explain the distinction between intended and non-intended self-initiated movements: In one experiment, a movement of the hand has been defined as task. Here, initiation and execution of this particular hand movement is closely related to the experimental demands. The same subject may be instructed to solve cognitive tasks in another experiment which requires no hand movements. He may perform hand movements which now are not task-related and per se not intended. In fact, cortical activation patterns differ between intended and non-intended self-initiated movements (I. Keller, personal communication) indicating that intentionality for action is a major source of variance for movement-related brain activity. Intentions precede and accompany actions but do not strictly initiate them. We may intend to move the finger but, as can be experienced by ourselves, an additional impulse is necessary to act at

a certain moment. This requires a neuronal system which is responsible for transducing motives and the intention to act into effective actions (Kornhuber, 1984a,b; Deecke *et al.*, 1985b; Kornhuber *et al.*, 1989). The existence of such a system is often not recognized. Rather, it is believed that cognitive representations of an action ("Vorstellung" or imagination) initiate actions as originally proposed by Liepmann (1900).

Volitional actions as investigated in our studies are self-initiated and intentional. Furthermore, they are considered to be planned, at least in part, in advance by use of memory-based models of movement outcome and consequences (Bernstein, 1984). The initiation of such volitional actions is preceded by the Bereitschaftspotential (BP); (Kornhuber and Deecke, 1964, 1965).

The Bereitschaftspotential is a slow, surface negative potential shift which starts about one second or more prior to movement initiation (Fig. 1, 2). The BP has a rather consistent temporo-spatial distribution over the scalp. It starts in recordings overlying the dorso-medial frontal cortex (FCz or Cz), where it has a maximum in amplitude. In the beginning, the BP is bilateral-symmetrically distributed in centro-lateral (C3, C4) and parietal recordings (P3, P4). In the last 500 ms, the BP becomes lateralized in unilateral finger movements with the higher amplitudes contralateral to the performing hand (Deecke *et al.*, 1969, 1976; Kristeva and Deecke, 1980; Grözinger *et al.*, 1979; Boschert *et al.*, 1983; Deecke *et al.*, 1984; Lang *et al.*, 1984).

2. *Sources of the Bereitschaftspotential in Simple, Rapid Limb Movements*

Three cortical areas have been identified so far as being active prior to the initiation of a simple, rapid limb movement: the dorso-medial frontal cortex, which mainly contains the supplementary motor area (SMA) and the primary motor cortices (MI) of both hemispheres.

The contribution of the MI cortex to BP topography could be demonstrated by varying side and part of the body which performs the movement. Movements of the fingers and those of the toes have different BP topographies which can be modeled by current dipoles in the respective representation areas of the MI cortex (Boschert and Deecke, 1986). Topographical analyses of movement-related potentials have indicated that not only the contralateral MI cortex but also the ipsilateral one becomes activated in unilateral movements (Kornhuber and Deecke, 1965; Cheyne, 1988; Lang *et al.*, 1989a,b). The MEG has been used to study changes of

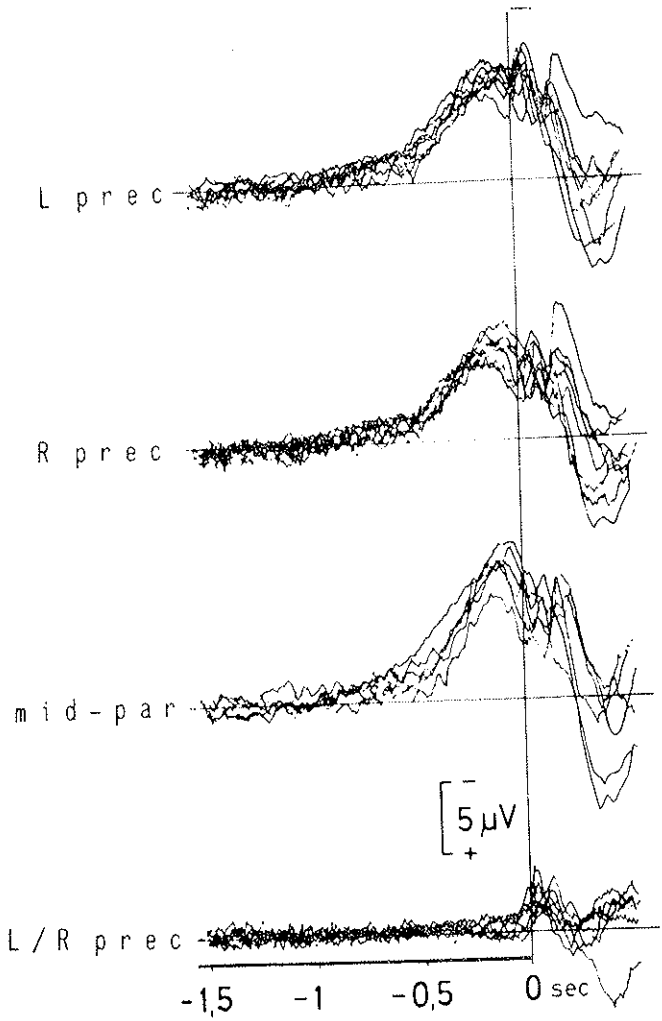

FIG. 1. Slow shifts of the cortical DC potential (Bereitschaftspotential, BP) preceding volitional, rapid flexions of the right index finger (t = 0, vertical line). Recording positions are precentral left (L prec, C3), precentral right (R prec, C4), mid-parietal (Pz). Unipolar recordings with linked ears as reference. The difference between the BP in C3 and in C4 is displayed in the lowest graph (L/R prec). Superimposed are the results of eight experiments as obtained in the same subject on different days. Data obtained by Deecke, Grözinger and Kornhuber, 1976.

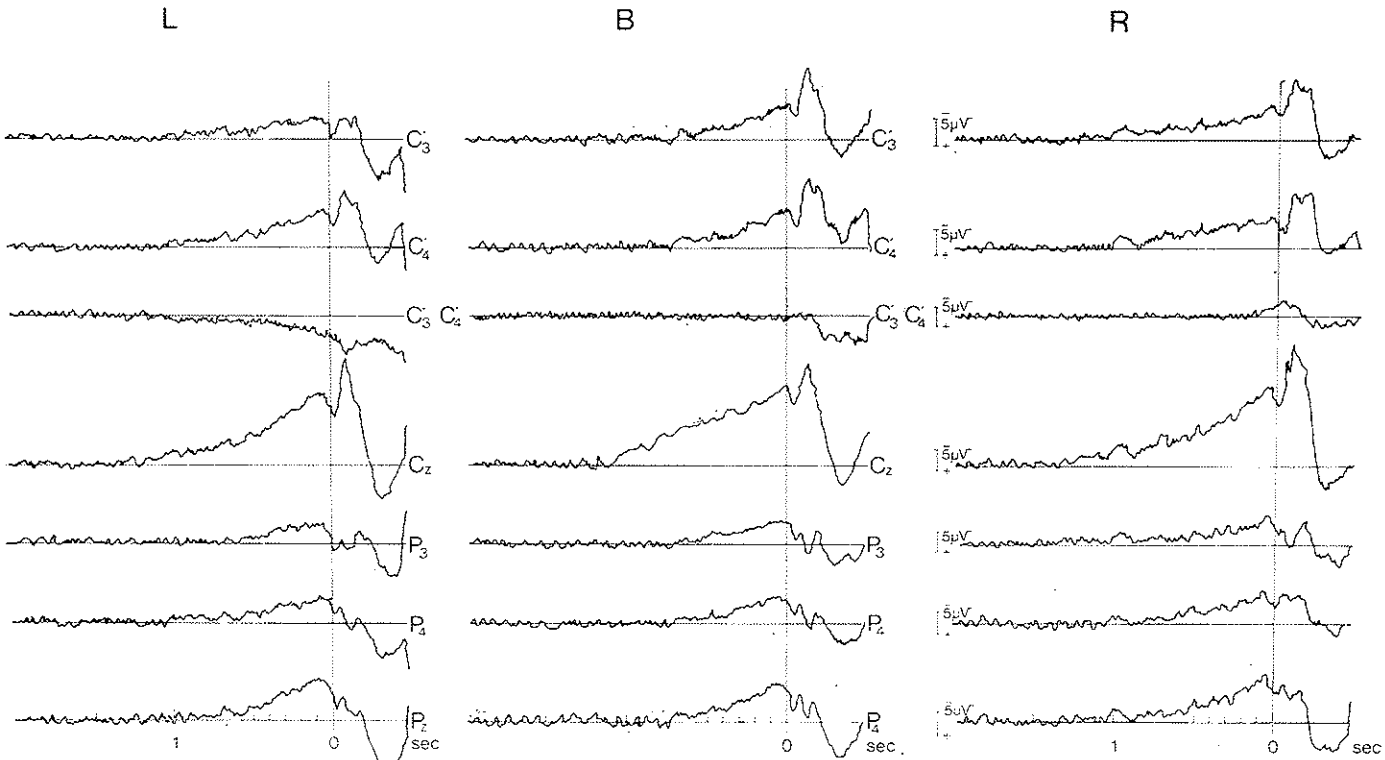

FIG. 2. Cerebral potentials preceding left unilateral (L), bilateral simultaneous (3) and right unilateral (R) index finger flexions in a left-handed subject. Averages were derived from 128 artifact-free movements. Bereitschaftspotential was maximal at the vertex. In precentral leads it showed a contralateral preponderance in the unilateral conditions and symmetry in bilateral movements. Premotion positivity was best seen in parietal leads, typically in Pz in L. Monopolar recordings were referred to linked mastoids. From Kristeva and Deecke, 1980.

magnetic fields preceding simple, rapid finger movements since 1982 (Bereitschaftsmagnetfeld, BM; Deecke *et al.*, 1982, 1983; Cheyne, 1988). Initial experiments could clearly localize the current dipole within the MI cortex (Fig. 3). Meanwhile, the BM has been re-examined by using a 14-channel MEG system in the electrically and magnetically shielded chamber of the Neurological University Clinic, Vienna. It was possible to map the homunculus of the MI cortex with a precision that even allowed to separate neuronal activities caused by movements of different fingers (Cheyne *et al.*, 1989). MEG measurements as well as EEG recordings using subdural electrodes in humans demonstrated an activity of the MI cortex preceding EMG onset of volitional movements about 250 to 500 ms (Deecke *et al.*, 1982, 1983; Cheyne, 1988; Cheyne *et al.*, 1989; Neshige *et al.*, 1988).

Studies of cerebral blood flow and metabolism in humans have demonstrated the SMA as being active during movements of fingers, eyes, tongue and mouth (in speech, Lassen *et al.*, 1978; Roland *et al.*, 1980; Ingvar, 1983; Fox *et al.*, 1985). However, only measurements of electric and magnetic fields have the temporal resolution sufficient to distinguish between activation preceding and that accompanying the movement. Activity of the dorso-medial frontal cortex including the SMA has been shown to cause the early component of the BP (Deecke and Kornhuber, 1978; for review see Deecke *et al.*, 1985b; Deecke, 1987). Various further BP investigations have substantiated the hypothesis of an SMA participation in the initiation of volitional acts: (1) BP recordings with subdural electrodes in patients having epilepsy indicated a pre-movement activity of the dorso-medial frontal cortex (Neshige *et al.*, 1988). (2) Movement-related DC shifts at the vertex (Cz) can functionally be separated from those in C3/4 (Lang *et al.*, 1988b, 1989b). (3) Topographical studies also enable separation of cortical activity over the dorso-medial frontal cortex from that of the MI cortices. In addition, time series of such maps indicate that the activity in the dorso-medial frontal cortex precedes the activity of MI cortices (Fig. 4). Additional support for an SMA participation came from MEG studies. Fig. 5 shows that there is not only a reversal of directions of magnetic fields in the MI cortex but another earlier one in the frontocentral midline (Deecke *et al.*, 1985a). In monkeys, neuronal activity in the SMA preceding self-paced movements was found to precede movement initiation by 1 to 2 seconds (Okano and Tanji, 1987). Interestingly, in one study neuronal activity in the SMA occurred on occasion that the self-placed movement was task-relevant (Mann *et al.*, 1988).

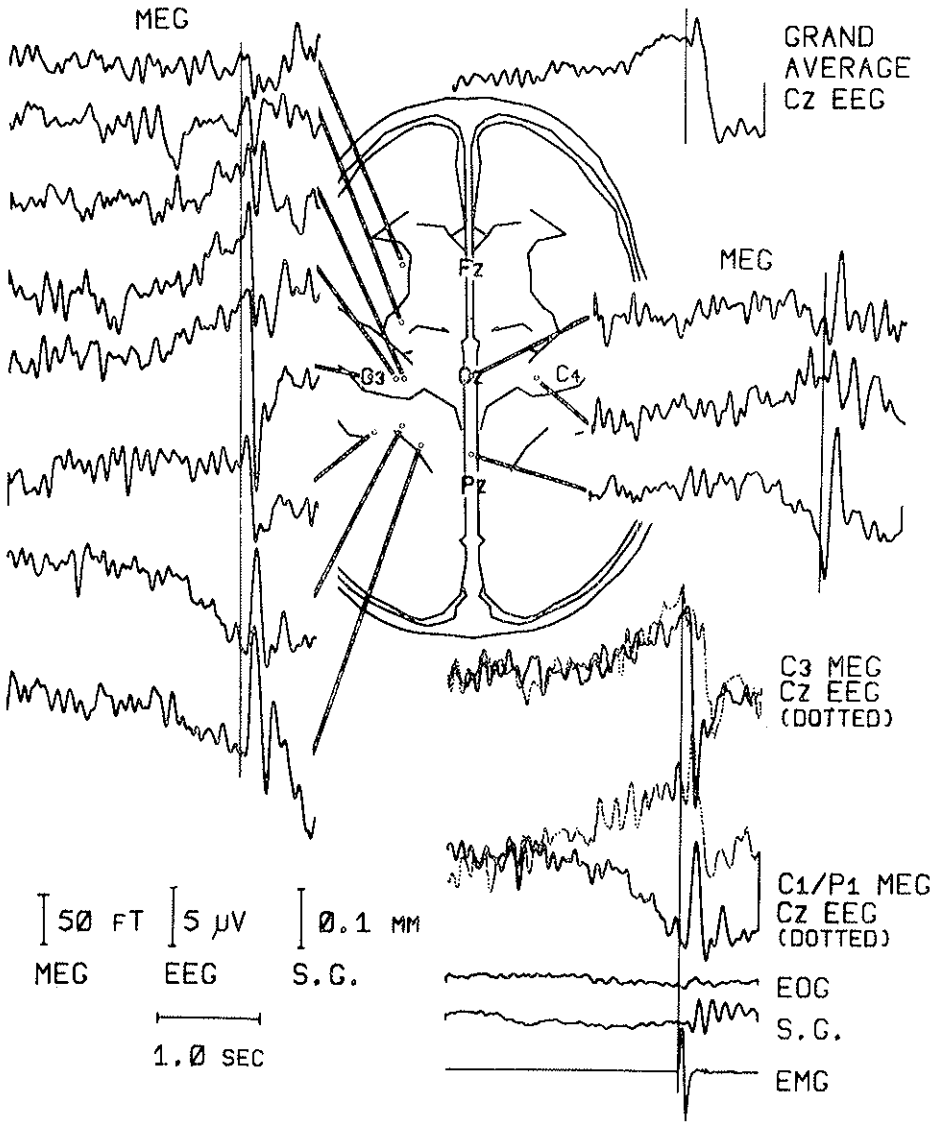

FIG. 3. Averaged MEG recordings over different locations of the scalp as indicated on the sketch showing upper cortical convolutions. Subject P.B. All averages are the result of successive blocks of 80 self-paced right finger flexions except for the grand average Cz EEG in the right upper corner. Vertical line indicates onset of electrical muscle activity (EMG). At the lower right is the MEG recorded over the precentral (C3) and postcentral (C1/P1) locations with the simultaneous Cz EEG superimposed for comparison. Shown below are the EOG, head displacement (SG) and EMG. All recordings were done with breath holding. From Deecke *et al.*, 1982.

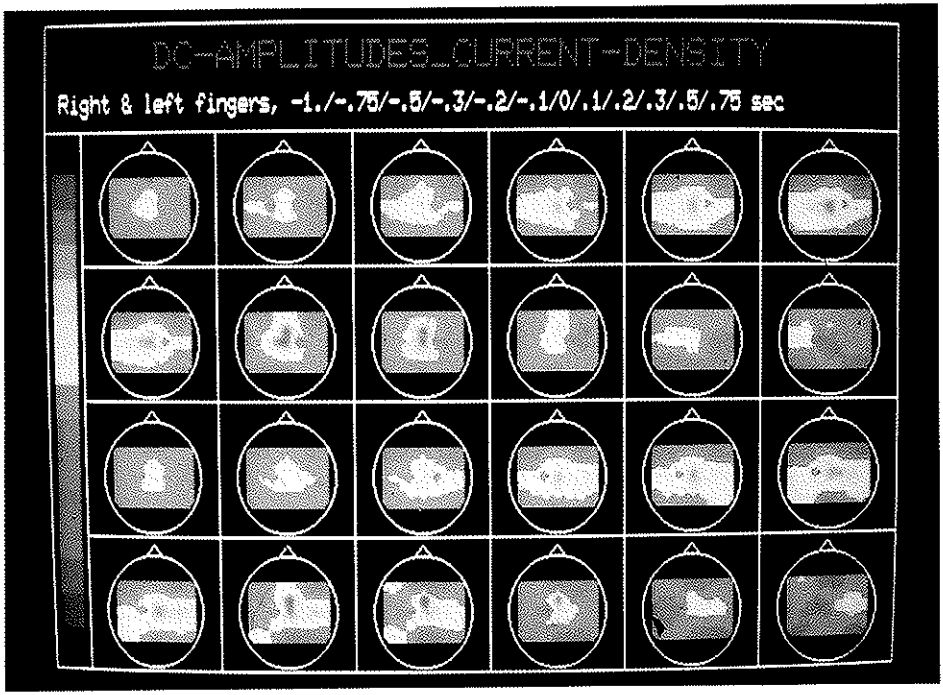

FIG. 4. Maps of radial current density across the scalp. Colour "green" indicates that current density is zero, current flow entering the scalp (due to cortical surface-negativity) is indicated by red, exiting the scalp by blue colours. For both directions, scaling of colours is proportional to radial current densities. All maps are equal scaled. The upper two rows display radial current density maps when voluntarily moving the right index finger; the lower two rows present data of a voluntary movement of the left index finger. Maps have been calculated at times before movement onset (from left to right: −1.0 s, −0.75 s, −0.5 s, −0.3 s, −0.2 s, −0.1 s), at movement onset (0.0 s), and after movement onset (0.1 s, 0.2 s, 0.3 s, 0.5 s, 0.75 s). The first activity of the EMG of the M. flexor indicis was taken as marker for movement onset. Note, before movement onset, there is an initial activity of the mesial fronto-central cortex, then the contralateral MI cortex is activated.

3. *Function of the SMA in Simple and Rapid Movements*

BP maximum in recordings over the mesial, fronto-central cortex is the characteristic feature of voluntary movements and can be found prior to limb movements (Deecke *et al.*, 1976; Boschert and Deecke, 1986), speech production (Grözinger *et al.*, 1979; Deecke *et al.*, 1986), and saccadic eye movements (Becker *et al.*, 1972). This is particularly

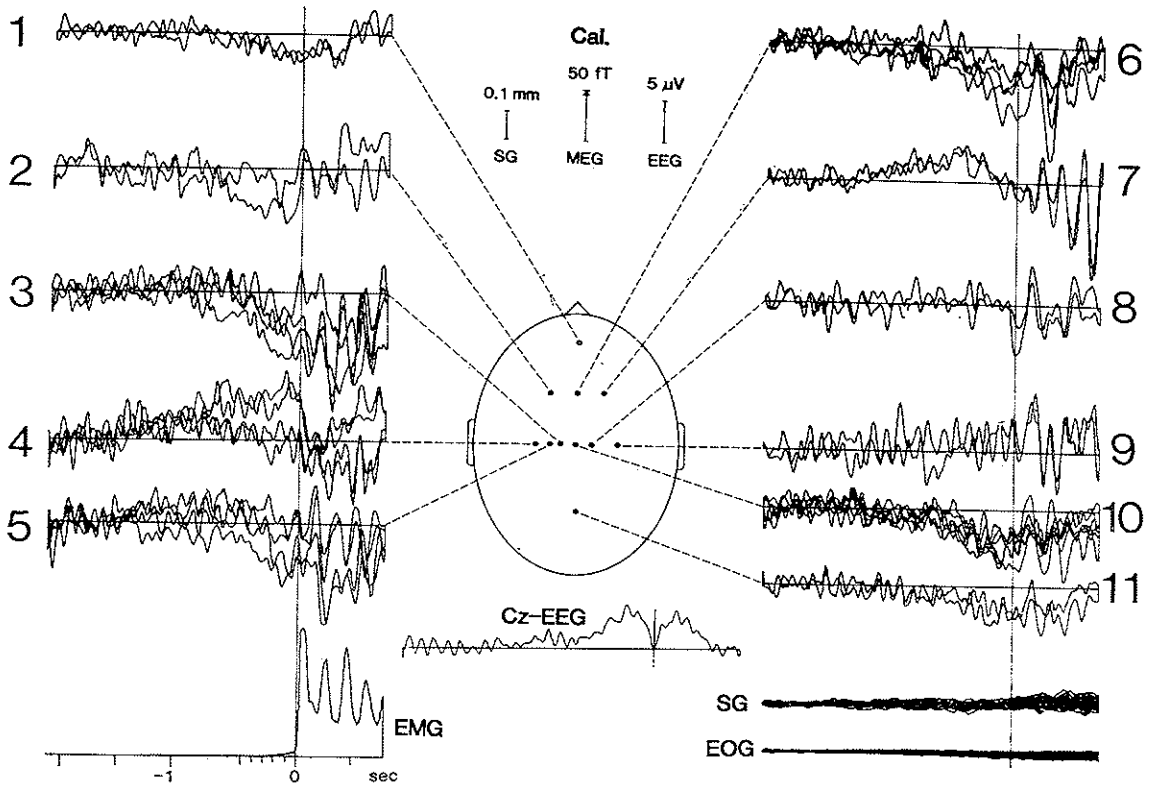

FIG. 5. Bereitschaftsmagnetfeld (BM) or readiness magnetic field preceding a complex right finger tapping task in a right handed S. Each trace represents 40 artifact-free trials. SG = train gauge recording of head displacement. Upward deflections correspond to fields exiting the head (MEG) or negative potentials (EEG). From Deecke *et al*, 1985a.

remarkable since it is known that execution and control of different kinds of movements are widely decentralized in the human brain.

For example, saccadic eye movements are organized in many parts of the brain, ponto-mesencephalon, superior colliculus, parieto-occipital cortex, frontal eye field. Programming of saccades depends on the behavioural context: lesions of the frontal eye field impair self-initiated, volitional saccades but preserve reflexive saccades, whereas posterior lesions disrupt visually initiated eye movements (Kennard and Ectors, 1938). Neuronal activation in visually triggered saccades has been found in the parietal cortex; some neurons in the frontal eye field show pre-saccadic firing in the absence of visual input (Bruce and Goldberg, 1985). Despite the known decentralization of saccadic eye movements, PET studies in humans demonstrated activation of the SMA in all types of saccadic eye movements (targeted as well as untargeted, stochastic as well as rhythmic, auditorily as well as visually cued; Fox *et al.*, 1985). Animal research has substantiated this finding (Schlag and Schlag-Rey, 1985) but emphasized that SMA neurons are in particular active when initiating and executing learned, goal-directed eye or arm movements (Mann *et al.*, 1988).

Considering the wide distribution of the motor system, it is not likely to assume that the SMA is involved in the detailed elaboration of movement parameters. A role of the SMA for linking motor subroutines by internal-based models has been suggested by Goldberg (1985) and Roland *et al.*, 1980, 1984. But it may be difficult for one brain structure to do this work for all kinds of movements (speech, eyes, limbs). Rather, the SMA seems to be involved in one common process, that is, to initiate actions — or in other words — to transduce motives and intentions into action at the right moment (for review, see Kornhuber, 1984a,b; Kornhuber *et al.*, 1989; Deecke *et al.*, 1985b). This seems to be true for self-initiated movements which are intended (McAdam and Seales, 1968). Self-initiated actions which are not task-related are also preceded by a slow negative potential shift, which is, however, different from the usual BP distribution having no maximum in recordings of the mesial, fronto-central cortex (I. Keller, personal communication).

4. *After the Starting Signal has Been Released*

Systematic analyses of the BP potential course revealed that in approximately 85% of subjects the Bereitschaftspotential reverses to

positivity about 90 ms prior to movement onset in the electromyogramm (pre-movement positivity, PMP; Deecke *et al.*, 1969, 1976). About 50 ms prior to movement onset a sharp negative potential arises over the contralateral MI cortex. This negative potential has been called motor potential (MP); (Deecke *et al.*, 1969, 1976). It does not reflect the first activation of the MI cortices. As described above, the contralateral and, to a lesser degree, the ipsilateral MI cortices become activated already in the last 500 ms before movement onset. The MP may correspond to synaptic events in conjunction with the pyramidal cell firing in area 4 as the activity in the final motor pathway to alpha motoneurones in the spinal cord.

The latency of 30 to 40 ms between PMP and MP led to the hypothesis that the command to move is perhaps not transferred directly from SMA to MI but via subcortical loops (Kornhuber, 1974; Deecke *et al.*, 1976). Recordings of single neurons were in support of this view (Lamarre *et al.*, 1980; Melnick *et al.*, 1984).

5. *The Bereitschaftspotential Preceding Complex Movements*

The BP contains elements of anticipatory task-specific planning. Amplitudes and topography depend on structure and/or complexity of the forthcoming tasks. This has been demonstrated when comparing writing of one's own signature, drawing a pentagramma and scribbling (Schreiber *et al.*, 1983). Subjects performed the movement with a pen in their right hand which had a trigger in the tip. Preceding drawing and writing, the BP starts earlier than before simple finger movements; namely, about 2 s prior to EMG onset. As a sign of hemispheric specialization, BP was lateralized to the left hemisphere (significant in dorso-lateral frontal recordings) in writing but to the right hemisphere during drawing.

In another experiment, a simple volitional movement such as the flexion of the index finger started either a visual or a tactile stimulus which had to be tracked. Here, BP topography differed considerably from the one observed in simple finger movements. The forthcoming sensory event which was of motor relevance led to an additional activation of primary sensory areas and of the parietal lobe which was superimposed on the BP preceding movement initiation (Fig. 6; Lang *et al.*, 1984).

Learned motor sequences are known to be pre-programmed (Keele, 1968; Sternberg *et al.*, 1978). The BP preceding different kinds of

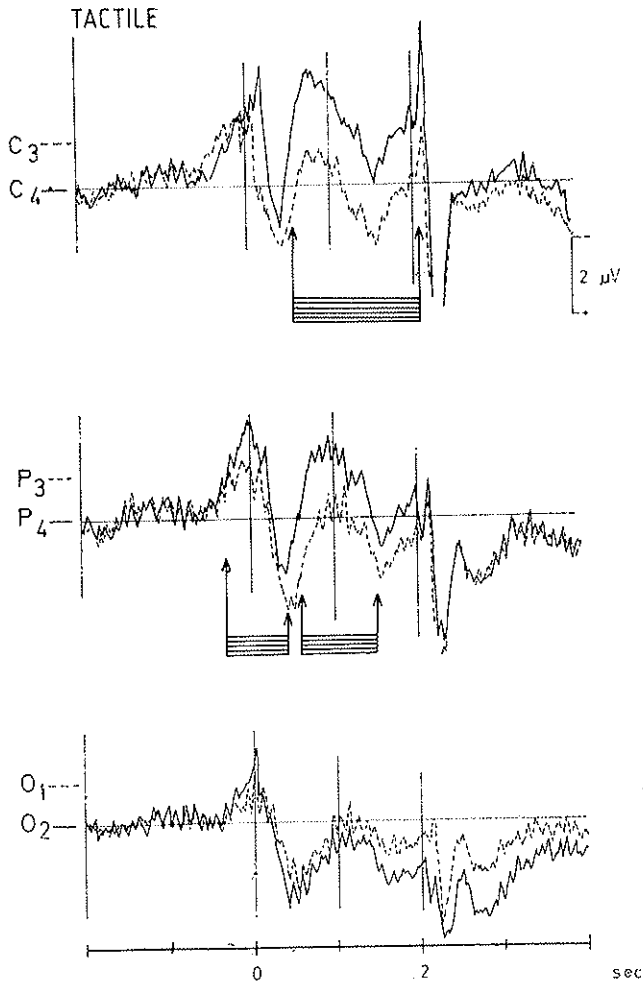

FIG. 6. Hemispheric differences for the tactile tracking experiment. Grand averages across 16 subjects. Dotted lines indicate recordings of the left, solid lines indicate recordings of the right hemisphere. Intervals with significant differences of single data points are marked (two-tailed t-tests, $p < 0.05$). Note larger negativity over right central and parietal cortex as compared to left. Modified, from Lang *et al.*, 1984.

motor sequences differs from the BP prior to single movements, and amplitudes become larger when increasing task complexity (Lang *et al.*, 1989b). Taylor (1978) found a close relation between increase of BP amplitude (particularly in fronto-lateral and fronto-mesial recordings) and the acquisition of a motor skill, which was taken as evidence that the BP reflects task-preparation.

In summary, task-specific preparation can be studied using the BP. Depending on the nature of the experimental manipulations, different parts of the cortex (fronto-lateral, fronto-mesial, parietal, primary sensory areas) become activated. The variability of cortical activation patterns due to task-specific preparation is in contrast to the view of Goldberg (1985), who claims that it is only the SMA which is responsible for internal-based and anticipatory motor planning. In our view, anticipatory preparation involves the cortical areas that are specific for the task and even subcortical structures such as the basal ganglia and the cerebellum. The characteristic feature of the BP with its maximum of activation in recordings over the dorso-mesial fronto-central cortex seems to be independent of structure and complexity of the task.

Variations of the BP due to task-specific planning are mostly considered to reflect planning processes — for instance, of creating, loading or linking motor subroutines. However, as mentioned above, volitional actions are intentional in nature, i.e., they are directed towards the achievement of goals. Variations of motor tasks and goals are likely to affect the intentional and motivational involvement which may cause differences of the BP as well (Kornhuber and Deecke, 1965; McAdam and Seales, 1968).

6. *The Use of rCBF Measurements in the Investigation of Volitional Actions*

Studies of regional cerebral blood flow (rCBF) give the possibility to visualize brain structures which are involved in volitional actions. In order to do so, the process of volitional actions was decomposed into states of rest, states of planning and those of performance which were separately measured. In principle, this approach has its shortcomings for the investigation of brain physiology in volitional actions. First, the process of movement initiation, i.e., to transduce motives and intentions into effective actions, is not assessed. Secondly, to study planning, the instruction was given to perform the task only in mind without actually

moving. This design enables the investigation of motor imagery but not the preparation to act. In other words, the reduction of planning in volitional actions to motor imagery ("Vorstellung", Liepmann, 1900) is only improvised. Furthermore, it means to simplify matters when assuming that brain activity during execution is composed of brain activity related to "imagination" and the activity of the primary motor cortex.

7. *SMA Activation in Motor Sequences*

Nevertheless, studies of regional cerebral blood flow and metabolism have confirmed that the SMA is activated when subjects perform complex motor sequences such as finger tapping in a certain order. Simple repetitive finger movements caused no particular activation of the SMA (Roland *et al.*, 1980, 1982). This led Roland (1984) to propose that "the SMA either elaborates or retrieves from memory the necessary information to form a short sequence of motor commands in which the elementary movements to be executed are specified exactly. With an example from the motor sequence test one could say that the SMA specified: (1) the fingers to be moved in the near future, (2) which were the movements of the individual fingers (i.e., opposition, flexion, extension) and (3) the sequence of (1) and (2)" (pp. 209-210). In a more general frame, Goldberg (1985) concluded: "It is suggested that the SMA has an important role to play in the intentional process whereby internal context influences the elaboration of action. It may be viewed as phylogenetically older motor cortex, derived from anterior cingulate periarchicortical limbic cortex, which, as a key part of the medial premotor system, is crucial in the 'programming' and fluent execution of extended action sequences which are 'projectional' in that they rely on model-based prediction" (p. 567).

In contrast to the concept of Goldberg and Roland, it is suggested by Kornhuber (1984a,b), Deecke *et al.* (1985b) and Kornhuber *et al.* (1989) that the SMA has the function to transduce motivation and intention into action by giving the starting signal. Motor programming is supposed to be organized in other parts of the brain, whereas the internal-based decision about "when to move" in a motor sequence may be the actual function of the SMA.

In a first experiment (Lang *et al.*, 1988b), 20 subjects performed four different kinds of bimanual motor sequences. In all tasks, Ss held their index fingers in an intermediate position during the resting period and started to move the fingers in order to repeatedly reach three positions,

a flexed, an intermediate and an extended one. In SI-S, movements of both index fingers were performed simultaneously in the same direction. In SE-S, the right index finger started, the left finger followed with a delay of one movement (sequential). In SI-D, the two fingers moved simultaneously in different directions: the sequence was initiated by simultaneously flexing the right and extending the left finger and so on. In SE-D, movements were performed sequentially in different directions. Since it was our goal to study the planning and execution of learned movement sequences, Ss practiced each sequence thoroughly in pre-experimental sessions. In the experiment, Ss started the motor sequence at their own volition and performed the task for at least 6 s. An epoch of 5 s before and 6 s after movement onset was analysed. The main finding is illustrated in Fig. 7: In sequential tasks, SE-S and SE-D, task execution was accompanied by a large and sustained negative DC-shift (N-P; performance-related negativity) in recordings over the mesial fronto-central cortex (Cz). In contrast, in the two simultaneous tasks, SI-S and SI-D, performance-related negativity (N-P) declined rapidly during the epoch. This difference between SE and SI tasks was restricted to recordings of the mesial fronto-central cortex and had its maximum in Cz ($F=18.9$; $p<0.0001$). Performance-related DC shifts did *not vary* by the factor "spatial organization", i.e., there was no difference whether Ss moved

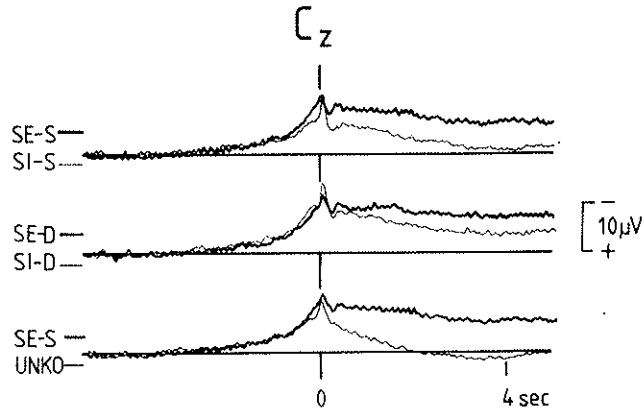

FIG. 7. Grand averages obtained in Cz. The vertical line indicates movement onset (t = 0). Sequential tasks are compared to their corresponding simultaneous conditions, SE-S to SI-S in the upper row and SE-D to SI-D in the middle row. In the lower line, SE-S is compared to the control task (UNKO), in which bimanual movements of index fingers were performed in an uncoordinated manner. From Lang *et al.*, 1988b.

their index fingers in the same or in different directions (for Cz: $F=2.2$). How strict, by the task-specific feature of sequentiality, negativity is localized in the mesial fronto-central cortex of the SMA is displayed in Fig. 8. Mapped are differences SE minus SI, i.e., this figure demonstrates the additional activation of the mesial fronto-central cortex present in the sequential task as compared to the simultaneous task, as shown in Fig. 7.

In the sequential tasks, subjects were required to switch between

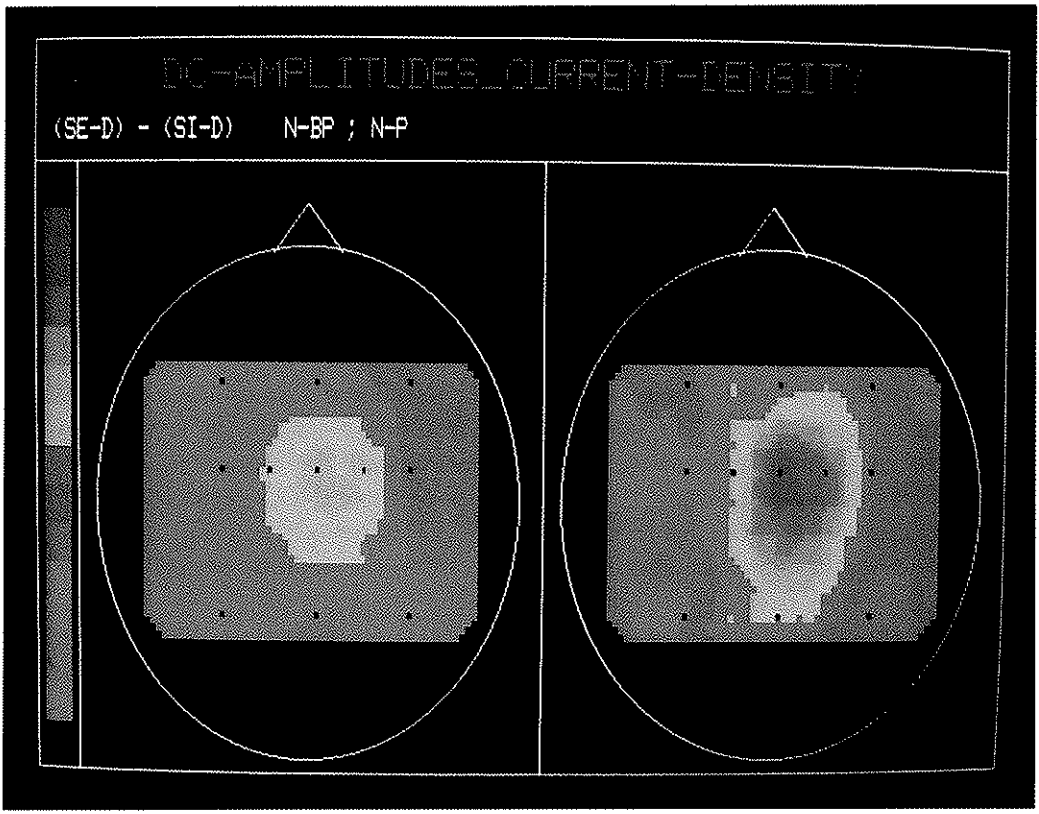

FIG. 8. Comparison between SE-D and SI-D. Differences of amplitudes have been calculated for the Bereitschaftspotential (dN-BP; left side) and the performance-related negativity (dN-P; righ side). Based on dN-BP and dN-P, topographical distributions of current density at the scalp surface have been calculated and displayed. Current flowing into the scalp is indicated in colours of yellow and red, current flowing out of the scalp in colours of green and blue. Note current flowing into the scalp in the area of the central midline (overlying the SMA) indicating increased negativity of the mesial central cortex in SE-D as compared to SI-D.

the two hands for the initiation of a movement, whereas in simultaneous tasks, they started with both sides together. This difference in the way of initiating finger movements caused great differences in movement-related DC potential shifts with larger amplitudes in sequential tasks as compared to simultaneous ones. In conclusion, it is the temporal characteristic of sequentiality versus simultaneity which brought the SMA region to stronger activation and not the spatial characteristic of whether the fingers moved in the same or different directions.

In another experiment (Lang *et al.*, 1989a), subjects had to meet two demands, (1) to switch for movement initiation from one side to the other and (2) to act according to the precisely defined timing pattern of tapping different rhythms. In 15 musicians, cortical DC-potentials were recorded from the scalp before and during the execution of four bimanual motor sequences: (1) RH-S (right hand - simple): subjects started at t_1 to tap with their right finger at a frequency of about 2/s (quavers). After a self-selected time, at t_2, the left index finger joined in to move in synchrony. (2) RH-C (right hand - complicated): as before, the right finger started to tap 2/s and the left finger joined in at t_2 but now tapping a differing rhythm of 3/s (triplets). (3) LH-S (left hand - simple): corresponding to RH-S, but with the left finger starting at t_1 and the right one joining in with 2/s at t_2. (4) LH-C (left hand - complicated): corresponding to RH-C, but now with the left finger starting at t_1 and the right finger joining in at t_2. Ss were free to start the sequences, i.e., to determine the onset times t_1 and t_2. Shifts of cortical DC potentials were averaged twice; (1) time-locked to t_1 and (2) time-locked to t_2. In both averages, the same baseline was taken from the resting period before initiating the first sequence (4 s to 3 s before t_1).

Musicians are known to have acquired the skill to move both hands at different rhythms (e.g., quavers against triplets). It is believed that they do this by integrating the two rhythms into a "common time base" for starting movements of either side (Klapp, 1979; Vorberg and Hambuch, 1984). Outgoing from the previous experiment, it was our experimental hypothesis that the mesial fronto-central cortex (SMA regions) has the function to coordinate initiations of movement elements during this bimanual motor sequence.

Fig. 9 gives the example of a single subject: the slow negative DC shift of the Bereitschaftspotential (BP) precedes the initiation of the tapping task having its maximum in recordings of the central midine (Cz, C1, C2). When tapping quavers (2/s) with the left hand, a sustained negative DC

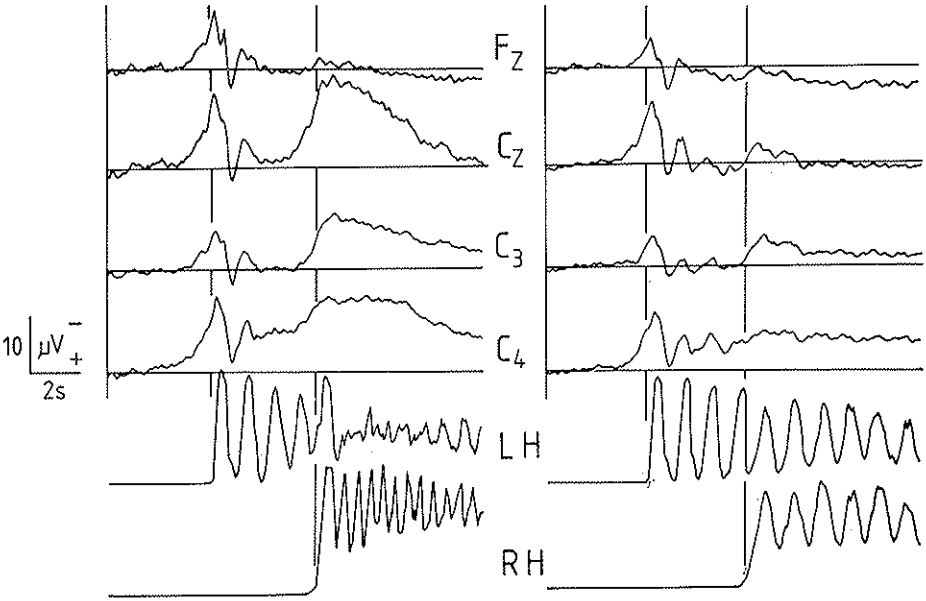

FIG. 9. Movement-related DC shifts of a single S, time-locked to t_1 (vertical line when the S starts to move the left hand (LH). LH-C: left side, LH-S: right side. Bottom: Goniometer readings for the left hand (LH) and the right hand (RH); averages across all trials. Starts of LH and RH are marked by vertical lines. Note, there is a large negative DC shift before RH starts to tap the triplets (LH-C). From Lang *et al.*, 1989a.

shift is present in central recordings (C3, C4) with the larger amplitudes over the right hemisphere (C4), i.e., contralateral to the movement. A large negative DC shift occurs in the Cz recording over the SMA region when the subject joins in with the complicated 3/s rhythm (triplets). However, when the right hand joins in with the simple synchronous tapping of 2/s (quavers), there is no negative DC shift in recordings over the SMA region. Topographical distributions of radial current densities are displayed and described in Fig. 10. In general, maxima of radial current densities with current flow entering the scalp were found in three different areas of the maps: left centro-lateral (area of C3), right centro-lateral (area of C4), and centro-mesial (area of Cz). In the simple tasks (RH-S, LH-S), current flow into the scalp was found in centro-lateral areas: when tapping with the right finger, radial current density was high in the left centro-lateral area; when tapping with both fingers, high

radial current densities were found in centro-lateral areas of both sides. Current flow entering the centro-mesial area of the scalp (area of Cz) was almost absent in the simple rhythm. In contrast, when moving quavers against triplets very high current flow densities were present in the centro-mesial area (SMA region) of the scalp with a maximum in Cz. When subtracting maps of corresponding complicated and simple rhythms

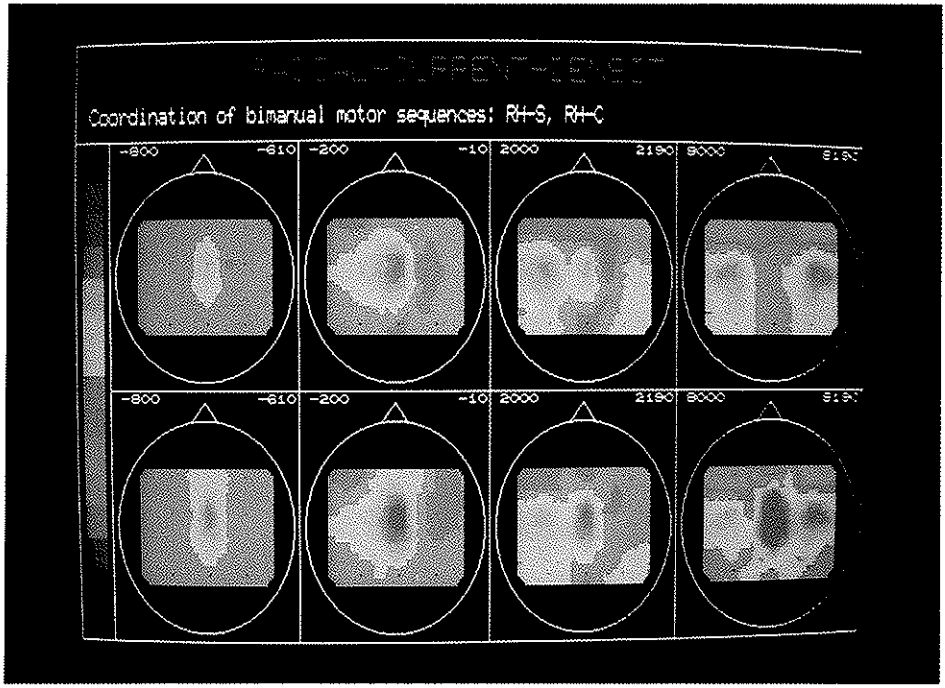

FIG. 10. Maps of radial current density across the scalp. Maps are based on DC-potential amplitudes as measured time-locked to t_1.
Upper row: RH-S; lower row: RH-C. Maps from left to right: The first two maps are taken from the BP period preceding the initiation of the first sequence (600 to 800 ms, or 200 to 0 ms, resp., before t_1). The third map from the left displays current densities when tapping 2/s (quavers) with the right finger (2 s to 2.2 s after t_1). The fourth map displays the radial current densities during the bimanual performance (8 to 8.2 s after t_1, a time at which bimanual movements were executed in all trials).
Colour "green" indicates that current density is zero; current flow entering the scalp (due to cortical surface-negativity) is indicated by red, exiting the scalp by blue colours. For both directions, scaling of colours is proportional to radial current densities. All maps are equally scaled.
Note, there is a large current flow entering the dorso-medial front to central cortex (SMA) when tapping different rhythms ("2 against 3").

(RH-C minus RH-S; LH-C minus LH-S), it became obvious that the extra activation of the centro-mesial cortex (SMA region) in the complex situation constitutes the main physiological difference between these tasks. As can be seen in Fig. 11, there is a large difference of negative DC shifts in recordings of the mesial, fronto-central cortex for the complicated rhythms. During bimanual tapping, the difference of DC potential ampli-

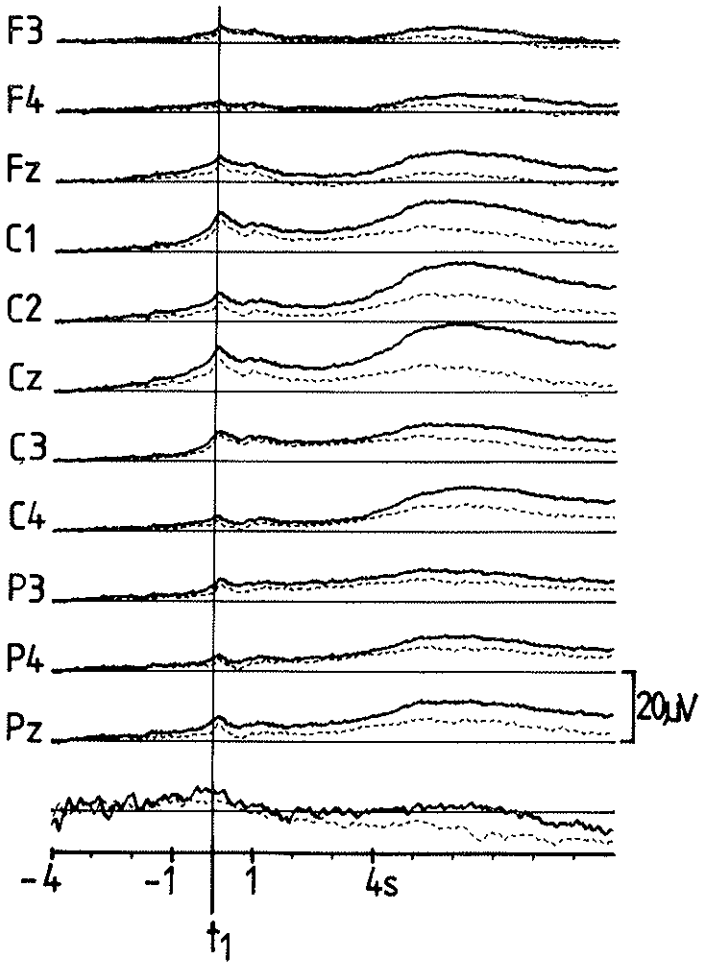

FIG. 11. Grand average across all 15 Ss, time-locked to t_1. RH-S is displayed by the solid line; RH-C by the stippled line. Negative up. Bottom trace electro-oculogram (EOG). From Lang *et al.*, 1989a.

tudes between the complicated task (RH-C) and the corresponding simple one (RH-S) is as much as 13.9 μV in Cz ($F=63.1$; $p<0.0001$; ANOVA). Complicated and simple tasks differed significantly not only during the bimanual performance but also about 4 s before joining in with the second hand at t_2 ($F=11.9$; $p<0.01$). On approaching t_2, this difference between complicated tasks and simple ones increased in size.

The difference between synchronous tapping and tapping of different rhythms was 14 μV in Cz, which is three times larger than the difference between the sequential and simultaneous movements of the previous experiment (4.2 μV; Lang *et al.*, 1988b). This may be due to the fact that now the subjects not only had to switch between the two sides for movement initiation but also to initiate the single movements according to a precisely defined time base. But why does DC potential shift differ between simple and complicated tasks already about 4 s before the actual bimanual performance? There may be two explanations: (1) Differences of DC potentials reflect differences in task-specific anticipatory "programming". It is known that not only the first movement is preprogrammed in motor sequences but rather a number of movements (Keele, 1968; Sternberg *et al.*, 1978). Thus, not only the first tapping is programmed in advance when the second hand joins in but rather the whole sequence or a longer period of it. Furthermore, the intended action — to join in with the second hand — has consequences for the ongoing performance. These consequences are conflicting when moving quavers against triplets. Therefore, not only the 3/s rhythm has to be programmed but also its integration into the 2/s performance being under way. (2) Task-specific programming takes place in many parts of the brain and not exclusively in the SMA. The critical function of the SMA is to transduce the intention to act into the effective action and to select the right moment of initiation. However, in order to do so (selecting the right moment for giving the starting signal), the SMA should have access to or control over anticipatory motor planning and its integration into actions being under way (for review see Kornhuber *et al.*, 1989). Constraints of the central timing system to use one time base for movement initiations in volitional acts (Klapp, 1979; Kelso *et al.*, 1983) point to the centralization of this system in the brain. Such a rigid control of movement initiation may be necessary because of the consequences for posture and other motor behaviour being under way.

8. *Performance of Motor Sequences in Patients Having Chronic Unilateral Lesions of the SMA*

Fifteen patients with chronic unilateral lesions of the SMA were examined using the SE and SI tasks (Lang *et al.*, 1988c). Latencies between the acute state of SMA lesion and date of examination ranged between 8 and 84 months (mean: 34). 8 patients had the lesions in their right, 7 in their left hemisphere. They had no paresis and performed at normal rates in a unilateral tapping test. In the study, they performed 64 trials of two different movements: simultaneous flexions and extensions of the two forefingers (SI task) and sequential movements of the two forefingers (SE task; motor sequence: extension on the right side, then extension on the left, then flexion on the right, then flexion on the left, etc.). Trials were voluntarily initiated and lasted 6 s. Movements were measured using goniometers at the proximal finger joints. The following symptoms were observed: (1) bradykinesia contralateral to the lesion in SI and SE, (2) marked deceleration of initial movement, (3) switching from sequential performance into simultaneity and (4) frequent omissions to initiate a movement at one side or to inhibit at the other (as demonstrated in the goniometer readings of Fig. 12).

These findings substantiate the results which have been found when investigating negative DC shifts in sequential and simultaneous tasks. The SMA region may be involved in the process of switching between the two sides for the initiation of movements.

9. *Functional Separation of Dorso-Mesial and the Dorso-Lateral Parts of the Frontal Cortex*

According to Kornhuber (1984a,b), Deecke *et al.*, 1985b, and Kornhuber *et al.*, 1989, we suggest a tripartition of the frontal lobe: (1) the fronto-orbital cortex, (2) the dorso-lateral frontal cortex, and (3) the dorso-mesial, frontal cortex including the SMA. These parts subserve different aspects of volitional action, selection of goals (orbital part), goal-directed adjustment of behaviour and resistence against interference (dorso-lateral part), and (3) selection of the right moment to act (dorso-mesial part).

An experiment has been designed to examine goal-directed behaviour and the ability of subjects to (1) develop new patterns of stimulus-response behaviour, and (2) to resist against interference of inadequate

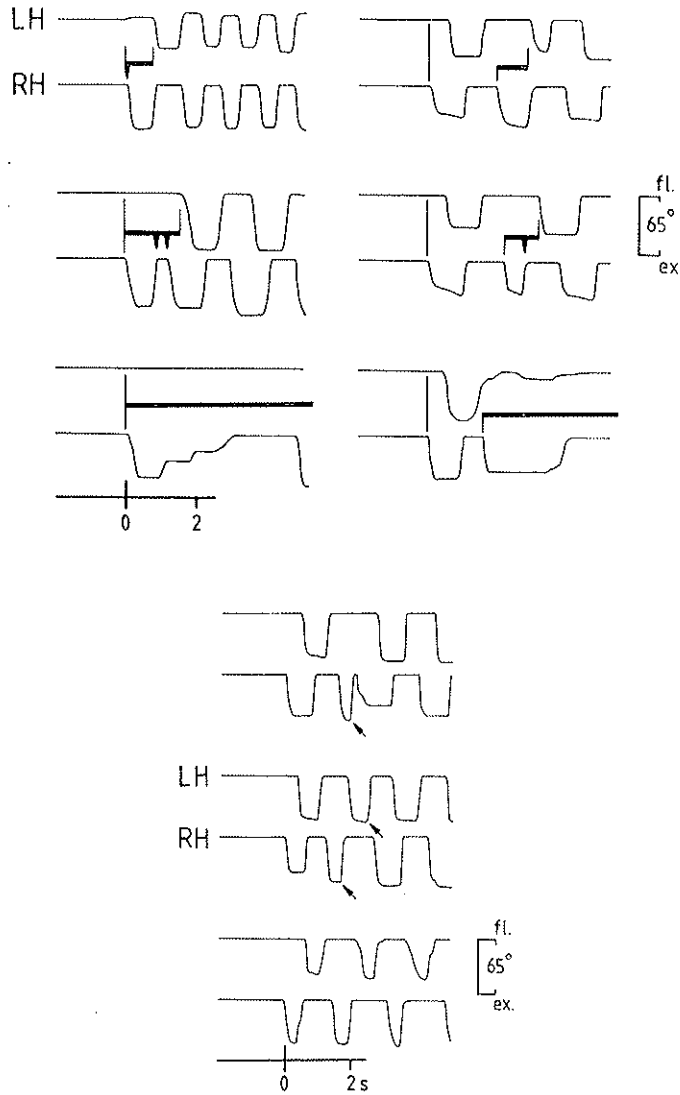

FIG. 12. Finger movements of the right (RH) and left (LH) hand were measured by goniometers. Patients with SMA lesions had to perform extensions and flexions in a sequential manner starting with an extension of the right index finger. Upper part of the figure shows examples for omissions of movements of the left finger in various patients (disturbance of movement initiation). An omission is indicated by an arrow. In the lower traces the left finger is not moved at all (left side) or stops moving (right side). As shown, the degree of the symptom "omission of movement" is varying. Lower part gives examples for the tendency to continue movements on one side instead of alternating between left and right (lack of movement inhibition; indicated by arrows).

stimulus-response patterns (Lang *et al.*, 1983, 1986, 1988a). In these experiments, two conditions were compared. In a visuomotor learning task, Ss were required to track a visual target in an inverted manner; that means, movements of the target to the left required manual tracking to the right and vice versa. Up and down remained either non-inverted or were inverted as well. This learning task was compared to the simple, non-inverted tracking. A recent experiment, which has been described in detail by Lang *et al.*, 1988a, will shortly be reported here. Two parameters of brain activity have been assessed, performance-related DC shifts and ^{99m}Tc-HMPAO uptake measured by the SPECT technique.

Seventeen Ss participated in the SPECT study; in 16 of them performance-related DC shifts were measured as well. Each subject performed two tasks. The order of tasks was balanced across subjects. Ss held a stylus in their right hand equipped with a light at the tip (Fig. 13). By voluntarily lowering the pen to the plate, a visual target (small circle) started moving at constant speed in three successive random directions for 1.5 s each. Thereafter, the target jumped back to the center of the screen. Ss had to track the target by moving the stylus with their right hand and then returned to the starting point. After reaching the starting position, Ss started the trial again. This experimental design provided a continuous feed back tracking performance. The position of the moving right hand was coupled back as a light spot on the TV screen. Accuracy of tracking was determined by the difference between target and light spot, and it was the subjects' task to keep the light spot within the circle. In the visuomotor learning task (Inverted tracking, IT), Ss had to track the stimulus in an inverted manner, i.e., movements of the target to the right required hand moving to the left and vice versa (horizontal inverted tracking; movements up and down were not inverted). In the control task (Tracking, T), Ss had to track the target in the normal non-inverted manner.

Performance-related DC shifts in inverted tracking (IT) and tracking (T) were measured in the same subjects. After the 4.5 s of tracking, Ss moved the stylus to the starting position and had a resting period before voluntarily starting the task again. Inter-trial intervals ranged between 8 and 12 s.

Performance-related DC shifts are shown in Fig. 14. The volitional initiation of the stimulus program was preceded by a BP; visuomotor performance was associated with a slow negative DC-potential shift with larger amplitudes in IT as compared to T. Differences of amplitudes

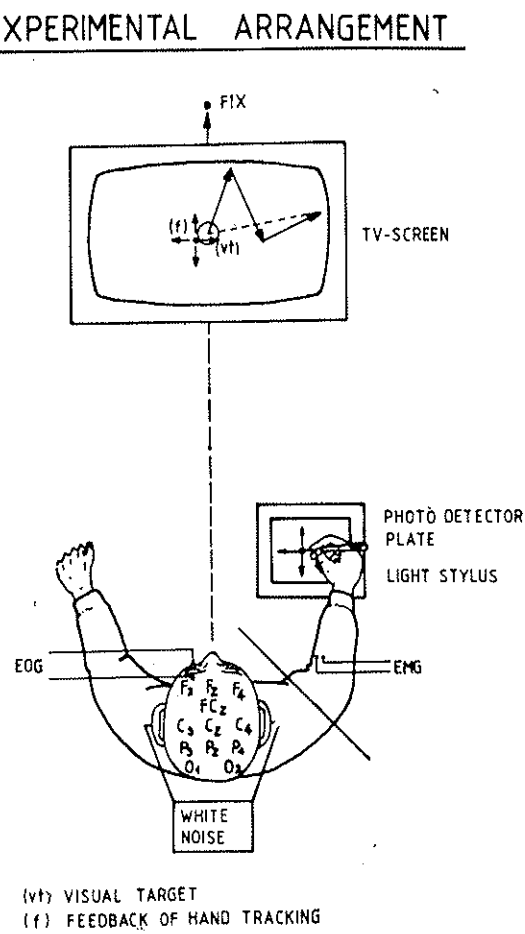

FIG. 13. Subjects tracked the visual target (vt: circle) with the stylus in their right hand. Horizontal and vertical coordinates of tracking movements were transmitted to the TV screen in a linear ratio and displayed as light spot (f: feedback). In the learning task, transmitted coordinates either of the horizontal (as in the SPECT study) or the vertical direction (as in the DC potential study) were multiplied by the factor (−1). In the DC potential study, subjects fixed their gaze on a fixation point (FIX) in order to prevent artifacts in the EEG recordings caused by eye movements. Thus, the stimuli were given in the lower field of vision. Subjects were prevented from watching movement of the right hand. From Lang *et al.*, 1986.

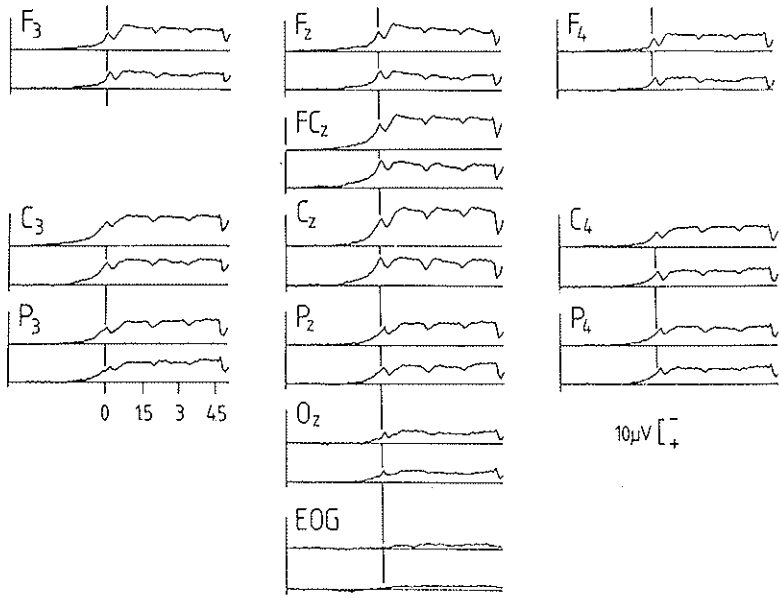

FIG. 14. Topographical distribution of performance-related DC-potential shifts, averages across all subjects. The vertical line indicates the onset of the stimulus program (t = 0). Stimulus directions changed at t = 1.5 and t = 3 sec, end of the stimulus program at t = 4.5 sec. Upper row: Inverted Tracking (IT), lower row: Tracking (T). Negativity up. The volitional initiation of stimulus onset is preceded by a Bereitschaftspotential (BP), task performance is accompanied by a slow negative potential shift, the performance-related negativity. From Lang *et al.*, 1988a.

(dN) had a clear fronto-central distribution and were significant in frontal recordings, C3 and Cz. In these recordings, dN was correlated with the individual success of visuomotor learning, and the coefficients of correlation "r" ranged between 0.6 and 0.8. Thus, the electrophysiological findings of previous experiments (Lang *et al.*, 1983, 1986) could be replicated. The conclusion of the DC potential study, that frontal lobes are critically involved in visuomotor learning, was confirmed by the results of the SPECT study. In IT, there was an increased relative tracer uptake in frontal areas as compared to T (dorso-lateral parts, in particular middle frontal gyrus of both sides, and fronto-mesial cortex) in IT as compared to T. In addition, the SPECT study showed an increased relative tracer uptake in basal ganglia and cerebellum (Fig. 15).

In another visuomotor learning task (Lang *et al.*, 1986) the feed-

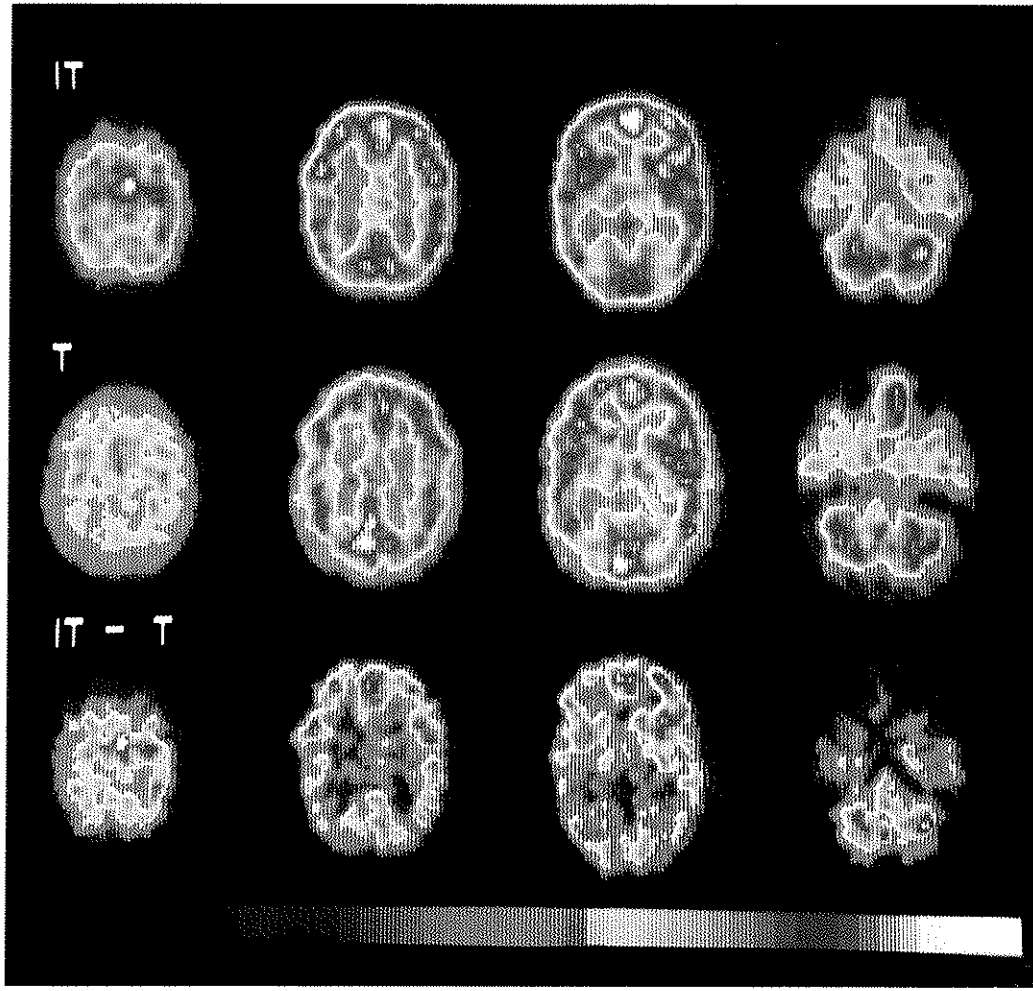

FIG. 15. HM-PAO brain SPECT of one subject. Four axial slices from cranial (left) to caudal (right). Upper row: Inverted Tracking (IT); middle row: Tracking (T); lower row: subtraction (IT minus T) after normalization of count rates. The relative tracer distribution is displayed in colours ranging from blue (low) to white (high concentration). In the lower row, colours of red and white display areas having a higher relative tracer concentration in IT as compared to T. This is particularly true in the mesial fronto-central cortex, the dorso-lateral cortex of both hemispheres (mainly congruent with the middle frontal gyrus), basal ganglia and cerebellum. From Lang *et al.*, 1988a.

back signal to the TV screen was distorted by imposing a sine wave when starting to track the target (DT; distorted tracking). This manipulation created a rather complex manner of distortion which had to be compensated during tracking. In contrast to the other experiments, a simple cognitive strategy such as the inversion of horizontal and/or vertical direction could not be used. Subjects were still able to significantly reduce the error of tracking although they could not verbalize and were not consciously aware of the strategy they used, as they were in the other experiments. Amplitudes of negative DC shift were larger in DT as compared to a simple tracking control (T). This difference (dN) was again significant in frontal recordings and correlated with the success of learning in Fz, FCz and F4 ("r" ranging between 0.5 and 0.6). This time a correlation between cortical negative shifts and success in learning could not be found in F3 (as it had been in the inverted learning tasks).

In conclusion, the frontal lobes are critically involved in visuomotor learning tasks. Such tasks require subjects to rely on an inner representation of the goal, to maintain it against interference of other thoughts and to develop adequate response patterns in order to achieve the goal. When developing these new stimulus response patterns, interferences of old associations have to be overcome. Possibilities to use cognitive concepts and predictive strategies varied between the tasks. Visuomotor learning, including horizontal and/or vertical inversion, enabled subjects to use a strategy in their prediction of trajectories that they could verbalize, whereas learning in the distorted tracking situation was mainly based on feedback recognition and utilization which could not be verbalized and consciously experienced. This is why distorted tracking was associated with right frontal activation while inverted tracking caused a more bilateral frontal activation. When imagining to track in an inverted manner without actually moving, the left frontal lobe but not the right one was activated (unpublished results by Lang, Uhl, Lindinger, Deecke).

Conclusions

In the experiments presented here, functions of the human cortex have been displayed by various techniques of functional brain imaging. Evidence has been given that the dorso-mesial (including the SMA) and the dorso-lateral part of the frontal cortex have different functions in volitional actions. The SMA region with its afferents from limbic structures, basal ganglia and sensory motor cortex is critically involved in

transducing motivation and intention into action by determining the right moment to start. This is true for the initiation of a single volitional action as well as for initiating single movements in motor sequences. The SMA region is activated in self-initiated actions which are intended. Motor sequences in which single movements run automatically, i.e., are not intended, cause no SMA activation during execution. In contrast to the concept of Goldberg (1985) it is argued that the SMA which gives the starting signal has control over or access to task-specific anticipatory programming but is not necessarily involved in this process itself. The motor system is highly distributed and, depending on the task under study, anticipatory programming is carried out in different parts of the brain.

Actions that require subjects to develop new motor programs in order to achieve a certain goal cause an activation of the dorso-lateral frontal cortex (learning).

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DISCUSSION

GOLDMAN-RAKIC

Since all of the tasks that bring out the negativity are more difficult than the tasks that don't, are other areas also increasing in negativity? How selective is the SMA with respect to activation by the complexity or difficulty of the task?

DEECKE

Kornhuber proposed that in the course of phylogenesis the motor centres of the brain stem went up to the cerebral cortex. As soon as they are there, they have a higher hierarchical order and dominate the lower ones. We think that we have more than one motor area in the cerebral cortex. One can even go so far that the Broca speech centre is the motor area for speech. One can also say, if we do tracking movements which are visually guided, maybe one of the visual association areas is doing the tracking job. Also another area is necessary for the somatosensory guided movement, and not so much for the auditory or visually guided movement. The motor cortex was overestimated clinically because it is the last station in the final common pathway. Our suggestion is that, when so many motor areas have direct access to movement, you have to have one structure which coordinates this in time and this may be the task of the SMA.

GOLDMAN-RAKIC

I have a follow-up. That's very relevant and interesting, but do other areas also increase their negativity in your tasks, such as dorso-lateral prefrontal?

DEECKE

That's right. In earlier tracking experiments we found that with the visual tracking the contralateral occipital region had this negativity at 200 milliseconds. This made us believe that the occipital regions may also guide this movement.

LIBET

I just want to come back to the question of the sustained negativity, for example with the inverted successive trackings. I think you were indicating that this might be a kind of CNV expectancy potential, which then resolves. But you really have two components there. You have expectancy waiting for the cue to move, and preparation to move when the cue appears. So the question is, is it really an expectancy potential or is it a sustained readiness potential preparing to move? As I mentioned to you, in our 1982 paper we tried to resolve this point. We got the subjects in one kind of test not to expect to move at all. In your case they are expecting to move. In order to resolve that point we got them not to expect to move at all and simply wait for a sensory cue to appear which had a task assigned to it so that they had to pay a lot of attention. There was no prepotential. They were not preparing to move.

DEECKE

We do not think that the CNV is a completely different thing from the BP. One is, by convention, preceding voluntary movement and the other is, by convention, preceding stimuli. But what I would like to point out is that, in our opinion, the task, the job of the SMA is not just to prime the initiation of the movement but also in sequential movement to prime or coordinate all the sequences. So it is not only a pre-movement phenomenon but is also active after movement onset.

LIBET

Yes, that may well be, but it's still related to a kind of preparation to move rather than expectancy per se, that's the point. You may recall the earlier work of Donald Lindsley and his collaborators, in which they were having evidence that the CNV itself may also be a form of readiness potential because it's also associated with preparing to move in relation to the second signal that arrives.

DEECKE

Well it has the two aspects. There is the late component of the readiness potential. You would distinguish between the two components. They may be

very similar also in the CNV paradigm, especially when you put the S1 and S2 stimuli far apart from each other.

FREUND

I think the data you show are convincing that the SMA is involved in what is required in your tests. What worries me is that you don't see much activity in other parts which are for some reason likely to participate in those tasks. For example, there is evidence from the literature that the premotor area is very much involved in the sequencing of motor acts, in particular of establishing higher order sequences. We have found evidence from our lesion data, but also from experiments, that the lateral premotor cortex is certainly involved in these tasks. So the question I would like to raise is simply, why is there no evidence in your recordings for the participation of this big premotor cortex for this type of task? May it have to do with the method, that the SMA is so close to the mid-line that the potentials are larger and smaller at the sides?

DEECKE

I think you gave the answer. Our method is too crude to distinguish between prefrontal and precentral, for instance. The SMA has been called a third speech centre by Penfield and Jasper, as you know. Ploog and Jürgens could elicit vocalization there in the squirrel monkey by electrical stimulation. I think it is also necessary for speech — no speech without SMA. In the early cases of SMA lesions, clinically, you have patients who are aphasic.

INGVAR

I had a question about the mental symptoms of patients who had lesions in that area. You showed a sort of a defect in changing pattern, complex movement pattern. This is a defect which is common, as you know, in another disease, namely schizophrenia, and in patients who have functional disorder of the dorsal lateral cortex. Did you find any form of neuropsychological defect in these patients?

DEECKE

No, we did not. On neuropsychological test batteries of the normal kind they scored like the controls. But there is in the acute stage another strange

phenomenon which has been called clinically "the alien hand sign". The hand contralateral of the lesion can do things which the patient is not conscious of and then he takes the other hand to pull it back. The bimanual coordination is impaired by an SMA lesion.

BAUMGARTNER

I wonder why you conclude that SMA is especially important for temporal sequential control. The paradigm you used was only more complex, and the increase in negativity could be very easily explained just by more involvement of neuronal activity. I don't understand the point that it is a special device for sequential ordering.

DEECKE

Is it simple or complicated which increases the activity of the SMA? We did not find a significant difference there. Then we asked is it more the variation of the spatial parameter which turns up the SMA or is it more the variation of the temporal parameter, and it was the variation of the temporal parameter.

MOUNTCASTLE

I would like very much to know what you can tell us about neuronal mechanisms producing these DC shifts on the cortex.

DEECKE

We know from Szentágothai and others that all the cortical areas are anisotropic so to say, because they have columns and the dipole is generated by this columnar structure of the brain.

MOUNTCASTLE

I really wanted to know whether any direct observations have been made in waking monkeys on the cellular mechanisms of the CNVs.

DEECKE

My opinion is, and also according to Creutzfeldt, that it's not the spike activity which can be seen in the EEG, but it is the EPSPs of the upper apical dendrites. I think it's a synaptic driving process which we see with this method.

DESMEDT

I am certainly very happy to see that human studies can be ahead of animal studies on certain items. You quoted my work on the interpretation of P300, and it is true that we showed that in regular sequences, when the subject has got a warning signal by the preceding stimulus, there is a negativity that is resolved in the CNV, if it is a target, but can be resolved otherwise if it is a non-target. I would like to mention in this relation that P300 is not just a resolution of a negativity. It has definite functions, namely closure on one hand and updating and working memory on the other.

DEECKE

Thank you. Still I think that the psychologists make too many implications. For instance, to relate the P300 with updating of memory is adventurous I think. You have no proof whatsoever to relate such potential with such a distinct psychological or neurophysiological phenomenon. So I think we should be cautious about putting too many things into P300. It can simply just be the resolution of the negativity built up before.

ANDERSEN

I wonder, particularly in relation to our discussion of the other day, is there any way to calibrate the system as to the number of cells participating? From hippocampus studies we do know a little about the size of the field potentials contributed by an individual cell, and surely that sort of data must exist in the neocortex. I would feel it is a question of a few hundred cells and not of millions.

DEECKE

Yes. I think experimenters should include the field potential measurement with their single unit recordings. Why not combine the two?

LIMBIC ASSISTANCE IN TASK-RELATED USE OF MOTOR SKILL

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ABSTRACT — Behavioral, physiological and anatomical evidence is reviewed which suggests that during motor learning, and probably also thereafter, the limbic system assists in task-related use of motor skill. As an example, limbic modulation is proposed for the establishment of motor "set", that is preparation for motor acts and readiness to use motor skill in the appropriate task context. This modulation might be conveyed by converging projections from the amygdala and anterior cingulate cortex to nonprimary motor cortex such as the premotor and supplementary motor areas. A mechanism for the limbic modulation could be the adjustment of set-points for those neurons in nonprimary motor cortex that discharge in anticipation of instructional signals and/or in relation to motor set.

1. *Preamble.*

One of the puzzles of current neuroscience at the systems level is how task-related cell assemblies are formed. For instance, how are they formed for motor actions such as crossing the street when the light turns green? The question may sound simple but it is as complicated as all of neuroscience because "voluntary" responses are generated by interactions of many factors, including learning from previous experience, ability to plan, the state of general alertness, attention to the circumstances of the moment, physical condition, etc. These in turn are affected by motivation, mood and other modulators of the central state of the brain. Voluntary action thus involves many neural processes in many parts of the brain, some that solve general questions and others that define particular details of which many overlap in time and in the distributed neural systems involved. This description posits participation of serial and parallel proces-

sing in the brain as well as its modulations. I believe that study of these central processes, burying inwards from peripheral inputs and outputs, will bring us closer to understanding how task-related cell assemblies are formed from a shifting population of neurons that *could*, but *need not*, form groups of input-output couples. This is how I imagine we will build a bridge to approximate brain functions that underlie thought.

2. *Why Ask about Motor Skill and the Limbic System?*

Learning to perform purposive motor acts shares some properties with learning to associate objects with one another or with required responses. The important shared property is that an *association* forms in the subject's brain between the neural representation of the task context and its execution: motor performance or object recognition as the case may be. Several kinds of associative learning depend on the limbic system. For instance, one-shot, "trial-unique", association of an object with a reward is diminished equally by removal of the amygdala or the hippocampus (Spiegler and Mishkin, 1981). Gradually acquired visual or tactual object-reward associations fail when both the amygdala and the hippocampus are removed, although amygdalectomy alone produces only mild deficits and hippocampal ablations produce none (Murray and Mishkin, 1984). The amygdala are particularly important for "crossmodal" associations between vision and touch because amygdalectomized monkeys can accurately recognize objects both visually and tactually but fail to recognize by vision an object that they have previously recognized by touch in the dark. Hippocampal ablations do not yield this deficiency that appears to be in long-term, crossmodal, associative memory and cannot be attributed to perceptual, attentional, or motivational loss, or loss of short-term memory in either sensory modality (Murray and Mishkin, 1985). The amygdala are thus one of a number of distributed neural centers that are essential for access to particular forms of long-term memory. In a recent case report amygdalectomy of a patient failed to affect crossmodal association (Lee *et al.*, 1988), but this could have been due to subtotal excision or to different tests used. The limbic system is not essential for a different, slower kind of associative "rote" learning acquired by repetitious practice which has been mooted to depend on basal ganglia function (cf. rev. Mishkin *et al.*, 1984; Squire, 1987). Stimulus-specific classical conditioning depends on cerebellar function (cf. rev. Thompson *et al.*, 1984) as does motor programming (cf. rev. Ito, 1984; Brooks and Thach, 1981).

Both can proceed without limbic intervention, although in task context they normally interact with it.

How the limbic system might be involved in motor learning became of interest when I realized that the use of contextual motor programming depends on *recognition and association* of the context and furthermore that motor learning, like visual or tactual learning, can proceed in two ways: a repetitious one that develops slowly and an abrupt one that initiates assured use of predictive movements (see Figs. 3 and 4 later) (Brooks *et al.*, 1983; cf. Brooks, 1986a; Brooks and Watts, 1988; 1989; cf. rev. Disterhoft and Buchwald, 1980; Olds, 1975; Sasaki, 1985). We will now compare some neural bases for recognition and association of objects with those of task context.

The limbic system is introduced in Fig. 1 with a cartoon of feedforward connections that reach the highest level (that selects *what* to do) as well as the middle and lowest levels (that guide *how* actions will be carried out). Interconnections and return paths are omitted but are considered in relation to Fig. 7. Some major limbic components are diagrammed in Fig. 2 together with the hypothalamus for regulating biological drives: a limbic "selection" (Kornhuber, 1973) consisting of the amygdala that relates to *relevant* events, memories, motivations and particularly affect, and the Papez circuit that in its hippocampal part assists in generating long-term potentiation, which is essential for creating long-term memory in neocortical targets of hippocampal projections (cf. rev. Eccles, 1977; Pandya *et al.*, 1981; Vogt, 1985; Zola-Morgan *et al.*, 1986). Hippocampal connections and functions are not considered in this paper. The reason that the amygdala is needed for crossmodal recognition of object relevance could be that it receives processed multimodal sensory inputs from the superior temporal sulcus, the final stage of the outward progression from primary sensory cortical areas. (Pandya and Kuypers, 1969; Jones and Powell, 1970; cf. Mishkin *et al.*, 1984). Fig. 2 also shows some limbic relations to prefrontal, parietal and nonprimary motor areas. Premotor and supplementary motor areas (PM and SMA) are part of nonprimary motor cortex and are essential for motor preparation. The discovery of cingulate projections to nonprimary motor cortex caused Pandya *et al.* (1981) to suggest that... "the cingulate gyrus is in a position to exert 'limbic' influence on motor behavior"... Prefrontal cortex is essential for long-term memory and parietal cortex is thought to support representational, short-term memory by means of reverberating loops to the prefrontal principal sulcus that is also linked reciprocally with posterior

cingulate cortex (cf. rev. Amaral, 1987; Goldman-Rakic, 1987). Distributed storage of long-term memory may include cortical areas dealing with the particular senses involved (cf. Mishkin *et al.*, 1984).

3. *Two Phases of Motor Learning; Association of "What" and "How".*

Fig. 3 illustrates training of monkeys that were rewarded for the sequence of making an elbow movement into a visually indicated target followed by holding a prolonged elbow posture in the target. They were rewarded for completing this movement-posture sequence which can be considered as a small act of "behavior" (what to do) but they were *not* rewarded for any particular way of executing the movements (how to do it). Knowing what to do means that the animals showed signs of understanding what behavior was expected of them in the task and by inference that they themselves had appropriate expectations of what would happen in consequence of their actions (1). The two kinds of skill, behavioral and motor, were not necessarily learned at the same rate. Fig. 3A shows that all monkeys gradually acquired motor skill movements by replacing poorly programmed task-related movements with predictive, accurately programmed ones (Brooks *et al.*, 1983; Brooks and Watts, 1988). They can be recognized by their single-peaked velocity profiles with smooth ascents and descents (Brooks, 1974; Polit and Bizzi, 1979) that depend on cerebrocerebellar interaction for the composition of reference trajectories for accurate vectors of direction and intensity (Polit and Bizzi, 1979; cf. rev. Brooks, 1979; 1985; Brooks and Thach, 1981). While moving in the right direction is thus part of knowing "how", associating instructional cues with getting ready to respond represents a translation of knowing "what" into "how". Fig. 3B indicates that initially behavioral skill outstripped motor skill, i.e., that the monkeys learned what was expected in the task more quickly than how to use predictive programming for it. Regular target alternation between flexion and extension positions served here, as in all our reports since 1970, as premovement "instruction" for the direction of the next movement (cf. Brooks, 1985). Use of predictive movements was unrelated to the number of rewards gained despite their briefer duration than non-predictive ones because, as illustrated in Figs.

(1) Use of behavioral paradigms to isolate physiological functions for study is of course not new. Usually, however, the sensory or motor functions under study are shaped by constraints in the paradigm and detailed tests are made only after the animals have been fully trained (cf. revs. Brooks and Thach, 1981; Evarts *et al.*, 1984; Mountcastle, 1981).

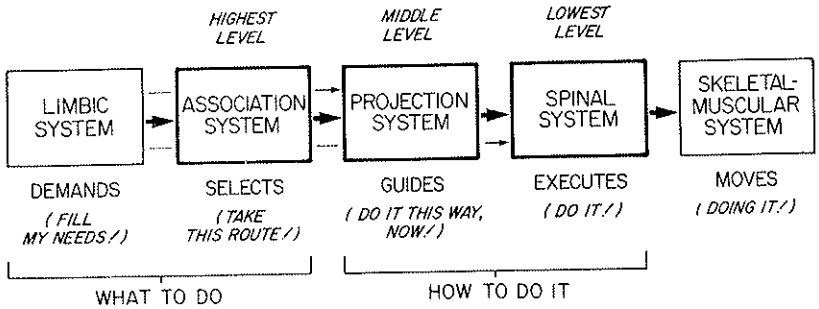

FIG. 1. Cartoon highlighting limbic feedforward connections to all brain levels concerned with the "what" and "how" of motor control. *Light* and *heavy* arrows indicate direct and indirect routes. (Modified from Brooks, 1986b).

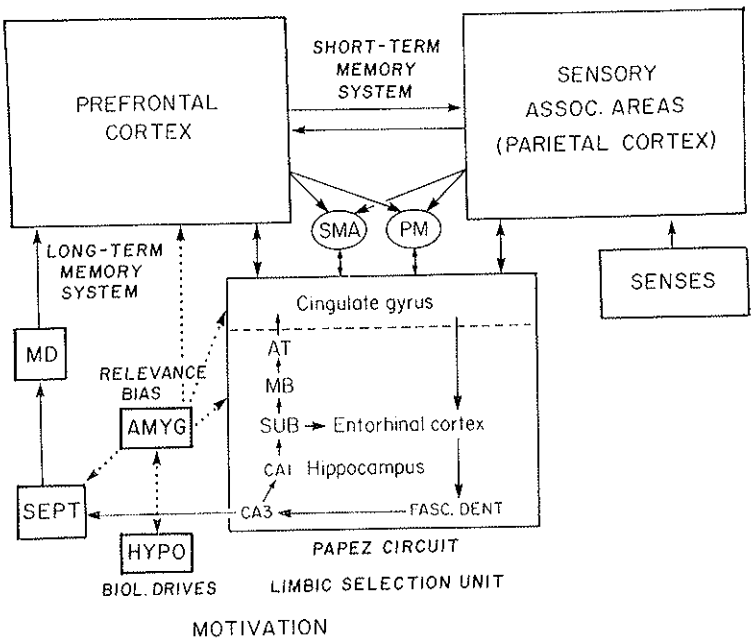

FIG. 2. Cartoon diagram of some connections of the prefrontal - nonprimary motor (SMA, PM) - parietal system (*upper row*), highlighting their roles in memory and learning with regard to selection of relevant inputs and to biologiral drives through the limbic system (*lower part of diagram*). AMYG, amygdala; AT, anterior ventral n. of thalamus; CA1, CA3, cell systems in hippocampus; FASC. DENT., fascia dentata; HYPO, hypothalamus; MB, mammillary body; MD, mediodorsal n. of thalamus; nonprimary motor: PM, "premotor" area; SMA, "supplementary" motor area; SEPT, septum; SUB, subiculum. (modified from Kornhuber, 1973 according to Brooks, 1986a; Eccles 1977; Goldman-Rakic, 1987; Zola-Morgan, Squire and Amaral, 1986).

3A, B, top row, the arm posture had to be maintained about six times longer than movement duration.

A surprisingly abrupt transition is revealed in Fig. 3C: when behavioral skill reached 45-60% practically all task-related movements suddenly became predictive, documenting that learning *how* had become *associated* with learning *what* (2). This sequence implies that the animals initially learned reference trajectories for movements and postures that fitted the required behavior and that, after associating the two, they could anticipate the task environment to generate trajectories for appropriately programmed movements. Such movements or their components are thought to be stored in the inferior olivo-cerebellar circuit at anatomically defined microzones in cerebellar cortex (cf. Ito, 1984). The animals thus learned motor skill in the task-context by finding adequate motor commands first by trial and error and then, after associating the two, by looking them up at their stored addresses. Bringing self-organizing cerebro-cerebellar programming under "cognitive", behavioral control resembles progress from "procedural" to "declarative" memory (cf. rev. Thompson *et al.*, 1984; Squire, 1987).

The learning sequences of four monkeys were studied and are plotted as session averages against time in Figs. 4B, C, D. Sudden, abrupt association of behavioral and motor skill after a slow beginning as for F22 was also seen for F36 and probably also for F21, but F37 associated behavioral and motor skill right from the outset. Fig. 4A provides an important orientation about electrocortical activity during a similar task, the behavior-oriented learning of a wrist movement, also without requirements how to carry it out (Sasaki and Gemba, 1982; cf. rev. Sasaki, 1985). Learning of those monkeys, like that of ours, progressed with the same two phases linked by a sudden transition as in Figs. 3 and 4. Their phases were defined by shortening of reaction times whose abrupt consolidation we found to coincide with the abrupt association of behavioral and motor skills as tested with our monkeys and so indicated in Fig. 4A (Brooks, 1986a; Brooks and Watts, 1988). Sasaki's recordings in pre-

(2) Self-selection of accurately programmed movements occurred also in the study of Weinrich, Wise and Mauritz (1984) who trained monkeys to make sequential moves and holds oriented by step-tracking target light spots. The horizontal arm movements were not forced except that they had to be concluded within 1.2 sec., and overshoots were allowed provided that they were corrected right away. The overtrained animals made programmed movements with reaction times that were well consolidated. All these points are much as in our trials.

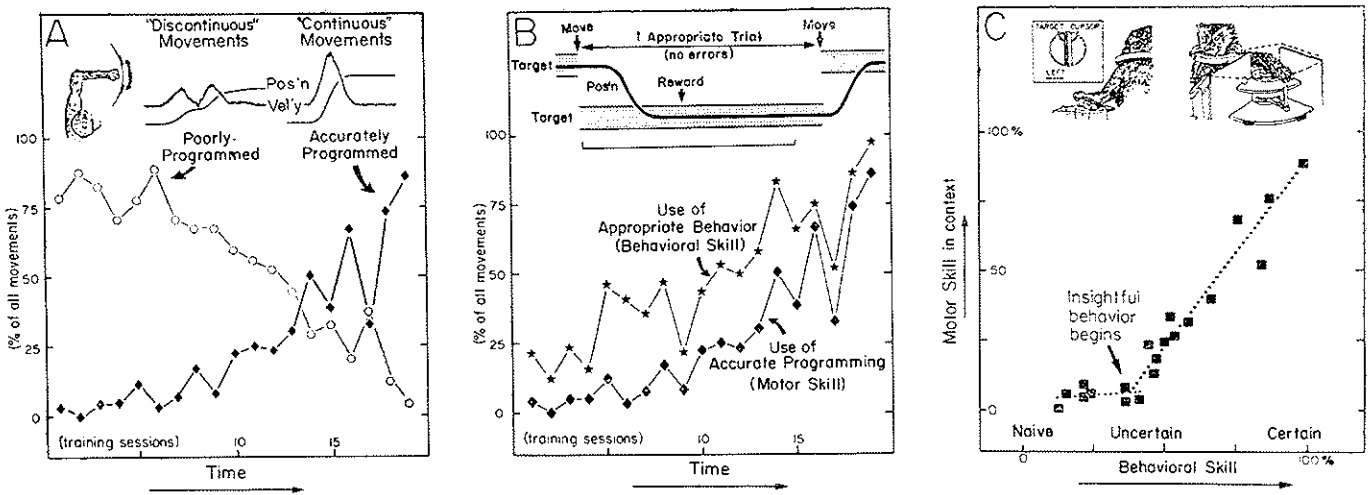

FIG. 3. Association between appropriate task-related behavior and use of accurately programmed, predictive movements in a motor task can at first proceed slowly and then, abruptly, become complete. Situation for step-tracking task is pictured at top of A, C; paradigm at top of B; time scale bar, 5 sec. Forearm movements, made by flexions or extensions of the elbow in the horizontal plane, had to be initiated towards the indicated target position within 1 sec of "Move" cue and had to be followed by uninterrupted holding of forearm in the target position for at least another 3 sec. Duration of accurately programmed movements was about 0.5 sec. A: Time course of replacement of poorly programmed movements by accurately programmed ones made in the task context. B: Time course of adoption of appropriate behavior (behavioral skill) and of accurately programmed movements (motor skill). C: Relationship of behavioral skill and motor skill in context. All *symbols* in A, B, C represent session averages for pooled flexions and extensions of monkey F22. (Modified from Brooks, 1986a).

frontal, premotor and prestriate cortex established that visuomotor associations were formed in the first phase, followed in the second phase by cerebello-thalamo-cortical potentials in primary motor cortex indicative of use of cerebro-cerebellar programming. The *limbic* system enters this story with a finding of special interest: near the transition period, under certain circumstances, unusual field potentials were recorded as marked by the boxed legend at the top of Fig. 4A, in anterior cingulate cortex.

4. *Cingulate Potentials: Limbic Participation in Recognizing "What to Do?"*

Field potentials were evoked in anterior cingulate cortex of monkeys learning the wrist moving task only in one special condition and only at one special time: when the animals engaged in *inappropriate task behavior*, and only during the transition from the first to the second learning phase (Figs. 5A, B). Transitional reaction times coincided for these animals with 45-60% appropriate behavior, (Gemba *et al.*, 1986, cf. Brooks, 1986a) i.e., with *high behavioral uncertainty*. The cingulate "error" potentials resemble "P300" event-related potentials of humans and monkeys (Arthur and Starr, 1984) in several ways. They peak near 300 msec after a response is initiated when recorded from the surface or the depth (not illustrated here; Figs. 5A, B are transcortical derivations: surface-minus-depth, see Fig. 5C). "P300" amplitudes relate to the relevance of a stimulus in the task context and to the amount of uncertainty that the stimulus resolves; they are largest when uncertainty is greatest about stimulus modality (Sutton *et al.*, 1965) or occurrence (Arthur and Starr, 1984). For instance, they can be highly dependent on feedback that a cue has been missed, such as for a motor action, particularly when the subject is uncertain about the cue (Campbell *et al.*, 1984). "P300" potentials are best recorded over the scalp midline or intracranially in the amygdala and hippocampus, but their origins are probably multiple (cf. rev. Hillyard and Picton, 1987). What we called cingulate "error" potentials in monkeys (Gemba *et al.*, 1986) could well be called "uncertainty" potentials. Their analogy to "P300" suggests limbic action on the "cognitive", higher level of the brain, which, however, is connected to the posterior cingulate cortex (cf. Fig. 7, later). The observed potentials could conceivably reflect activity in posterior cingulate, since its major corticocortical interconnections are with anterior cingulate. (cf. rev. Vogt, 1985). (Another, but perhaps less likely, possibility is that the functional message traffic flows the other

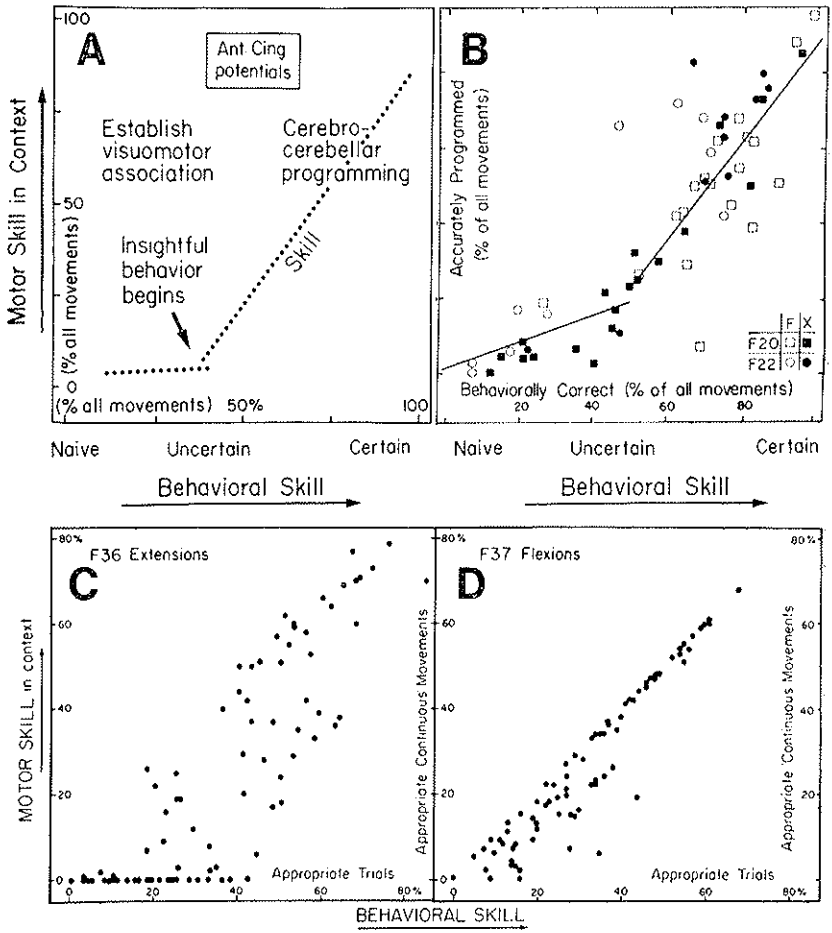

FIG. 4. Motor learning of four monkeys with the paradigm explained in Fig. 3. *Abscissae*: Behavioral skill; *ordinates*: motor skill (as in Fig. 3C). Sequential activity in higher and middle brain levels is summarized in A. Boxed legend: *Ant. Cing. potentials* indicates that field potentials in the anterior cingulate cortex may accompany inappropriate behavior when behavioral uncertainty is high (45-60% appropriate behavior, abscissa); *dotted lines* indicate session averages for pooled flexions and extensions of F22 as in Fig. 3C. B: Session averages for flexions and extensions of monkeys F20 and F22 (see *key*; *lines* represent averages of all four). C, D: session averages for F36; F37. (A, modified from Brooks, 1986a; B, modified from Brooks *et al.*, 1983; C, D, from Brooks and Watts, 1989 in prep..

way: anterior cingulate potentials could possibly be evoked through connections from PM and SMA and might be destined to influence posterior cingulate cortex). I pursue an alternate view, however, namely that the projections from anterior cingulate to nonprimary motor areas (e.g., PM and SMA, Fig. 2) serve limbic influences on middle level preparations for motor acts. This is discussed in detail with reference to Fig. 7 in section 7. In fact, the similarities have been noted between the time course as well as a relation to predictability between "P300" potentials and discharges of about 1/3 of PM neurons in anticipation of directional cues for the next movement (see section 6) (Wise and Mauritz, 1985; Mauritz and Wise, 1986).

5. *Association of "What" and "How" Depends on Nonprimary Motor Areas.*

Nonprimary motor areas help to translate *what* to do into *how* to do it. They help to prepare for motor action in task-context by linking behavioral knowledge with independently acquired motor ability. Motor "set" thus includes preparation for coordination and execution of relevant acts. These can involve postural adjustments associated with movements (cf. Wiesendanger, 1986; cf. Gahéry and Massion, 1981; Freund and Hummelsheim, 1985) or the conjoint use of the two hands for manipulating objects (cf. rev. Wise, 1985; Rizolatti, 1987). Ablations of nonprimary motor areas degrade dexterity through loss of previously learned motor responses to cues. SMA removal abolishes the ability to learn movements cued by (probably proprioceptive) input resulting from preceding motor acts (cf. rev. Passingham, 1987). Functionally, SMA removal degrades self-generated motor acts that can include bimanual cooperation. For instance, it can abolish predictive transport and shaping of monkeys' hands for expected use of the fingers to pick up small objects (Brinkman, 1984). Bilateral PM removal abolishes the ability to learn movements cued by visual or other signals (Passingham, 1988). It is of particular interest that temporary bilateral PM dysfunction temporarily puts the performance level of monkeys trained to move their wrist in response to a learned cue (as in Fig. 5C, lower picture) back into the first learning phase described in Figs. 3, 4. Sasaki and Gemba (1986) recognized this by the return to mostly self-paced movements despite continued visual attention and, in addition, by dispersed reaction times. The degradation of appropriate task-behavior to inappropriate behavior, in this case induced by

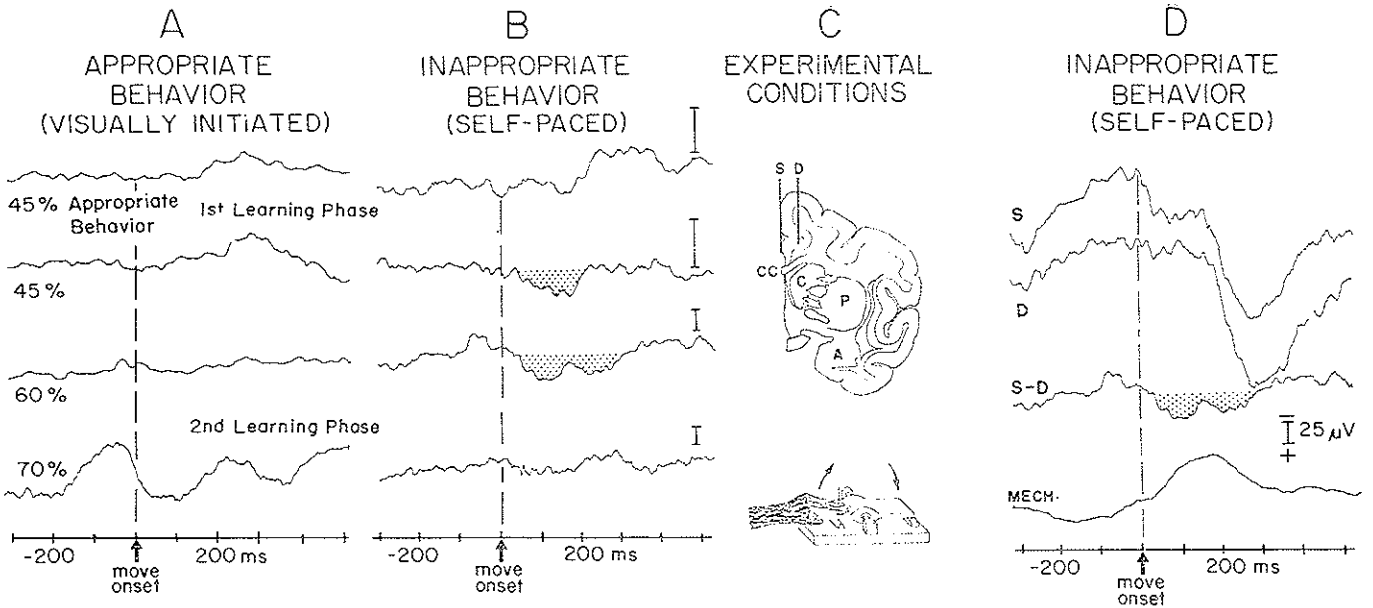

FIG. 5. Transcortical field potentials from anterior cingulate cortex during appropriate task behavior (A) when monkeys were trained to make visually initiated movements within 1 sec. of cue onset, and inappropriate behavior (B, self-paced movements). Potentials (*stippled, also see D*) appeared only during *high behavioral uncertainty*: 45-60% appropriate behavior as labeled on extreme left. Experimental conditions in C: *below*; task situation for wrist movement task; *above*, frontal brain section. S, D: surface and depth electrodes; A, amygdala; C, caudate n; CC, corpus callosum; P, putamen. D: comparison of P300-like appearance of S or D potentials with S-D derivation (*stippled, 60% appropriate trace as in B*). All traces are average of appropriate or inappropriate trials from a total of about 100 trials according to % labels. Traces aligned with movement onset (*vertical lines*) according to mechanograms (MECH.) of wrist extensions to lift lever. (Modified from Gemba *et al.*, 1986).

cooling the PM surface, was reversible: performance right afterwards matched precooling controls. The result highlights the role of PM in performance of previously learned actions through use of long-term associative memory, recalling the description in section 2 of the essential function of the amygdala for access to crossmodal longterm memory.

The above descriptions of dysfunctions caused by lesions of non-primary motor areas are best understood in the light of their connections to the middle level of the motor system. Its "guiding" function mentioned in Fig. 2 is based on the linkages of the cerebellum and basal ganglia to the primary motor cortex. This is illustrated in Fig. 6. Primary motor cortex is linked to the cerebellum through PM and to the motor ("putamen") loop of the basal ganglia through SMA. Only feedforward connections are shown in Fig. 6 and many brain parts are neglected, particularly afferent and other subcortical centers (some of which are shown in Fig. 7 in relation to limbic loops). Not shown in Figs. 6 and 7 are the reciprocal cortico-cortical connections between SMA, PM and primary motor cortex, and the corticospinal projection from SMA (cf. rev. Wiesendanger, 1986; Jones, 1987). Fig. 6 serves as a guide but it is important to remember that this flowsheet represents just one aspect of a distributed cortical-subcortical system with many parallel paths.

General strategy instructions about what to do are thought to emanate from prefrontal association cortex (area 46, at the principal sulcus) to three major cortical areas: cingulate, parietal and temporal, and subcortically to neostriatum, thalamus, claustrum, superior colliculus, and reticular formation (Selemon and Goldman-Rakic, 1985; cf. rev. Goldman-Rakic, 1987). Temporal targets include the input areas to the hippocampus (see Figs. 2, 7) which is not discussed in this paper. Prefrontal calls for motor action reach SMA and at least the face and hand areas of PM (Godschalk *et al.*, 1984; Pandya and Kuypers, 1969; cf. rev. Goldman-Rakic, 1987) that project to primary motor cortex (Godschalk *et al.*, 1984; Muakkassa and Strick, 1979; Schell and Strick, 1984), and thus could provide indirect routes for limbic influence on motor action (cf. Brooks, 1986a). The prefrontal-PM-parietal "neural net" is well suited for visuomotor tasks since PM cells receive their major cortical input from inferior parietal area 7, whose cells are predominantly active in directing attention in preparation for visuomotor acts (cf. rev. Mountcastle, 1981; Mountcastle *et al.*, 1987). The prefrontal-SMA-parietal system is well suited for self-generated motor acts. The influence of PM on primary motor cortex is just one of many modulations impinging on it, but it is a parti-

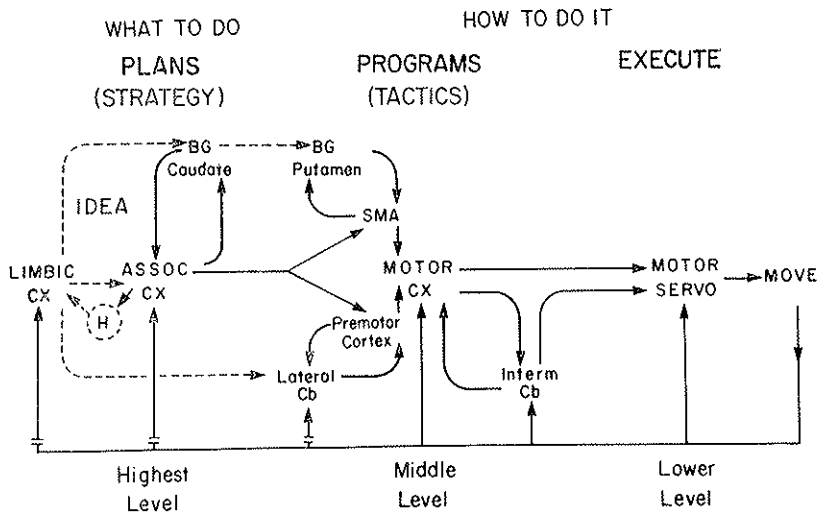

FIG. 6. Cartoon diagram of some aspects of information flow for voluntary movements, stressing connections of the cerebellum and basal ganglia but omitting most subcortical connections. Only some limbic connections are shown (*broken lines*). BG, basal ganglia; and Cb, cerebellum; are connected to primary motor cortex through loops traversing the SMA, (supplementary motor area, mesial area 6); and the premotor cortex (lateral area 6, labeled "PM" in Figs. 3; 7); not shown are reciprocal connections of PM, SMA and primary motor cortex, and corticospinal outflow from SMA. CX, cortex; H, hypothalamus. (Derived from Allen and Tsukahara, 1974; modified from Brooks, 1986b; cf. Wiesendanger, 1986).

cularly powerful one for visuomotor actions. SMA receives less input from area 7 than PM but instead more from superior parietal area 5, whose cells are predominantly active in relation to sensorimotor activity, some only when the animal engages in "exploratory, directed projections or manipulations aimed at satisfying an appetitive drive" (cf. Mountcastle, 1981). Static diagrams like Figs. 2, 6 and 7 thus resemble simplified snapshots at a given moment in time of preferred connectivities with high synaptic security. They portray temporary certainty in systems whose functional traces for multiple influences rest on probabilistic participation of particular cells or cell systems (cf. McCulloch, 1965). Nowadays changes of "central state" are regarded as normal, with an evergrowing list of regulatory mechanisms and participants. Limbic modulation of motor skill is just another candidate.

6. *PM and SMA Are Likely Candidate Targets for Limbic Modulation during and after Motor Learning.*

It has been suggested elsewhere (Brooks, 1986a) that limbic modulation of nonprimary motor areas could regulate motor preparation and thus contextual use of motor skill. The functional properties of neurons in nonprimary motor areas correspond to what might be expected on the basis of lesions described in section 5 and can be summarized as follows. They participate in voluntary activity in ways that are more specific than neurons in higher association areas (e.g., Rizzolatti, 1987) but less specific than those in primary motor cortex since neither PM nor SMA cells relate to movement parameters (Smith, 1979; Tanji and Kurata, 1985; Wise, 1985). Movement-related SMA cells tend to discharge after primary motor cortex, whereas those in PM tend to fire earlier. Many PM and SMA cells can discharge in relation to various sensory cues for task performance, but PM cells mostly do so only if the cue actually leads to movement (cf. rev. Wise, 1985). Many cells in PM and also in SMA discharge in relation to preparation for movement, but more cells in SMA than in PM link particular sensory cues to particular motor acts. SMA and PM could both prepare postural support for voluntary movements by anticipatory adjustments of spinal excitabilities; SMA directly through a substantial corticospinal projection, and PM indirectly via primary motor cortex (cf. rev. Wiesendanger, 1986; Wise and Mauritz, 1985; Mauritz and Wise, 1986; Kurata and Tanji, 1985).

What types of cellular responses in PM and SMA might indicate limbic influence during motor learning? This question is best approached by considering experiments with conditions that permit comparison to our observations (Fig. 3). The most comparable are those of Weinrich, Wise and Mauritz (1984), who recorded PM units in monkeys that had acquired accurately programmed movements without constraints or rewards to do so (cf. footnote 2 in section 3). In these, and also in other experiments that called for fast programmed movements (Weinrich and Wise, 1982; Wise and Mauritz, 1985), about 1/3 of PM neurons were related to "set". (Detection of set was defined as a sustained discharge during the required hold-period after the animals had seen the cue for the direction of movement to be made at the next Go! signal). They concluded that "set" units... "appear to be involved in the preparation for the general type and direction of movement that the animal intends to make in response to *expected* cues"... (*italics* mine). I take this to mean that 1/3 of PM

units became set-related when the animals had learned what was required of them in the task. *Association* of knowing "what to do" and getting set to do it is a likely limbic target, considering the essential role of the amygdala in cross-modal associations related in section 2. Another indication for limbic involvement may be discharges of PM neurons in anticipation of expected cues because associations for expectations are formed at the time when cingulate "uncertainty" potentials appear (end of section 4) ([3]). Arguing the case for limbic involvement on the basis of experiments with closely controlled behavior is not to deny that neurons in PM and SMA probably function in other, perhaps more selective, ways. In the absence of detailed observations to guide us, however, I favor here anticipatory and set-related discharges as the most likely targets for limbic modulation during motor learning. It is assumed that this modulation during practice aids not only in the establishment of short- and long-term memory but probably also thereafter by cueing memory-primed neurons to help recreate learned associations in contribution to skilled performance. In summary, there are indications that about 1/3 of PM neurons are modulated during motor learning by the limbic system to help activate primary motor cortex according to expectations about tasks that have been learned by the subject. Something like this may also be true for SMA, but no comparable detailed information is available.

7. *Amygdala and Cingulate Projections Converge on PM and SMA.*

So far the emphasis on limbic action has been on the amygdala (Fig. 2, 7) or on the anterior cingulate cortex (area 24; *left* side of Fig. 7). Now we need to consider them in relation to each other because they project to a surprising number of common targets (see the *broken lines* in Fig. 7). The examples of immediate interest are indicated by *heavy arrows* in Fig. 7A, B, highlighting convergence on PM and SMA. Projections from the basolateral complex of the amygdala end mostly in cingulate layers (II, III and some in V and VI) that give rise to axons to PM and SMA. Projections from the amygdala to PM and SMA reach mostly layer II, with minor projections to VI. It is still unknown and needs to be established

([3]) It might be a fair guess that anticipatory and set-related PM discharges develop in intensity and prevalence in parallel with appropriate task-related behavior and well consolidated brief reaction times; and that they might increment in sudden step-fashion to herald ubiquitous use of accurately programmed movements.

if cingulate projections to PM and SMA converge directly with those from the amygdala, i.e., on the same neural colonies in layers II and III, or whether they project to separate colonies (cf. for projections from the amygdala: Amaral and Price, 1984; Avendaño *et al.*, 1983; Murray and Saunders, 1987; from cingulate cortex: Baleydier and Maugiere, 1980; Jürgens, 1984; Pandya and Kuypers, 1969; Pandya *et al.*, 1981; van Hoesen *et al.*, 1981). Other points of convergence in Figs. 7A, B are considered elsewhere (Brooks, 1986a) and are contained in recent reviews (e.g., Amaral, 1987; Vogt, 1985) but brief mention should be made of the connections of posterior cingulate cortex (area 23, *right* sides of Figs. 7A, B; cf. section 4). It receives inputs from the amygdala and is closely linked to prefrontal, parietal and temporal association areas, themselves also all targets of amygdaloid projections. The cerebellum is not connected to this "higher function" circuit but the loop through the caudate nucleus of the basal ganglia is included. As mentioned in section 5, the prefrontal principal sulcus could thus channel limbic influences on motor actions. Taken altogether, the numerous points of convergence for projections from the amygdala and the cingulate cortex suggest that they could coordinate modulation of their common targets.

8. *Limbic Regulation of Output Setpoints in PM and SMA?*

The reason for stressing reports on converging limbic inputs to PM and SMA is explained in Fig. 8 as an abstraction from Fig. 7. A neural center is shown with two inputs: the first directly from the amygdala and a second, *corollary* one, from cingulate cortex. This cortically processed "second opinion" from cingulate could, after convergence with the original amygdala input, yield "*comparisons*" of the two inputs in the neural center if it can decode the difference between them. This view (Brooks, 1986a) is offered in analogy to comparisons in the ventral vestibulospinal tract where VSCT cells overhear first, through private line collaterals, what spinal interneurons receive from various sources and then, second, hear the responses of those interneurons (Lundberg, 1971). Fig. 8 is also an analogy to the design principle of the cerebellar circuit (Fig. 6): the cingulate cortex is shown on a sideloop to the neural center that functions as the main input-output device (Oscarsson, 1973; cf. Ito, 1984). The proposed comparator action would improve regulation of setpoints for motor preparation because two stages of limbic integration, rather than just one, are brought

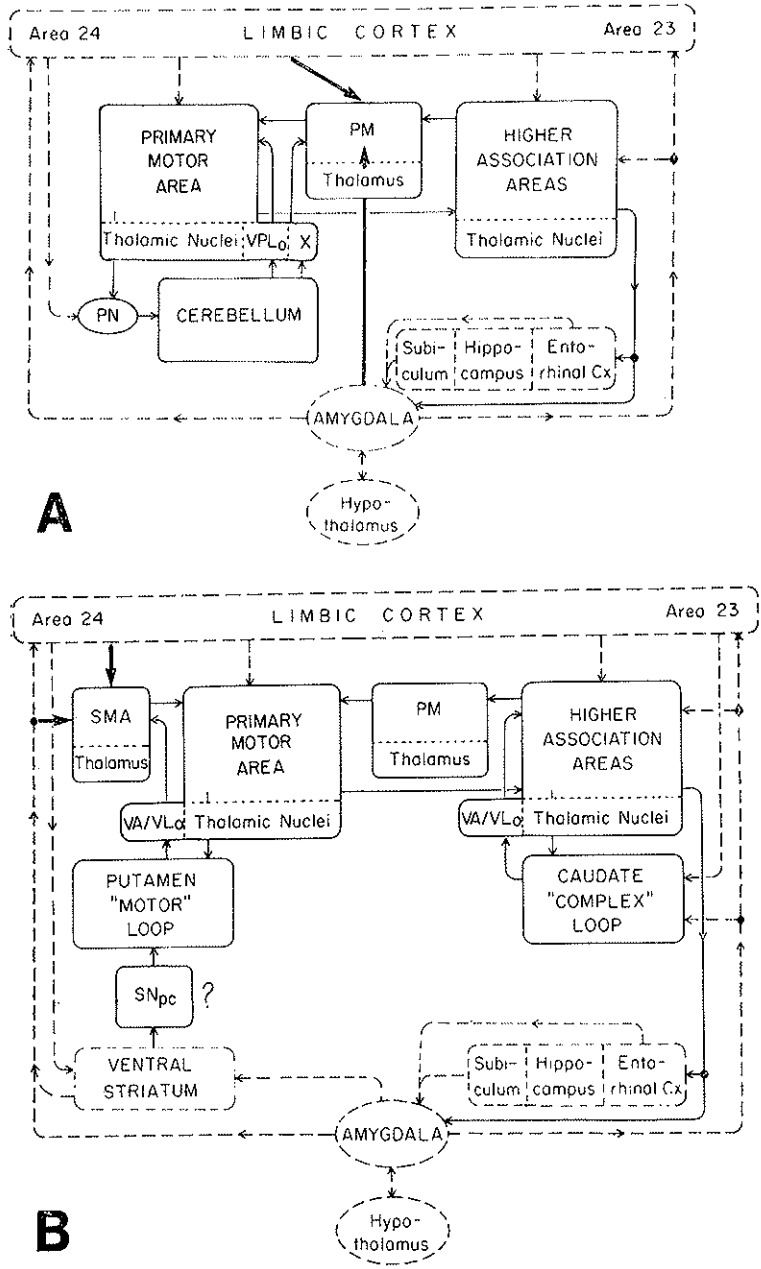

FIG. 7. A: Simplified diagram of information flow between the limbic system and the cerebro-cerebellar circuit, stressing points of convergence between projections from the amygdala and the cingulate cortex. *Heavy arrows* from amygdala and anterior cingulate (area 24) to PM, premotor cortex; PN, pontine nuclei; VPL_o, thalamic nucl. ventr. post.; X, thal. nucl. X. B: Equivalent diagram for the "motor" loop of the basal ganglia. Top left: Heavy arrows from amygdala and anterior cingulate to SMA, supplementary motor area; PM, premotor cortex; substantia nigra, pars compacta; VA/VL_o, thalamic nuclei ventralis anterior and lateralis, pars oralis; ? signifies uncertainty about projection in primates from ventral striatum to SN_{pc}. Compare to Fig. 2. (Modified from Brooks, 1986a).

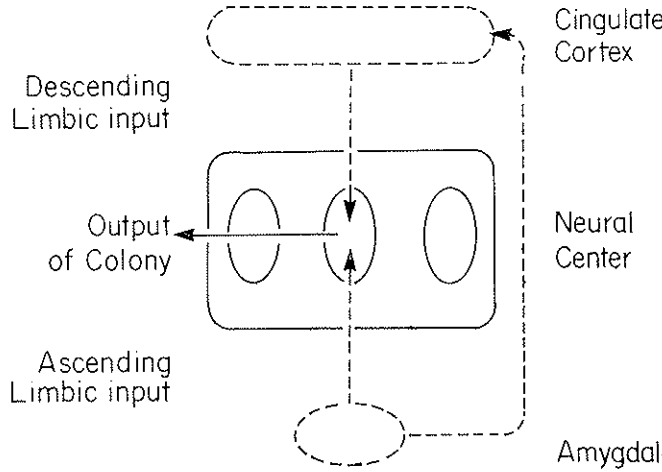

FIG. 8. A simplified scheme of information flow through a task-related cell assembly (colony) in a nonlimbic neural center, e.g., PM or SMA, to highlight possible modulation of colony output by neural "comparisons" of two limbic inputs. One input ascends from the amygdala and another, cortically processed, corollary one converges from the cingulate cortex that is on a side-loop to the main connection from the amygdala to the neural colony. Compare with Fig. 7. (From Brooks, 1986a).

to bear on the nonprimary motor areas. This design would refine how the brain can translate knowing *what* to do into knowing *how* to do it.

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DISCUSSION

DEECKE

When you told the story about the cooling, I think these were about the same regions where we found the extra activity in the inverted tracking tasks, so I think it's a good confirmation that these lateral prefrontal areas may well be important for learning. I would like to mention that in 1984 we published a paper on timing functions of the frontal cortex in human neurobiology. There, we actually put three questions in the motivational chain, about the how and the what and the when. Kornhuber makes three divisions of the frontal cortex. He is distinguishing between the frontal orbital cortex, the frontal lateral cortex and the frontal medial cortex. Just tentatively he suggests that maybe the "what to do" question is the task of the frontal orbital cortex: at least when you have lesions in patients, they lose the ethical structure and don't know what is good to do and what is bad to do. The frontal lateral cortex may answer the "how to do" question because this is the area which has the heaviest connection with the association areas, as Patricia Goldman-Rakic has shown. What is left then is to answer the "when" question, and our opinion is that the "when" question is answered by the medial frontal cortex, including the SMA, and maybe also including the anterior cingulate.

BROOKS

Thank you for pointing that out. I do think that for all of these statements that you and I have used about localization of function we must remember that we are always talking about what we have manipulated, and that doesn't mean it's the only part involved. What you say is right, but I wouldn't word it as saying, "this is happening there". I think the experimental test is perhaps the safer statement. Namely without this, it doesn't work. I would say, "That is one of the places where it is".

DEECKE

That is always the problem with cerebral localization — you don't know whether you have broken the chain.

BROOKS

It is relevant to this discussion because we are talking about the design principle. What I have shown adds a small amount by saying: there are parallel processes going on and one can identify where they go into execution.

ROLAND

We in 1980 suggested a kind of division between the supplementary motor area and the premotor area on the lateral side. At that time, on the basis of observations and activations in the intact human brain and their localizations, we suggested that voluntary movements needing some kind of sensory information for their execution were dependent on the participation of the premotor cortex and also of course of the supplementary motor area. However, if the movements were overlearned and not any more dependent on this external information, then the role of the premotor cortex was certainly not very big. At least we couldn't see any activation. So my question is, in your paradigm, when the monkey has learned the task and he becomes independent of external sensory information or even somatosensory feedback to a great extent, would that also apply? Would you then get rid of the influence of the premotor cortex?

BROOKS

I can't answer the question.

SINGER

Since you assign such an important role for the cingulate gyrus in putting signals to the cortex, I wonder whether you, or anybody else can give us more information about how this cingulate projection is wired into the cortical network.

BROOKS

You mean the anatomy?

SINGER

The organization of this control system.

BROOKS

I found very little.

ROLAND

I could add directly to this. I forgot to say also that in this learning paradigm, finger playing movement, there's a very strong participation of the anterior cingulate cortex, which would fit perfectly with your suggestions.

ANDERSEN

With reference to the cingulate connection, there are of course rather strong connections from the anterior cingulate gyrus to various prefrontal medial areas. However, the main point is that the cingulate cells are connected within themselves, going, on the whole, backwards from area 24 back to area 23. Connections to neocortical areas might well be significant. I was also very interested in your break point and in your behaviour versus motor skill diagram. How did the animals behave around that area? Was the motivation shooting up or did they behave in the same sort of way as before?

BROOKS

There was no sudden change in their motivation. There was a sudden change in how often they used programmed movements to carry out the motivated behaviour, because the curve rises when you plot one against the other.

ANDERSEN

Yes, I understand that, but the success doesn't mean much then. Is that it?

BROOKS

Well, the behavioural success gets them more rewards, but making programmed movements has very little to do with it because we arranged it that the difference in timing duration of the two kinds of movements should count for very little.

ITO

Is it correct to interpret your diagram that the limbic system, including the hippocampus, plays a role in the first stage of motor learning while the cerebellum plays a role in the second stage of motor learning?

BROOKS

I don't quite know how to answer this. The only bit of evidence that we have is that we saw those potentials when the animal was uncertain. Whether the increased efficiency of correct behaviour after that was still guided by the limbic system, I have no direct evidence.

ITO

There is a very puzzling observation by Thompson and others on the cerebellar conditioned reflex situation. There is enormous potential development in the hippocampus, during the period of acquisition. However, complete removal of the hippocampus does not impair at all the acquisition of the conditioned reflex.

THE MAIN FEATURES OF LONG TERM POTENTIATION: A MODEL FOR THE FORMATION OF MEMORY TRACES

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Types of synaptic plasticity. Activity-dependent improvement of synaptic efficiency can be found in many parts of the nervous system. *Facilitation* of the synaptic transmission is seen for a few hundred milliseconds after a single previous impulse. Following tetanic stimulation two additional forms of enhancement are commonly present: *augmentation*, decaying with a time constant of 4 to 10 seconds, and *post-tetanic potentiation* which can last a few minutes (Magleby, 1973; Magleby and Zengel, 1975, 1976; McNaughton *et al.*, 1978). *Long-term potentiation* of synaptic transmission - LTP (Lømo, 1966, Bliss and Lømo, 1973) adds a fourth type of increased synaptic efficiency which considerably outlasts the first three, by lasting hours, days and even weeks, depending upon the experimental conditions.

LTP has been proposed as a *model for cellular learning and memory* because of its long duration and fast induction, using physiologically acceptable signal patterns (Swanson *et al.*, 1982; Andersen, 1987). The process has been found in a number of tissues in many different species (Teyler and Discenna, 1984). The best developed cases (amount and duration) are seen in various *cortical areas.*

The production of LTP follows tetanic stimulation of an afferent pathway to a group of target cells. Effective stimulation regimes may be a single tetanus (10-20 Hz) for a few seconds, or a series of shorter (100-500 ms) high frequency trains (100-500 Hz), repeated with intervals of a few seconds. The LTP effect is cumulative with repeated tetani.

The expression of LTP appears as an increased release of synaptic transmitter (glutamate) and an enhanced synaptic transmission seen as a larger EPSP and an increased spike probability or as an increased extracellular population spike with reduced latency. The discharge probability and the associated spike latency do often change more than corresponding to the EPSP increase (E/S potentiation), probably reflecting a change in postsynaptic excitability (Andersen *et al.*, 1980). Neither recurrent nor forward inhibition are changed (Haas and Rose, 1982).

The requirement for induction is a sufficient regional (dendritic) postsynaptic depolarization paired with a local synaptic input (Kelso *et al.*, 1986; Sastry *et al.*, 1986; Wigström *et al.*, 1986; Gustafsson *et al.*, 1987; Hvalby *et al.*, 1987). Normally, the postsynaptic depolarization is caused by the summing of the EPSPs caused by the tetanic stimulation, which also serves as the second required event, the synaptic activation. Under physiological conditions, one may envisage that one set of fibres (Fig. 1,

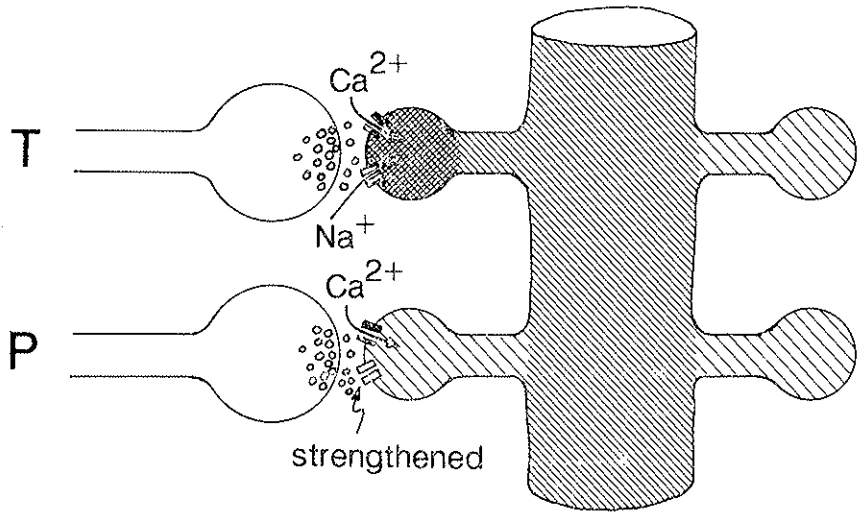

FIG. 1. Diagram of a small part of a CA1 dendrite with four spines. One is contacted by a fibre T that acts as a "teacher" by carrying a stream of high frequency impulses causing a standing depolarization by sodium and later, calcium entry. The attenuation of the depolarization due to electrotonic spread is symbolized by the degree of hatching. By being coactive with the "teacher", a "pupil" fibre P delivers a signal which, by being added to the existing depolarization and the associated calcium entry, leads to the potentiation of the P synapse.

fibre T = "teacher") delivers the required summating EPSPs, while other fibres (fibre P = "pupil") provide the synaptic activation. This *coactivation* is a central point in LTP induction and in the reasoning at the end of this article. In addition, synapses having a dendritic location near the tetanized input are potentiated more than remotely placed synapses (Andersen *et al.*, 1980). A central rule is, therefore, that potentiation requires *coactivation in time and space.*

The LTP effect has a definite stimulus threshold (McNaughton *et al.*, 1978; Yamamoto and Sawada, 1981; Lee, 1983), but it does not depend on cell discharges. The original explanation was that a certain number of afferent fibres had to be activated, referred to as *cooperativity.* Apart from the conjunction situations (see below), LTP is *homosynaptic* in that it only develops in tetanized afferents (Andersen *et al.*, 1977).

Calcium ions are necessary for LTP to develop, as seen by altering the extracellular calcium level during the inducing tetanus (Dunwiddie and G. Lynch, 1979; Wigström *et al.*, 1979), or by intracellular injection of chelating agents (G. Lynch *et al.*, 1983). An additional role of calcium in LTP beyond that of normal synaptic transmission is suggested by an increased uptake and retention of labelled calcium which parallels LTP (Baimbridge and Miller, 1981; Kuhnt *et al.*, 1985). Transient high calcium levels for a few minutes also led to long-lasting synaptic enhancement, similar or identical to LTP (Turner *et al.*, 1982; Higashima and Yamamoto, 1985).

Finally, blockade of the *N-methyl-D-aspartate* (NMDA) receptor with 2-amino-5-phosphono-valerate (APV) completely abolishes LTP production in spite of an unchanged synaptic transmission to single volleys (Collingridge *et al.*, 1983; Wigström and Gustafsson, 1984; Harris *et al.*, 1984). The inductive depolarization allows the NMDA-receptor operated channel to be relieved of its Mg^{2+}-blockade (Nowak *et al.*, 1984) with influx of Ca^{2+} as a result (Mayer *et al.*, 1984; Collingridge and Bliss, 1987).

Work with blockers of the quisqualate (QA) and the NMDA receptors have suggested that although the NMDA receptor is essential for LTP induction, the long-lasting expression (> 15 min.) is exclusively mediated by the QA receptor (Muller *et al.*, 1988).

Important facilitatory effects are produced by adrenergic afferents (Bliss *et al.*, 1983; Stanton and Sarvey, 1985), either through the depolarizing effect on the target neurones, or by blockade of accommodation, allowing the participating cells to deliver sustained high frequency

discharges in response to synaptic activation. Cholinergic facilitatory effects are possible, but have not yet been demonstrated sufficiently convincingly.

The nature of the cellular changes is not fully known. Four basic mechanisms could cause the sustained increase in synaptic efficiency characterizing LTP: 1) increased release of transmitter, 2) changed number or properties of receptors, 3) local postsynaptic excitability changes, and, finally, 4) morphological changes. The different aspects need not be isolated events, but could represent a string of processes, *coupled together in a cascade*. The extent to which the cascade will develop is likely to depend upon the strength of the inducing stimuli and the degree of repetition.

Presynaptically, the increased transmitter release seems coupled to an augmented level of Ca^{2+}, like in other cases of plasticity. Following LTP induction in the dentate area there is an increased resting release of aspartate and glutamate to afferent stimuli (Skrede and Malthe-Sørenssen, 1981; Dolphin *et al.*, 1982; Bliss *et al.*, 1986). The technique developed by Bliss' group (for reviews: Collingridge and Bliss, 1987; Bliss and M. Lynch, 1988) has provided strong evidence for a sustained increase in transmitter release during the maintenance of LTP. These presynaptic changes could be triggered either by a retrograde signal from the postsynaptic cell, or by a parallel activation of presynaptic and postsynaptic receptors by the released glutamate. Somewhat surprisingly, APV prevented both the LTP development and the increased release of glutamate in a reversible manner (Errington *et al.*, 1987).

Unfortunately, no convincing *quantal analysis* of transmitter release following LTP is available for dentate or CA1 synapses due to the contamination by spontaneous synaptic noise. Such studies should be possible for the mossy fibre synapses since Yamamoto *et al.* (1987) found that the mean quantal content increased due to phorbol ester application while the mean quantal size remained unchanged or diminished.

Candidates for postsynaptic LTP effects are: unmasking of dormant receptors; allosteric changes of receptors; closure of specific, phorbol ester sensitive ionic channels, either a dendritically located Cl^--current (Madison *et al.*, 1986), or the slow AHP K^+ current (Baraban *et al.*, 1985); aggregation of ionic channels (slow Na^+; Stafstrom *et al.*, 1985) in dendritic spines; insertion of new or an increased number of ionic channels; and morphological changes at or close to the dendritic synapses,

including changes in the shape or number of spines. Assuming a passive dendritic membrane, local resistance changes, such as a reduction in Cl^- conductance, would give a larger and more prolonged synaptic depolarization locally, thus providing both enhanced synaptic potentials and improved electrotonic propagation to central parts of the neurone. Both factors would increase the probability of spike discharge. An even more radical proposal involves the presence of active dendritic processes, which could undergo plastic changes during LTP.

G. Lynch and Baudry (1984) proposed that LTP could be associated with an *unmasking* of a covert population of glutamate receptors, thereby giving a sustained improvement in synaptic efficiency. Later, two other, independently working groups have been unable to verify the increased glutamate binding that was at the basis for this idea (Sastry and Goh, 1984; M. Lynch *et al.*, 1985). Further, no reports have appeared of increased responses to glutamate application during LTP (G. Lynch *et al.*, 1976; Turner *et al.*, 1982; Taube and Schwartzkroin, 1983; Mohan and Sastry, 1985). With available recording methods, such changes at remote dendritic levels cannot be ruled out.

The mechanisms producing the expression are multiple and may also be connected in a cascade of processes.

Presynaptically, there is an elevated turnover of phospho-inositides (Lynch, M.A. *et al.*, 1988) and good evidence for phosphorylation of a protein F1, also called B50 or GAP43 (Bär *et al.*, 1984; Akers *et al.*, 1986), which is associated with growth of axonal processes. Taken together with an observed translocation of diacylglycerol (DAG)-dependent protein kinase (protein kinase C, PKC) in synaptosomal membranes (Lovinger *et al.*, 1986), a role for PKC in the presynaptic LTP changes seems highly probable. Phorbol ester prolongs the action potential by closing a K^+ channel (Storm, 1987). This could explain the increased Ca^{2+} influx and thus the increased transmitter release, similar to the changes seen in the long-lasting synaptic changes in *Aplysia* (Kandel and Schwartz, 1982).

Postsynaptically, a set of changes is induced. Glutamate activation of the quisqualate (QA) receptor apparently triggers postsynaptic enzyme systems. Changes identical to LTP follow application of phorbol esters (Malenka *et al.*, 1986) and injection of PKC (Hu *et al.*, 1987), and LTP can be prevented by PKC inhibitors (Madison *et al.*, 1988; Malinow *et al.*, 1988). Thus, application of H7 transiently depressed an already estab-

lished LTP, suggesting firstly that PKC is important and secondly that PKC is continuously activated during LTP maintenance. One caveat is that the inhibitors so far used are relatively nonspecific, in that they also inhibit other kinases to various degrees.

Excitatory glutaminergic synapses on CA1 pyramidal cells probably activate the quisqualate or the kainate type of receptor during normal synaptic transmission (Collingridge *et al.*, 1983). Glutamate analogues like ibotenate, quisqualate and aspartate enhance the hydrolysis of membrane inositol phospholipids (Nicoletti *et al.*, 1986), while NMDA and kainate, in contrast, inhibit the phosphatidyl-inositol turnover induced by other transmitters (Baudry *et al.*, 1986). The report of a fourth subtype of glutaminergic receptors which prefers quisqualic acid as agonist and directly and rapidly activates inositol phospholipid metabolism (Sugiyama *et al.*, 1987) may help to clarify the link between receptor subtype and messenger activation.

Candidate substrates for PKC involve both ionic channels as alluded to above, but also proton pump mechanisms and growth-associated enzyme activation.

Morphological correlates of LTP. The synaptic efficiency might be controlled by activity-dependent changes in morphology. Cytoskeletal proteins, for example actin and fodrin, could provide a machinery for early rapid changes in shape (for reviews: Fifkova, 1985; G. Lynch and Baudry, 1984) while the slower changes would require protein synthesis *de novo*.

A variety of morphological changes has been reported to be correlated to LTP in the hippocampus since the initial reports by Fifkova (Fifkova and van Harreveld, 1977; Fifkova and Anderson, 1981). In more recent studies, a reduced variability of the head shape of dendritic spines and an increased number of shaft synapses have been reported (Lee *et al.*, 1980; Chang and Greenough, 1984). Needless to say, quantitative work demands identification of the types of boutons and the postsynaptic structures they contact. This task is often difficult when standard two-dimensional electron micrographs are used. Some uncertainty still exists as to target of the reported shaft synapses. Did all contact pyramidal cell dendrites, or were some of them located on interneurones? The density of shaft synapses was several times higher on identified interneurones than on pyramidal cell dendrites (Line Vaaland and Andersen, unpublished observations). The reported shape changes of the spine head

were relatively small. In addition, because of the roughly globular form and small dimension of most spine heads, the distribution of injected charge in an active spine would nearly certainly make its head isopotential. Even in calyciform spines the charges are likely to be evenly distributed. Alterations of the spine neck dimensions, however, could significantly change the dissipation of the injected charge, and thereby the size of the voltage changes in the more proximal dendrites and the soma.

Therefore, we made three-dimensional reconstructions of rat dentate granule cells, taken from areas where LTP had been recorded, with particular emphasis on spine shape and density. The results revealed significantly more spines per dendritic length, and more bifurcating spines than in control material (Andersen *et al.*, 1987). Also, a new reconstruction technique disclosed that a subset of spines had somewhat thicker necks. Because the material was fixed between 40 and 45 minutes after induction of LTP, these morphological studies suggest that surprisingly fast growth processes are associated with LTP.

A model for engram formation by convergence of hippocampal and sensory inputs in neocortical association areas. Suggestive evidence exists for a link between APV-sensitive hippocampal processes and the establishing of memory for spatial navigation (Morris *et al.*, 1986). It is also possible to see a role for hippocampal LTP in the *formation of a memory trace in association cortex* by remembering the extensive and elaborate connection between the entorhinal area and many neocortical association areas (Van Hoesen and Damasio, 1987). The trisynaptic loop inside the hippocampus has three outlets: The CA3 neurones signal through fimbria to septal and hypothalamic areas and, not least, to n. accumbens. Subicular neurones discharge through the dorsal fornix to similar destinations, but also to the entorhinal area. The latter, therefore, could serve as a bidirectional link between neurones in hippocampal areas and cells in neocortical association cortices.

Assuming an essential role for *coactivation* in strengthening synaptic connections, we may envisage simultaneous bombardment of neurones in an association cortex by signals entering through a sensory channel and impulses coming from an LTP-changed set of hippocampal neurones. In this way, the impulses derived from the hippocampus may serve as "teachers" in providing the postsynaptic depolarization while the sensory input activates the synapses to be strengthened (Fig. 2). Such strengthening is proposed to be the basis for the *deposition of an engram.* In

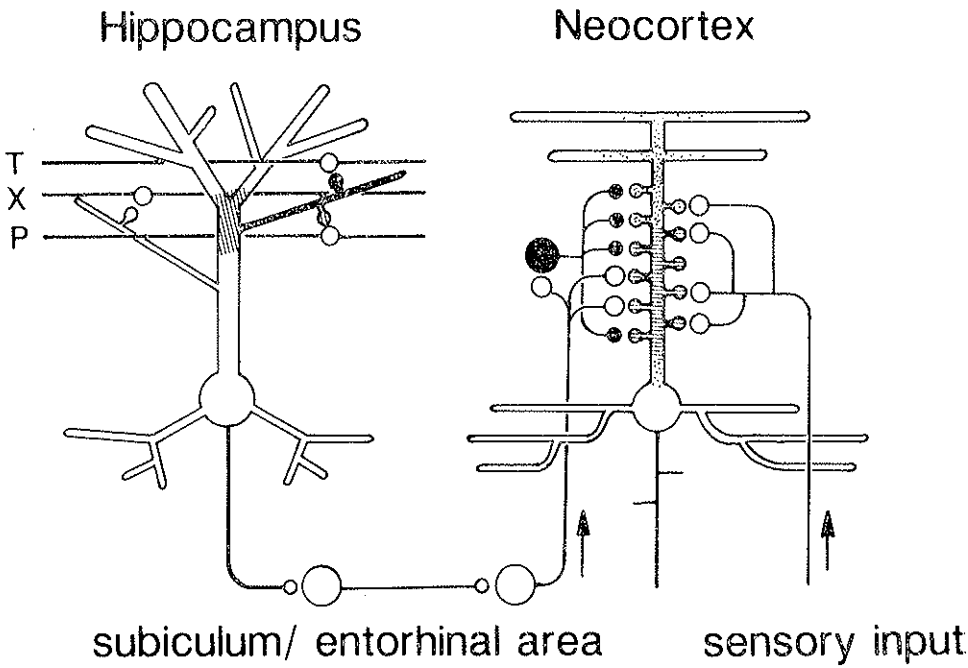

FIG. 2. The left hand side shows a diagram of a hippocampal pyramidal cell with three afferent fibres, synapsing on different secondary dendrites. Because of their contacts with the same dendritic branch, high frequency activity of the T fibre allows the synapse belonging to the P fibre to be potentiated while that of the X fibre terminates too far away. The output of the hippocampal pyramid is mediated to a neocortical pyramidal cell (right hand side) where it may serve as a depolarizing primer, permitting sensory afferent signals to strengthen endings on the same dendritic region. For both types of pyramidal cell, the hatching indicates the spread of the priming depolarization. The black cell represents a neurone with vertically coursing axonal bundles, able to distribute excitation over a large part of the apical dendrites of pyramidal cells (stippled).

the recall situation, signals which are initiated by a cue will arrive along the strengthened sensory pathway. Compared to non-strengthened connections, such impulses would have an improved chance of initiating the rest of the associative network, thereby facilitating the recall — in other words, *improved access to the engram.*

Certain anatomical differences in the organization of the afferent inputs may be important in this regard. The afferent impulses in the hippocampal cortex cross the dendritic tree at right angles, making on the average only one contact per cell (in CA1). The instructional effect (post-

synaptic depolarization) mediated by one fibre is therefore limited both in size and space. The single fibre EPSP in CA1 is about 130 uV. However, due to the small dimensions, the local depolarization of a spine head is likely to be more that 25 mV, possibly as large as 60 mV. This local depolarization will decay as it spreads to the environment, and will, therefore, most efficiently affect those synapses which are located on the same secondary dendrite (Fig. 1 and 2, fibres T and P). An associative effect will be distributed to inputs ending on nearly the same part of the cell. Fibres synapsing on other parts of the dendritic tree will have less chance of being potentiated. Since hippocampal fibres ending close together on a secondary dendrite also tend to lie in the same horizontal stratification, not only the potentiating synapses, but also their cells of origin are likely to be close neighbours. Therefore, groups of CA3 cells have the opportunity to reinforce each other's synapses on CA1 neurones, a sort of *learning through the good neighborhood.*

In contrast, the neocortical architecture displays a different pattern. Because the apical dendrites are relatively thicker with less branching than in the hippocampus (Sholl, 1956; Szentágothai, 1978), a spine-associated synapse may influence a larger part of the cell, thus having a larger synaptic "associative field" than can its hippocampal counterpart (Fig. 2, hatched areas on right side). Second, the afferent fibres arrive along the dendritic axis, providing opportunities for contacting the same cell at multiple neighbouring sites. Thirdly, the afferent fibres often branch profusely, an arrangement which also may support multiple contacts. Finally, neocortex contains particular interneurones with vertically running bundles of axonal branches (horse-tail axons), which may give rise to repeated excitation along the dendrites of layer II and III pyramids (black cell in Fig. 2). If the instructional signals have access to these "cellules à double bouquets" they could exert associational influence upon the synapses of a large number of convergent fibres. Hence, the neocortical architecture opens for associative coupling between synapses belonging to cells of widely spaced origins.

The recent observation of NMDA-dependent cortical plasticity, and the presence of LTP in both visual and somatosensory cortex increase the probability that processes similiar to those described above may take place in neocortical association areas as well.

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DISCUSSION

BROOKS

This very succinct paper is now open for discussion.

SINGER

Per, I am surprised you never see an enhancement of the NMDA-dependent EPSP component in hippocampal LTP. You would expect that if you close potassium conductance or if you have increased release, you would get over the magnesium block at some stage and use this then as an amplifier.

ANDERSEN

You see, in order to eliminate the magnesium block, you have to get quite a large depolarization, but you don't see any of that remaining depolarization under normal circumstances unless you have the train going continuously. So that's why you don't see that, I think. Wolf Singer was referring to the fact that there is a debate whether or not NMDA receptors are activated under normal circumstances. It's rather important because a single EPSP may have a trace of NMDA receptor mediated depolarization, but the train certainly has it. So if there is a change, there is a change of degrees rather than principle.

ROLAND

The situation seems to be slightly different from the neocortex where the NMDA dependent EPSP component is readily expressed and does increase with LTP.

ANDERSEN

You are referring to Alex Thompson's work. Yes, in the somatosensory cortex there is some very good evidence for LTP, in other words for NMDA mediated receptors, but other work has been questioning it, and other people

working with exactly the same preparations — a group from Hungary and one other in the United States — just can't see it. So there is still a little debate on how much you have in the neocortex.

ROLAND

During normal life it's not very likely that there is tetanic activity in the hippocampus, is there? This leads to the question whether long term potentiation is or isn't a good model of learning. I am quite well aware that it is certainly a good model of neuronal plasticity, but would this have anything to do with learning under natural conditions? Is anything known about that?

ANDERSEN

Well, as for the last part of the question, a lot is known about it. It is quite clear from the work of several groups that a lot of cells behave as you would expect them to, to be able to give LTP. Remember that a good way to get LTP is to send off 3 or 4 impulses at a repetition rate of the theta frequency, and theta activity is present all the time whenever an animal is searching, particularly in a new environment. So the possibilities are there. The other thing of course is to prove it, and nobody yet has proved it. There are ingenious ways to test it, but we haven't yet proved it. The spatial navigation of rats in water is knocked out by APV at the same concentration that knocked out LTP, for example. That's relatively good evidence. But the final proof is not in.

INGVAR

I had a question about the patient, the case that you showed initially. Would you mind commenting upon the molecular mechanisms that you would choose as being the active ones in killing these cells selectively?

ANDERSEN

Well, I have no personal experience, but people working on excitotoxicity feel that the NMDA channel, particularly in the depolarized state when you have lost a bit of potassium, would give you the glutamate influx which would turn on the calcium dependent enzymes.

INGVAR

Would you say that this region which is so vulnerable has primarily a very high metabolism, oxidative metabolism, and that is why it is so vulnerable?

ANDERSEN

No, I don't think you can relate it to the amount of oxidative metabolism, not to my knowledge.

DEECKE

My question was also on that patient. The lesion you have shown must have been bilateral.

ANDERSEN

It was bilateral, nearly symmetrical. I should add that there are also neocortical lesions in RB. There are about 30 small patches reaching into neocortical areas, spread around mostly in the temporal area. So I shouldn't think we should forget it, but they are rather small in volume in relation to the bilateral hippocampal damage.

ECCLES

I want to go back to the question of LTP in the cerebral cortex. I always thought that the cartridge synapses of János Szentágothai were excellently placed to be the triggers for putting calcium in to the pyramidal cell, and then the horizontal fibres would be able to potentiate it.

ANDERSEN

I fully agree. The cartridge synapse is perfectly placed to do the job.

FREUND

Is anything known about behavioural effects of AP on memory in man?

ANDERSEN

No, because even small doses of AP in man increase the epilepsy rate so dramatically that it prohibits any clinical studies.

McGEER

I'd just like to come back for a moment to the clinical case you presented, to ask two questions. First of all, since the cholinergic system, according to one school of thought, is an important contributor to memory, was the basal forebrain checked in that particular case?

ANDERSEN

It was, in fact. There was no reason to believe there was a specific defect in the cholinergic system.

McGEER

Neuropsychologists like to divide memory into acquisition, retention and recall. Was there any kind of division in this case? Was one component predominantly affected?

ANDERSEN

Yes, his acquisition was quite normal. When he was asked to copy complex figures, he copied them beautifully, just as an intelligent person would do. But he recalled very badly.

ITO

One very peculiar and disturbing fact about the hippocampus is the apparent lack of functional localization here. People recording from hippocampus during spatial tasks always find that some neurons discharged in connection with the task, but these cells were always scattered all over the hippocampus. There is no sign of concentration of a specific type of cells anywhere in the hippocampus and this seems to me a very strange and perhaps characteristic feature of hippocampus. Have you any thoughts on this?

ANDERSEN

No, you are pointing to a very serious question. The so-called place cells, which are specifically sensitive to one place in extrapersonal space are, as far as we can see, not localizable.

MOUNTCASTLE

Do you know of any case in which LTP has been established in other than pyramidal cells?

ANDERSEN

Yes, the granule cells of the dentate area, which couldn't be called pyramidal cells, I would say, could function.

MOUNTCASTLE

How about in the neocortex?

ANDERSEN

In the neocortex it has only been tested in what we believe are pyramidal cells, but the correlation there is not so good because it is very hard to identify cells.

WIESENDANGER

It's perhaps a difficult question, but I wonder whether you think that for one-trial learning, which occurs in humans at least, these mechanisms could play a role. What is, in other words, the minimum time of association or potentiation you need to get long term effects?

ANDERSEN

I can give you the last one. Gary Lynch claims he can do it with as little as 12 shocks, that is 4 or 3 consecutive trains which all takes place within about 200 milliseconds. That's the minimum I have seen. Whether or not you could compare this with one-trial learning, I doubt very seriously. Personally my view is that LTP should not be regarded as a memory model without qualification.

THE PREFRONTAL CONTRIBUTION TO WORKING MEMORY AND CONSCIOUS EXPERIENCE

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A Duality of Memory Systems

The concept that memory is divisible into several forms represents a major contribution to the study of memory from the field of cognitive psychology. The historical development of this field and the empirical evidence derived from cognitive studies in normal and brain-damaged individuals are well documented (for review see Baddeley, 1986). In the present chapter, my aim is to show that studies in nonhuman primates support the distinction from human studies and, beyond that, provide hints about the neural mechanisms subserving these separable forms of memory in mammals. Furthermore, as working memory and consciousness have in common a short-lived "of the moment" quality, I will suggest that the two evanescent processes may be related.

Working Memory

Working memory is the term applied by cognitive psychologists and theorists to the type of memory that is active and relevant only for a short period of time, usually on the scale of seconds. A common example of working memory is keeping in mind a newly read phone number until it is dialed and then immediately forgotten. Another common example is the bridge hand that was just played (Roitblat, 1987). The criterion — useful or relevant only transiently — distinguishes working

memory from the process that has been termed reference memory (Olton *et al.*, 1979), semantic memory (Tulving, 1972) and procedural memory (Squire and Cohen, 1984) — all of which have in common that their contents are always true and, in principle, remain stable over time, e.g., someone's name, the color of one's eyes, the shape of an apple. In contrast to working memory, all of these other forms of memory can be considered associative in the traditional sense, i.e., information is acquired by repetition of association between stimuli and responses and/or consequences.

A common misconception about working memory is that it is equivalent to the concept of short-term memory considered as a stage through which information entering long-term memory must pass. This was indeed a major assumption of the field in the late sixties (Atkinson and Shiffrin, 1968), but by the end of the next decade decisive evidence had accumulated to show that short-term and long-term memory had to be viewed as independent, dissociable mechanisms. A particularly significant piece of evidence was a case report by Shallice and Warrington (1970) of a patient that exhibited profound loss of short-term memory (digit-span) but excellent long-term memory (paired associate learning).

In this chapter, I will review evidence that the brain obeys the distinction between working and other forms of memory and I will argue that the prefrontal cortex has a specialized, perhaps even preeminent role only in working memory processes. Further, several lines of evidence suggest that there may be multiple working memory domains in prefrontal cortex, each organized according to a common functional principle but dedicated to a different information-processing system. Perhaps through the study of experimental animals more can be learned about the neurobiological principles underlying these fundamental processes which govern our behavior and which decompose in numerous neurological diseases.

Functional Significance of Working Memory: Representational Knowledge vs. Sensory Guidance of Behavior

The significance of working memory for higher cortical function is not necessarily self-evident. Perhaps even the quality of its transient nature misleads us into thinking it is somehow less important than the more permanent archival nature of long-term memory. However, the brain's working memory function, i.e., the ability to bring to mind events in the absence of direct stimulation, may be its inherently most flexible

mechanism and its evolutionarily most significant achievement. Thus, working memory confers the ability to guide behavior by representations of the outside world rather than by immediate stimulation and thus to base behavior on ideas and thoughts. The difference between guidance of behavior by symbolic representations and guidance by external stimuli cannot be overemphasized. At the most elementary level, our basic conceptual ability to understand that an object *out of view* exists nevertheless, depends on the capacity to keep events in mind beyond the direct experience of those events. For some organisms, including humans under certain conditions, "out of sight" is equivalent to "out of mind". Working memory has been invoked in all forms of cognitive processing, including language. Cole has recently argued that the failure to keep a word in mind (stimulus persistence, in his terms) after it has been uttered would lead to a grave restriction in the span over which contextual interactions can occur (Cole, 1989). Working memory is certainly needed to perform mathematical operations (carrying over), to play chess, to play bridge, to play the piano without music, to deliver speech without reading (or by rote) and finally to fantasize and plan ahead.

Tests of Working Memory in Nonhuman Primates

The capacity to keep events "in mind" for short periods can be studied in nonhuman primates by delayed-response paradigms. The classical delayed-response task was designed and introduced to psychology for that very purpose by the comparative psychologist, Walter Hunter (Hunter, 1913). His intention was to devise a test that would differentiate among animals (including humans) on intelligence — which he defined as the ability to respond to situations on the basis of stored information, rather than on the basis of "immediate" stimulation. The classical version of the delayed-response test is well known: the subject is shown the location of a food morsel that is then hidden from view by an opaque screen (Fig. 1). Following a delay period of several seconds, the subject chooses the correct location out of two or more choices. In this situation, the subject must remember where the bait had been placed a few seconds earlier. A crucial feature of the delayed-response task is the lack of a fixed relationship between stimuli and correct responses: the correct response is different on every trial and information relevant to the response on one trial is irrelevant on the next trial and actually would best be forgotten, lest it interfere with the new response. This

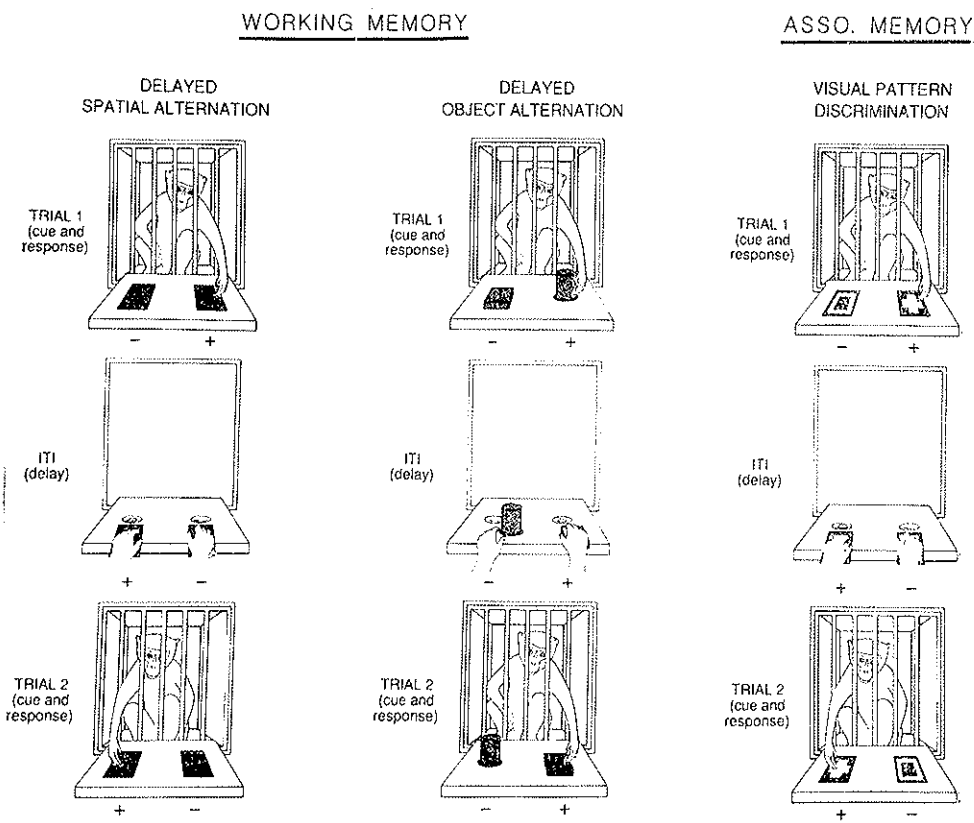

FIG. 1. Examples of two working memory tests, delayed spatial alternation and delayed object alternation. Dorsolateral prefrontal lesions produce impairments on these tasks, but not on associative memory tasks such as visual pattern discriminations [modified from Friedman and Goldman-Rakic, 1988 (see Goldman-Rakic, 1987a for review)].

is unlike the procedure employed in associative learning or conditioning paradigms, in which the correct response is the same on each subsequent trial. The underlying principle of delayed-response operates in other commonly used behavioral paradigms: spatial delayed alternation, object alternation, matching-to-sample or nonmatching-to-sample tasks.

Delayed-response function has been associated with prefrontal cortex since the early discovery that monkeys with prefrontal cortex damage were severely impaired on this and related tasks (Jacobsen, 1936). Although the association between the capacity to perform delayeyd-

response tasks and the functional integrity of the dorsolateral prefrontal cortex is firmly established, the nature of the process(es) tapped by these tasks has been the subject of continuing discussion and seemingly contradictory interpretations. Interestingly, Jacobsen himself stressed the mnemonic or temporal-sequential processes required by delayed-response tasks (and hence mediated by prefrontal cortex), but this explanation somehow did not take hold. In retrospect, it seems evident that in the thirties and for several decades later, memory was considered a unitary mechanism thought to have a specific localization. Because frontal patients, as well as monkeys with prefrontal lesions, displayed surprisingly adequate performance on associative learning and recognition memory tasks and, in addition, patients displayed remarkably normal scores on conventional IQ tests, the deficit of prefrontal monkeys was not global enough to fit the neuropsychologist's midcentury concept of a memory loss. Thus, other explanations of prefrontal dysfunction were offered; for example, impairments in spatial perception and/or spatial orientation, attention, perseveration and disinhibition, general motor control functions; and some considered disturbance in the central representations of kinesthesis or proprioception as basic to the prefrontal deficit. All of the theories of prefrontal impairment were strictly psychological without reference to a neural mechanism or physiological processes. In spite of Hunter's and Jacobsen's formulations, none of the later theories of prefrontal function considered short-term memory a viable explanation. And, of course, the concept and term "working" memory had not yet been invented.

Neurophysiological Evidence for Working Memory

A major development in our understanding of delayed-response tasks and prefrontal cortex came in the early seventies when unit recording studies were performed for the first time in awake behaving monkeys trained on delayed-response tasks (Kubota and Niki, 1971; Fuster and Alexander, 1971). These studies revealed that neurons in the prefrontal cortex became activated during the delay period of a delayed-response trial. It was difficult to resist the hypothesis that the prefrontal neurons examined were the cellular equivalent of a mnemonic event. Earlier studies on the behavioral effects of selective lesions of the prefrontal cortex had already posited that the cortex in and around the principal sulcal cortex was involved in what we termed at the time "modality-specific" memory

(Goldman and Rosvold, 1970; Goldman *et al.*, 1971). Our studies showed that monkeys with principal sulcus lesions were impaired only on tasks which contained both spatial cues/responses *and* a delay, but performed well in tasks which contained only a delay or only a spatial cue/response. The full significance of these experiments and conclusions is clearer now than it was in the early seventies when they were done, for they provided early evidence of a working memory system dedicated to spatial vision — that did not overlap with memory mechanisms for other (e.g., non-spatial) domains of knowledge.

The evidence from neurophysiological studies of prefrontal neurons has been steadily accumulating since 1970. Since that time, numerous studies have provided evidence that certain classes of prefrontal neurons are particularly activated during delay periods (for review, see Fuster, 1985). Yet the interpretation that such activity reflected a memory process was and is still not widely appreciated outside of a narrow circle of scientists working on the primate prefrontal cortex. Perhaps one reason is that neurons activated during the delay of a delayed response trial are not necessarily holding specific information "on line" but rather are engaged in some sort of general preparatory or motor set to respond. And preparation to respond could invoke postural mechanisms not necessarily central processing. However, recent evidence from studies in my laboratory have provided the most convincing evidence yet of mnemonic processing in prefrontal cortex. Shintaro Funahashi, Charles Bruce and I have been using an oculomotor delayed-response paradigm to study prefrontal function (Funahashi *et al.*, 1989). The advantages of this paradigm over other methods of studying delayed-response performance are many. We require the animal to fixate a spot of light on a TV monitor and maintain fixation during the brief (.5 sec) presentation of a stimulus followed by a delay period of variable length. Visual stimuli can be presented in any part of the visual field, and importantly, we have complete control over the specific information that the animal has to remember on any given trial. The fixation spot is turned off only at the end of the delay period and its offset is our instruction to the animal to break fixation and direct his gaze to where the target had been presented. Because the animal's behavior is strictly controlled in all phases of a trial, we believe that the animal can perform correctly only if it uses mnemonic processing. In the oculomotor task, as in manual delayed-response tasks, prefrontal neurons increase (or often decrease) their discharge rate during the delay period of a trial. The neuron displayed in

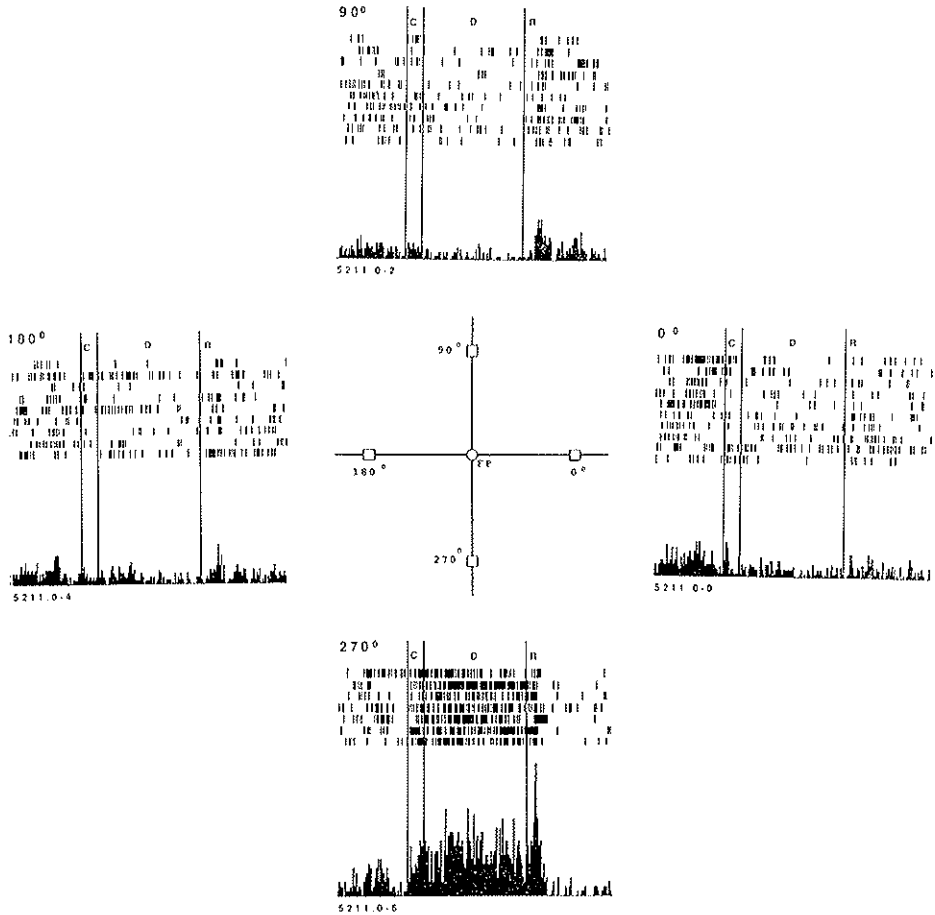

FIG. 2. Single unit activity of a prefrontal neuron recorded during performance on an oculomotor delayed-response task. Targets were presented randomly in one of four locations while recordings were made from the same neuron. As the monkey was required to fixate during the presentation of the target, the retino-topic location of the stimulus was precisely controlled; fixation was also required throughout the subsequent delay as a means of preventing "rehearsal" as well as a standardization of delay-period behavior. The neuron's "memory field" is for the target at 270°. Activity was enhanced during the delay period only when the target to be remembered was at that location and not at any other tested (modified from Funahashi *et al.*, 1989).

Fig. 2 is an example: its activity rises sharply at the end of the 270° stimulus, remains tonically active and then ceases rather abruptly at the end of the delay.

The activation of prefrontal neurons when a stimulus disappears from view and the maintenance of that activation until a response is executed, are highly suggestive of a working memory process, and perhaps, of a conscious experience. It cannot be argued that the delay period activity reflects simply the motor set of the animal to respond at the end of the delay, as has been described for neurons in premotor fields (Tanji, 1985; Godshalk *et al.*, 1985; Mauritz and Wise, 1986), because we have shown that prefrontal neurons exhibit increased or decreased discharge only for targets in specific locations within the visual field (see Fig. 2). We have termed this directionally specific activity the "memory field" of a prefrontal neuron (Funahashi *et al.*, 1989). Thus, even though an animal is set to and does respond correctly at the end of the delay period on every trial, regardless of target location, any given neuron is attuned to only one or a few locations. A general motor set explanation cannot easily explain this result.

If prefrontal neurons are involved in mnemonic processing, one would expect their activity to be sensitive to changes in the duration of the delay period. Indeed, it has been shown that the activity of prefrontal neurons that occurs during the delay period expands and contracts as the delay is lengthened or foreshortened (Kojima and Goldman-Rakic, 1982). Again, this would be expected if the neuron is holding information "on line" that is to be retained until the end of the delay period.

Finally, if prefrontal neurons were coding only a preparatory set to respond, one would expect them to be activated before incorrect as well as correct responses. However, neurons that have memory fields, i.e., have a "best direction" of discharge, either falter in activity during the delay or even completely fail to increase their rate preceding responses in the nonpreferred incorrect direction (Fig. 3, Funahashi *et al.*, 1989). The fact that incremental firing precedes only correct responses indicates that the activity may be part of the internalized code needed to guide the correct response. Thus, it would serve a mnemonic function.

Neural Networks Subserving Working Memory

The principal sulcus in the prefrontal cortex is the anatomical focus for spatial delayed-response function, and knowledge of its connections

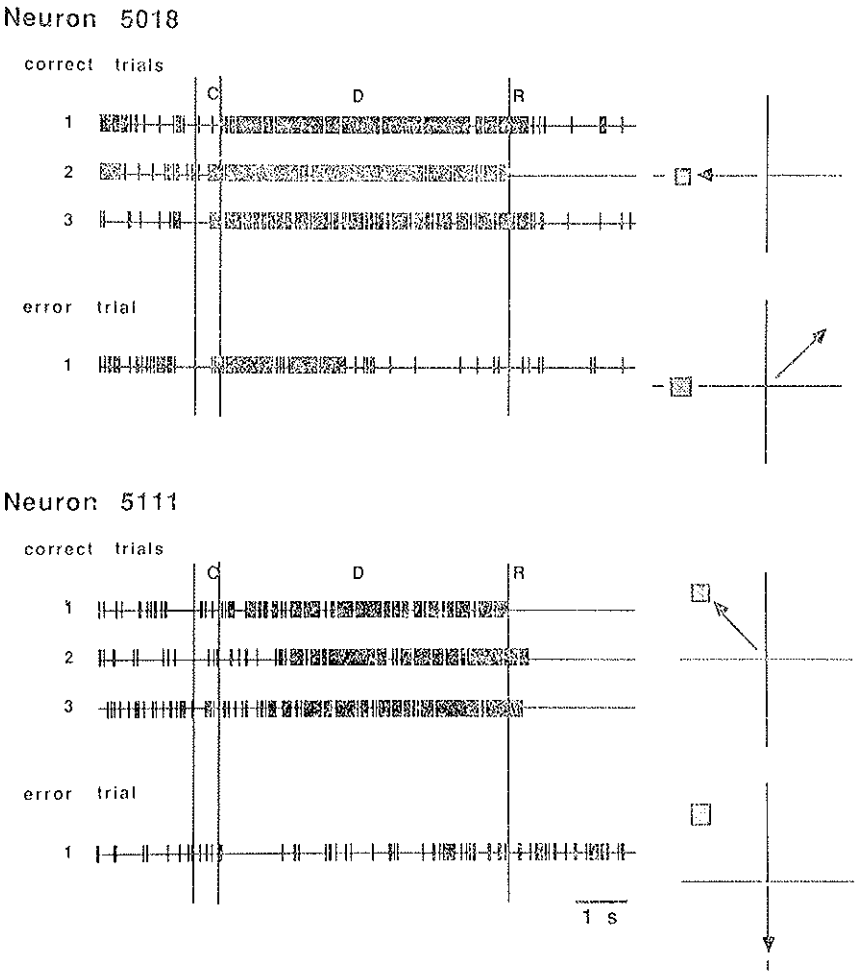

FIG. 3. Discharges of two principal sulcus neurons with directional delay period activity during correct performance on the oculomotor delayed-response task and during trials with errors. For each trial depicted, discharge traces are shown on the left and cue locations and saccade directions are shown on the right. *Top*: The neuron's (5018, right hemisphere) strongest delay period activity was associated with leftward cue presentations. On an error trial, its discharge ceased about midway through the delay period. *Bottom:* This neuron's (5111, right hemisphere) strongest delay period activity was associated with cue presentations in the upper-left visual field. On an error trial, its discharge in the delay period was absent.

with other structures is helping to understand the circuit and cellular basis of working memory. It has become clear from our anatomical investigations that this prefrontal subdivision has reciprocal connections with more than a dozen distinct cortical association regions, with premotor centers, with the caudate nucleus, superior colliculus and brain stem centers (for review see Goldman-Rakic, 1987b). Each of these connections presumably contributes different subfunctions to the overall capacity to guide a response by the mental representation of a stimulus. Elsewhere I have suggested that the reciprocal connections between the prefrontal and parietal cortex carry information about the spatial aspects of the outside world (Goldman-Rakic, 1987a). In studies conducted with C. Cavada, we have traced several pathways from distinct visual centers concerned with peripheral vision to the principal sulcus via relays in the posterior parietal cortex (Cavada and Goldman-Rakic, 1989a; 1989b). By our anatomical account, the principal sulcus is but three synapses removed from the primary visual cortex.

Connections with the caudate nucleus (Goldman and Nauta, 1977b; Selemon and Goldman-Rakic, 1985) and superior colliculus (Goldman and Nauta, 1976), among other motor centers, are thought to play a role in transmitting directional commands to the motor centers. The principal sulcus projects to premotor centers, including the supplementary motor areas, and through these centers has access to the primary motor cortex (Goldman-Rakic, 1988). Therefore, these latter connections of the principal sulcus place it but two synapses removed from primary motor neurons.

Finally, the mechanism for holding information "on line" in the short-term memory buffer is unknown at this point and it is unclear what role any of the connections which the prefrontal cortex has with limbic memory centers, play in this process. We have described several multisynaptic routes of connectivity between the prefrontal cortex and the hippocampal formation and have speculated that these connections imply a cooperative relationship between the hippocampus and the prefrontal cortex with regard to working memory (Goldman-Rakic *et al.*, 1984). Our recent evidence of elevated metabolic activity in the dentate gyrus and the several fields of Ammon's horn in monkeys performing working memory tasks support this line of thinking (Friedman and Goldman-Rakic, 1988). Also, increased neuronal activity during the delay period of delayed-response tasks has been recorded from neurons in Ammon's horn (Watanabe and Niki, 1985). Finally, working memory tasks like nonmatching-to-sample are just the type of task that is impaired in

monkeys with lesions of the hippocampus (e.g., Mishkin, 1982). In the matching tasks, as in delayed-response tasks, information (the sample) is relevant only for one trial, and each trial is independent from the last. It seems clear that the hippocampus and prefrontal cortex are functionally as well as anatomically related. Thus, the cellular and molecular mechanisms underlying hippocampal physiology discussed in this volume by Anderson may well be helpful in explaining the reverberating activity in prefrontal neurons. The interaction of these two structures is an exciting area for future investigation.

Modular Organization of Networks

It has been recognized since the mid-seventies that both thalamo-cortical and cortico-cortical connections are organized in a columnar or stripe-like fashion (Hubel and Wiesel, 1977; Goldman and Nauta, 1977a; Goldman-Rakic and Schwartz, 1982). These findings have led to the theory of the modular operation of the neocortex (e.g., Mountcastle, 1979; Eccles, 1984; Szentágothai, 1983). Some new findings relevant to these theories have recently been revealed by the use of double anterograde labeling strategies, in which two distinct tracers were injected into the prefrontal and posterior parietal cortex in the same animal (Selemon and Goldman-Rakic, 1988). Our study produced the surprising finding that prefrontal and parietal afferents converge in virtually every cortical target to which each area independently projects (Fig. 4). The areas of convergence include: (1) the superior temporal sulcal cortex; (2) the insular cortex; (3) the fronto-parietal operculum; (4) the orbital prefrontal cortex; (5) the anterior arcuate cortex; (6 and 7) the ventral and dorsal subdivisions of premotor cortex; (8) the supplementary motor cortex (Brodmann's medial area 6); (9) the anterior cingulate cortex; (10) the posterior cingulate cortex; (11) the medial parietal cortex; (12) the medial prestriate cortex; (13) the caudomedial lobule; (14) the presubiculum; and (15) the parahippocampal gyrus. [Further, each target that receives a prefrontal or parietal projection issues a reciprocal projection (Selemon and Goldman-Rakic, 1988)].

Convergence takes several forms related to the columnar organization of the cortex. In the superior temporal and temporal opercular cortex, parietal and prefrontal efferents assume complementary positions within different laminae of the same cortical column(s) (Fig. 5). In these areas, the parietal efferents are most concentrated in layers IV and VI,

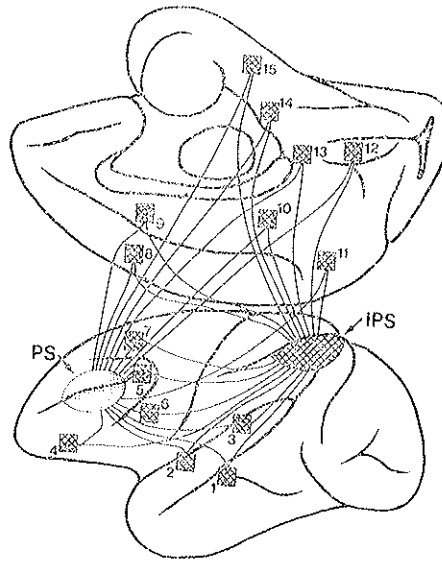

FIG. 4. Summary diagram of lateral and medial views of the cerebral cortex illustrating the approximate location of injections (^{3}H-AA, tritiated amino acids in prefrontal cortex and WGA-HRP in the posterior parietal cortex) in one of the three double label cases) of one of the cases examined in this study. The injection in prefrontal cortex extended into both banks of the caudal two-thirds part of the principal sulcus [Brodmann areas 9 and 10; Walker's area 46 (Walker, *J. Comp. Neurol.* 73:87-115, 1940)]; the parietal injection was confined to the area between the intraparietal and superior temporal sulcus and thus encompassed Brodmann's area 7; the figure depicts the fifteen cytoarchitectonic regions (marked 1-15) that were sites of double anterograde labeling, i.e., the sites where prefrontal and parietal afferents converged. The numbers on the figure correspond to the order in which target structures are mentioned in the text. The locations of some of the target areas (e.g., 1, 2, 3, 13, and 14) are indicated only roughly because the projection sites are buried in the sulci and cannot be seen on the surface view. PS, principal sulcus; IPS, intraparietal sulcus.

while prefrontal efferents terminate preferentially in layers I, III and V in a group of cortical columns (Fig. 5). Variations on this pattern (occupation of different combinations of laminae by prefrontal and parietal terminals) are observed in the insular cortex and parahippocampal gyrus. To our knowledge, these findings are the first indication of a stacking pattern of two distinct cortical projections in the same column of a third neocortical area. Although superimposition of two inputs does not in itself constitute evidence of convergence on a single cell, the finding that prefrontal and parietal projections terminate in complementary layers

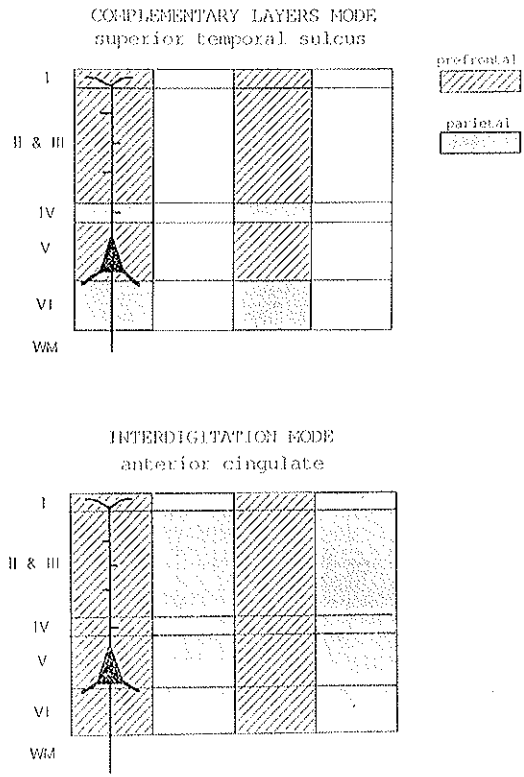

FIG. 5. Modes of distribution of prefrontal and parietal projections in "third" party targets. In the superior temporal sulcus, and also in the fronto-parietal operculum, the two areas of cortex project to different layers of the same columns: prefrontal cortex mainly to layer I and less densely to layers III and V; parietal afferents terminate heavily in layer IV. By contrast, in anterior cingulate (and other medially situated) cortex, parietal and prefrontal fibers both terminated in a more diffuse manner across the depth of the cortex but in adjacent columns.

within a given cortical column raises this possibility for future investigation. In all other convergence areas, with the exception of the presubiculum (where afferents were superimposed), the prefrontal and parietal afferents terminated in the same layers (I-VI) of adjacent, sometimes overlapping, sometimes interdigitating, columns approximately 0.5-1.00 mm in width. An example is the supplementary motor area, where parietal and prefrontal efferents extended throughout the cortical thickness, being most concentrated in layer I and least in layer IV (Fig. 4).

The pattern of prefrontal and parietal afferents is reminiscent of the organization of ocular dominance columns or the interdigitation of callosal and associational columns and shows that the alternation of afferents can apply to two separate sources of connections within one hemisphere and is not simply a means of interocular or interhemispheric integration. Interactions of the two pathways with each other as well as with their targets could be achieved both directly or through interneurons (Szentágothai, 1983).

Our study revealed that the two areas covered by our injections — the caudal principal sulcus and posterior parietal cortex — converge at fifteen cortical points, but did not resolve the question of the minimal cortical unit of convergence. It seems to us unlikely that a single neuron in parietal or prefrontal cortex sends a collateral axon into every one of the divergent targets. However, it may not be unreasonable to suppose that different subsets of neurons within a cortical column can project to distinct targets or perhaps cells in adjacent columns have their preferential cortical targets. Our working hypothesis is that separate neurons within each cytoarchitectonic area contact each of the dozen or more targets and that these neurons may be concentrated in different columns, much as alternating thick and thin cytochrome oxidase-defined stripes in V2 project to visual areas V4 and V5, respectively (Shipp and Zeki, 1985) and adjacent columns of cells in the principal sulcus project to the contralateral principal sulcus and ipsilateral parietal cortex, respectively (Schwartz and Goldman-Rakic, 1982). Finally, we think it unlikely that the network of association cortical connections described by our double label study is the only such network in cerebral cortex. One can envisage that connections between a posterior "sensory" association area and an anterior "motor" association area interconnected with a dozen or more other cortical areas represent a general plan for the association cortical networks and that a number of such networks may be organized in parallel.

Sensory vs. Memory Guided Behavior: Evolutionary Significance of Working Memory

The type of behavioral regulation subserved by working memory can be contrasted with classical conditioning and the formation of simple stimulus-response associations which depend in an obligatory manner on the repeated association of stimulus-response pairings and/or the strength,

duration and frequency of stimuli in the environment. Indeed, the evolution of a capacity for representational knowledge may provide a mechanism for overriding the governance of behavior by conditioning or by reflexive or innate or prepotent responses whenever such behavior could be maladaptive for the organism. The fact that delayed-response impairments produced by prefrontal lesions can be severe at delays of 1-2 sec. between stimulus and response and yet be absent at nil delays suggests a sharp dissociation in the neural mechanisms that mediate representational versus sensory guidance of behavior (Goldman, 1971). A data-holding capacity such as has been ascribed to working memory would allow information coming in at one point in time to be held "on line" and connected to information occurring after many seconds. In contrast, the operations of classical conditioning are designed to establish permanent associations between events occurring within less than 1 sec. of each other. Finally, efficient representational memory allows information to be dismissed as efficiently as it is accessed; this type of memory demands a flexible, nonbinding relationship between a given stimulus and a given response. If anything, then, the mechanisms of prefrontal cortex would be antithetical to the requirements of conditioning, as behavioral regulation by conditioning requires that the same stimuli be repeatedly associated with the same responses and reward contingencies.

The functional dissociation of conditioned and conditional responses is supported by anatomical localization studies. Certain types of classically conditioned behaviors are spared by decortication while neural circuits underlying classical conditioning have been localized to cerebellar structures, amygdala, brain stem, and spinal cord (for review see Thompson *et al.*, 1985). It therefore seems possible that there is a division of labor between the prefrontal cortex and other areas of cortex and/or subcortical structures; the type of behavior which utilizes memory in the representational sense requires participation of the cerebral cortex, whereas that involving classical conditioning may rely on cerebellar and other nontelencephalic mechanisms. The evolution of a capacity to guide behavior on the basis of representations of the outside world rather than on the trigger of immediate stimulation introduces the possibility that concepts and plans may govern our behavior. One way they may do so is by regulating, facilitating or inhibiting the associatively conditioned or reflexly organized responses of motor centers to which the prefrontal cortex projects (Goldman-Rakic, 1988).

The capacity to guide behavior by mental representations is not easily

won: prosimian primates have much greater difficulty learning delayed-response tasks than do rhesus monkeys and some normal galagos even fail to learn this task (Preuss and Goldman-Rakic, unpublished observations). The galago seems to respond to the first foodwell that catches its eye or to the just previously reinforced side rather than to recently stored information about the location of the reward. Cats and dogs are not able to perform delayed-response tasks given in the same manner as they are given to monkeys. Only if the animals are allowed to keep the hidden object *in view* during the delay period as in a Nencki test apparatus, is delayed-response performance attained (Warren *et al.*, 1972). The opportunity to view the desired object or even a discriminative cue during the delay period could obviate the whole purpose of the delayed-response task (Goldman-Rakic and Preuss, 1988). The description, "out of sight; out of mind" (Jacobsen, 1936) or "animal of the moment" (Bartus and Levere, 1977) applied to the mindless performance of frontal lobe patients or experimentally lesioned animals can also characterize the sensory-dominated behavior of intact animals with poorly developed frontal lobes.

Working Memory and Conscious Experience

If the phenomenon of consciousness involves the ability to bring past experiences to mind for the purpose of contemplation, thought or action, then it is difficult to conceive of a neural basis more suited than one which is activated during contemplation, thought and preparation for action. As pointed out at this conference, consciousness is possible only in the context of the present; the storage of past events is useless if they cannot be brought to bear in the context of ongoing actions. In this respect, the working memory modules of the prefrontal cortex offer a potentially fruitful neural model for conscious phenomena.

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DISCUSSION

INGVAR

I have a question about these neurons that apparently memorize things. Is there an upper time limit for their discharge?

GOLDMAN-RAKIC

We don't know what the upper time limit is because the animals will not perform very well for us if we extend the delay beyond 4-5 sec. We have never found a unit holding information over a delay that the animal couldn't perform well at.

ZEKI

I get the impression from your results that you have a massive projection to the temporal lobe from the parietal cortex, which is exactly what Boullier has found and what we have found, with the difference that your projection is to the medial side of the temporal lobe.

GOLDMAN-RAKIC

There are reciprocal connections to the lateral temporal lobe and the superior temporal sulcus bilateral which might indicate that the parietal cortex has information about object vision as well as spatial vision.

ZEKI

Now the other point is: I thought I heard you say there was anterograde label in layer 4 and layer 1 of the temporal cortex.

GOLDMAN-RAKIC

Layer 4 is the territory or target of the parietal; the supragranular and infragranular layers were the target in this instance of the prefrontal. In other

words, in the temporal lobe, the parietal cortex was the feedforward and the prefrontal the feedback.

ZEKI

I see. That picture that you showed is not the typical one. I don't know if Ted Jones wants to comment on that. It's not the typical feedforward type, is it?

JONES

I think it's just another example in which we too readily accept these statements, feedforward and feedback, from one particular system, that is the visual system. Personally I do not believe that they are represented in that form necessarily in any other part of the cortex.

MOUNTCASTLE

These areas are several junctions away from primary central input. The phrases upper and lower, forward and backward mean nothing in a distributed system.

GOLDMAN-RAKIC

I agree with you that we have to say what is the information represented in each layer, and we won't know that until we record from those areas. But we can at least think of layer 4 as being an important input layer because that's where you have granule cells.

NEURONAL DEGENERATION AND MEMORY LOSS IN ALZHEIMER'S DISEASE AND AGING

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SUMMARY — The aging brain shows a modest decline in weight. Evidence is controversial as to whether this is associated with significant cortical neuronal loss. Several subcortical neuronal populations, including the cholinergic nucleus basilis of Meynert, the noradrenergic locus coeruleus and the dopaminergic substantia nigra pars compacta, which have diffuse projections to the neocortex, show distinct losses with age. In Alzheimer's disease, there are substantial losses of neocortical pyramidal neurons, in addition to subcortical neuronal groups which project diffusely to the neocortex. Areas receiving cortical afferents are relatively spared. Such data favor the hypothesis of retrograde spread of the disease. The entorhinal cortex, hippocampus and amygdala are sites of early involvement. In vivo correlation with the cortical neuronal losses is possible using the technique of positron emission tomography (PET). Metabolic rates for localized regions of the cerebral cortex determined by PET using ^{18}F-fluorodeoxyglucose as the imaging agent, indicate little change in normal aging but substantial regional deficits in Alzheimer's disease. These deficits are greatest in the parietal, temporal and frontal cortices and parallel areas reported to show the greatest neuronal losses postmortem. They are also the anatomical areas known to be the last to myelinate postnatally. In addition, there appears to be a significant cortical asymmetry in metabolic deficit, with left-sided decrements being more prominent than right. The etiology of Alzheimer's disease is unknown, but responses of the immune system indicate a chronic inflammation of brain tissue. Large numbers of HLA-DR positive reactive microglia, as well as T-lymphocytes of the helper-inducer and cytotoxic-suppressor subclasses, are found in areas affected by the disease process.

Introduction

This chapter will review briefly the state of knowledge regarding neuronal loss in the neocortex and in certain subcortical nuclei which project diffusely to it, providing distinct neurotransmitter innervation. Alzheimer's disease will be discussed in terms of its selective effect on

mental processes while leaving, at least in the early stages, sensory and motor functioning relatively intact. The types of neurons, both cortical and subcortical, that are preferentially diseased will be described. The use of positron emission tomography as a tool for providing in vivo correlations of metabolic state with psychological functioning, and ultimately of neuronal pathology, will be summarized. Finally, the role of the peripheral immune system in the pathogenesis of Alzheimer's disease will be discussed.

Neuronal Losses in Aging

The inability of neurons to divide renders the nervous system the most susceptible of any organ to damage of all kinds. In late embryological and early postnatal life, there is modeling of brain connections which involves extensive neuronal pruning. This is followed by long-term stability of neuronal populations, although there is evidence for considerable plasticity of their synaptic connections (for a review, see McGeer, Eccles and McGeer, 1987). Nevertheless, neuronal attrition occurs in some brain areas during life in the absence of any known disease process. Figure 1 demonstrates dramatic losses with aging of three types of neurons in three different areas of brain. These are the cholinergic neurons of the nucleus basalis of Meynert (NBM), the dopaminergic neurons of the substantia nigra pars compacta (SNC), and the noradrenergic neurons of the locus coeruleus (LC). The NBM contains 400,000 to 500,000 neurons at birth (McGeer *et al.*, 1984), and is the principal source of cholinergic innervation of the neocortex. The SNC has a similar complement of dopaminergic neurons (McGeer *et al.*, 1977). It provides innervation of the neostriatum. The LC has fewer than one-tenth as many neurons (Vijayashankar and Brody, 1979). It provides the principal noradrenergic innervation for both the forebrain and the cerebellum (Ungerstedt, 1971). The rate of drop-out of cells from these three groups is strikingly similar. By age 70, only about half of the initial complements remain. It is evident that these particular cell groups, possibly because of the unusual metabolic demands of their wide terminal arborizations, are particularly vulnerable to the aging process.

Much less is known about the rate of cell loss with age in the neocortex. Numerous computerized tomographic (CT) and magnetic resonance imaging (MRI) studies of the past decade have established that CSF volume

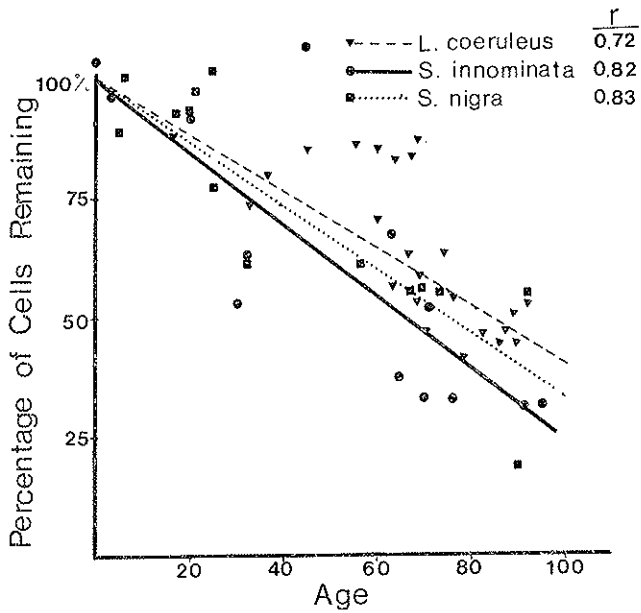


FIG. 1. Percent of neurons remaining versus age in three areas of human brain. Initial values for the locus coeruleus are 30,000 (Vijayashankar and Brody, 1979); 450,000 for the substantia innominata (NBM) (McGeer *et al.*, 1984); and 450,000 for the substantia nigra (McGeer *et al.*, 1977).

increases with age, being relatively modest before age 60 but increasing in an exponential fashion thereafter (for a review see McGeer, 1986). This indicates the possibility of substantial neuronal loss, although simple shrinking of tissue could also account for the changes. Terry *et al.* (1987) in a careful study of clinically and neuropathologically normal individuals ranging in age from 24 to 100 years, found brain weight to decrease with age, consistent with the CT and MRI studies in vivo, but total neuronal counts to be unchanged. Shrinkage of large neurons was observed, which could account for the loss in tissue weight. However, in other studies relatively large cortical neuronal losses have been reported. Anderson *et al.* (1983) concluded that neuronal losses of around 1% per annum occurred in the neocortex and medial hippocampus between the ages of 69 and 95 years. Devaney and Johnson (1980) reported neuronal population densities in the visual cortex fall from 46 million neurons per gram of tissue at age 20 to 24 million at age 80. By contrast, Leuba and Garey (1987) reported a slight increase in density in the visual cortex, from

about 35 million neurons per gram in young adults to 44 million at age 80. Further studies are clearly required to establish whether cortical neuronal dropout, uncomplicated by any neuropathological process, occurs in aging.

Neuronal Losses in Alzheimer's Disease

Alzheimer's disease is the most common pathological cause of neuronal loss in the aging population. For this reason, it is also one of the major medical problems of our time. It is relatively uncommon before age 65, but it may affect as many as one-third of individuals over age 80. Recent memory, interpretative ability and abstract reasoning are sharply affected. At least in the early stages, consciousness, as well as primary sensory and motor functions, with the possible exception of the olfactory system (Pearson *et al.*, 1985; Mann *et al.*, 1987), are relatively undisturbed. Thus, an understanding of the relationship between the early pathology of Alzheimer's disease and functional deficits should provide neuroscientists with insight into aspects of higher order intellectual functioning that are not readily accessible by animal experimentation.

Alzheimer's disease is characterized not only by significant neuronal losses, but also by the almost unique pathological combination of neurofibrillary tangles and senile plaques. The senile plaques have an amyloid core which has a different protein make-up from that seen in other forms of amyloidosis (Glenner and Wong, 1984; Selkoe *et al.*, 1986). The only other condition displaying such pathology is Down's syndrome. It has long been noted that an apparent familial relationship exists between Down's and Alzheimer's disease, although Down's is a much rarer syndrome. The reason for mental deficiency in Down's is still unknown. Recently, a genetic linkage has been demonstrated in some families having early onset dominant Alzheimer inheritance with RFLP markers on chromosome 21, possibly accounting for the familial relationship with Down's syndrome (St. George-Hyslop *et al.*, 1987). However, such linkage does not occur in some other families (Schellenberg *et al.*, 1988), and it would appear as if the beta-amyloid precursor protein, also located on chromosome 21, has been ruled out as a cause (Tanzi *et al.*, 1987; Van Broeckhoven *et al.*, 1987).

Considerable literature now exists as to the types of neurons most vulnerable in Alzheimer's disease. These are the pyramidal neurons of

layers II, III and V of the cortex (Terry *et al.*, 1981; Pearson *et al.*, 1985), as well as certain subcortical populations (Mann *et al.*, 1986).

Of the subcortical populations, the NBM cholinergic neurons are highly vulnerable (Whitehouse *et al.*, 1981; McGeer *et al.*, 1984). However, noradrenergic neurons of the LC, serotonergic neurons of the raphe system and histamine neurons of the hypothalamus have also been reported to be severely affected (Mann *et al.*, 1986). Thalamic neurons, particularly those of the midline nuclei, are also affected, but their biochemical classification is unknown (McDuff and Sumi, 1985). These neuronal groups differ in their neurotransmitters, but have in common diffuse projections to the neocortex.

As far as neocortical populations are concerned, there are regional as well as cortical layer differences in vulnerability. The superior parietal lobule, and medial temporal, inferior temporal and certain frontal cortical areas are disproportionately diseased (Brun and Englund, 1981; Pearson *et al.*, 1985; Terry *et al.*, 1981). Within the visual cortex, layers II, III, IVa and IVcβ seem to be the most affected (Beach and McGeer, 1988); the latter may account for the deficits in color vision reported in Alzheimer's disease (Cohen *et al.*, 1988; Sadun *et al.*, 1987). Still other regions may be the ones initially affected. Layer II of the entorhinal cortex, and the amygdala are said to be the site of earliest lesions in both Alzheimer's disease and Down's syndrome (Mann and Esiri, 1988).

Two questions are of particular importance in assessing these data. The first is whether any clues are offered as to the method of spread of the disease. The second is what functional contribution is made by these various cell masses to the higher cognitive functions which are especially affected in Alzheimer's disease.

The pattern of pathology would favor the hypothesis of a retrograde spread of the disease process. Subcortical areas projecting to the neocortex are heavily affected, despite differing anatomical localizations and neurotransmitter physiologies. Also heavily involved are pyramidal neurons associated with long cortico-cortical interconnections (Pearson *et al.*, 1985). Non-pyramidal neurons, associated with cortical circuitry, are spared, as are areas receiving heavy cortical projections, such as the neostriatum and pontine gray matter. The site of initiation is in doubt, but the early and heavy involvement of the entorhinal cortex and amygdala has suggested to some that it may be the olfactory system (Mann *et al.*, 1987; Pearson *et al.*, 1985).

The contribution of the various cell masses affected in Alzheimer's

disease to the functional deficits is equally in doubt. A prominent theory relates the memory loss to the cholinergic neuronal deficit (Bartus *et al.*, 1982; Whitehouse *et al.*, 1981; Perry *et al.*, 1978). However, results with acetylcholinesterase antagonist therapy (Moss and Rodriguez, 1987), designed to enhance cholinergic activity, have generally been disappointing. A major contributor to short-term memory loss may be pathology in the perforant pathway from the entorhinal cortex to the CA-1 area of the hippocampus. Such a lesion bilaterally produced short-term memory loss in the well-known case of R.B. (Zola-Morgan *et al.*, 1986). Deficits in interpretative capability and abstract thinking may be related to pathology in the parietal and frontal cortices, respectively.

Substantial cell losses have been recorded in these areas in Alzheimer's disease on postmortem examination (Brun and Englund, 1981; Mann *et al.*, 1987; Pearson *et al.*, 1985). Pyramidal neurons are the principal type lost in these cortical areas. Phosphate-activated glutaminase has been shown to be an immunohistochemical marker for cortical and hippocampal pyramidal neurons (Kaneko *et al.*, 1987). Table 1 offers some very preliminary data we have recently obtained on a small sample of Alzheimer cases. In these cases, phosphate-activated glutaminase was measured in numerous cortical areas and compared with choline acetyltransferase activities in the same samples. The data show heavy losses of both enzymes, but in these cases glutaminase was reduced to 18% of normal while ChAT was reduced to only 28% of normal. These data imply, but certainly do not establish, that losses of cortical glutamate neurons are even heavier in Alzheimer's disease than the losses of subcortical cholinergic cells.

TABLE 1 - *Mean* (±S.E.) *choline acetyltransferase* (ChAT) *and glutaminase activities in cortical samples from cases of Alzheimer's disease and neurologically normal controls.**

Type of Case	Number of Cases	Number of Samples	Glutaminase	ChAT
Controls	3	20	50.20 ± 13.12	0.57 ± 0.05
Alzheimer	3	48	9.11 ± 0.97*	0.16 ± 0.02*
			18%	28%

* Significantly different from control at $p < 0.001$. Activities are in μmoles/hr-100 mg protein.

Positron Emission Tomography

Positron emission tomography (PET) is a technique well suited to the study of *in vivo* brain function in health and disease. Numerous PET studies have been conducted in normal aging and on clinically diagnosed Alzheimer cases using ^{18}F-2-deoxy-2-fluoro-D-glucose (FDG) uptake (rCMR), $^{15}O_2$ oxygen consumption (rCMRO$_2$), or ^{15}O-H_2O (rCBF) as imaging agents. In some studies, modest decrements with age have been reported (Frackowiak, 1987), while in others no significant age effect has been found (De Leon *et al.*, 1987; Duara *et al.*, 1984). However, significant regional brain deficits in uptake and metabolism of these compounds have been consistently recorded in Alzheimer's disease. These have been correlated with various signs and symptoms of the disease (see Cutler, 1986; Haxby and Rapoport, 1986; McGeer, 1986 for reviews). All studies, including the one reported here, have yielded essentially comparable results. There is a substantial deficit in energy metabolism and blood flow in affected regions, varying according to the severity of the disease. Temporal, parietal and frontal lobes are severely involved. These regions are not equally affected in all individuals, and frequent bilateral asymmetries occur (Grady *et al.*, 1986; Perlmutter *et al.*, 1987; Reivich *et al.*, 1983; McGeer *et al.*, 1986a). Some correlation exists with the areas of greatest metabolic deficit and the nature of the neuropsychological loss. For example, deficits in memory have been correlated with low metabolic rates in the temporal lobe, interpretive deficits with the parietal lobe, and cognitive deficits with the frontal lobe.

One problem with these studies is that the diagnosis of Alzheimer's disease is presumptive. We have performed 34 PET scans on 26 consecutive clinically diagnosed Alzheimer cases using FDG as the scanning agent. Six of these cases were established to be Alzheimer's disease at later autopsy, and two of the six were in the group that had received multiple scans. They were compared with 11 age-matched controls. The results are summarized in Figure 2. Local cerebral metabolic rates of glucose (LCMR) for each region of interest are plotted for the controls (open circles) and the Alzheimer cases (filled circles). Odd numbered areas are for the left hemispheric regions and even numbered areas for the corresponding right hemispheric regions. The graph shows reduced metabolism in every area for the Alzheimer cases but it also shows more severe deficits in the temporal, parietal and frontal areas. The graph also demonstrates a lower average LCMR in the left hemispheric areas of the

Alzheimer cases, and even a tendency to lower left hemispheric values in some areas of the normals. The data suggest that the left hemisphere, and particularly the parietal and temporal areas, are the most vulnerable to the pathological changes which characterize Alzheimer's disease. Of the 26 cases averaged in Figure 2, 20 had predominantly left hemispheric deficits, while only 3 had predominantly right hemispheric. The remaining 3 showed no hemispheric asymmetry.

The pattern of cortical CMR reduction seen by PET-FDG corresponds well with cerebral areas reported by Fleichsig in 1920 to be the last to myelinate (J.C. Eccles, personal communication). The pattern of reduction also corresponds with areas previously reported by Brun and Englund (1981) to show the greatest neuronal loss in Alzheimer's disease (cf. Figure 3). We have previously noted a correspondence between the degree of gliosis and loss of metabolism by PET-FDG in an autopsied Alzheimer case (McGeer *et al.*, 1986b).

In general, repeat scans of Alzheimer cases demonstrate a progressive loss of metabolic rate in all areas of the cortex. This is universally ac-

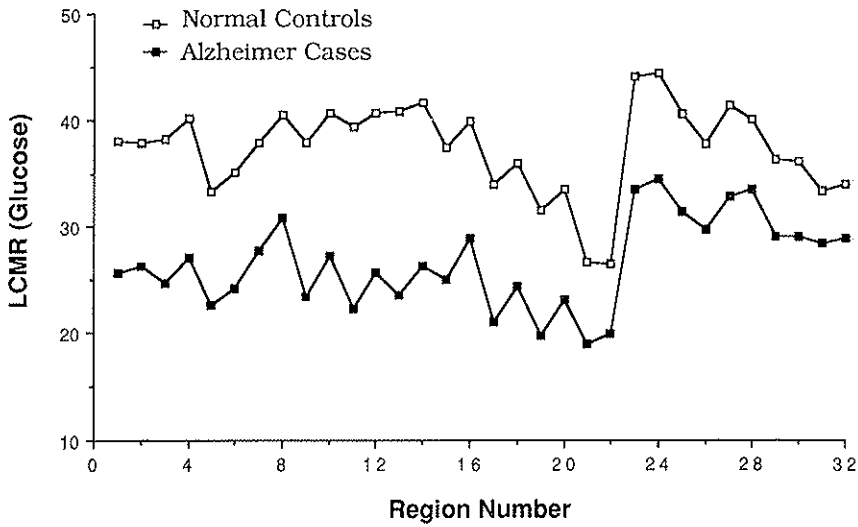
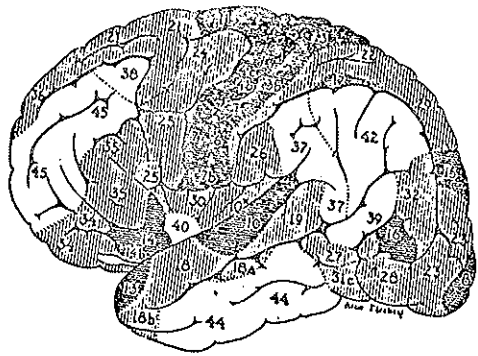
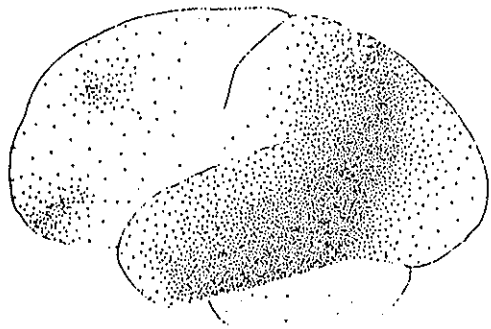


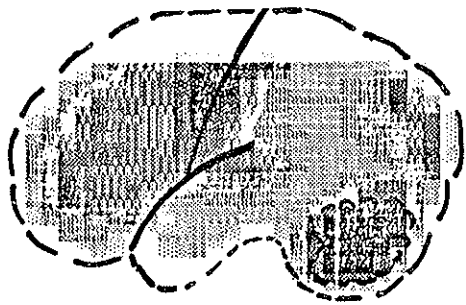
FIG. 2. Plot of cerebral metabolic rates for control (□) and Alzheimer (■) cases in 32 regions of interest. Odd numbered regions are in left hemisphere and even in right. 1-2, superior frontal; 3-4, middle frontal; 5-6, orbitofrontal; 7-8, pericentral; 9-10, supramarginal; 11-12, angular; 13-14, superior parietal; 15-16, superior temporal; 17-18, middle temporal; 19-20, inferior temporal; 21-22, medial temporal; 23-24, medial occipital; 25-26, caudate; 27-28, putamen; 29-30, thalamus; 31-32, cerebellum.



A. MYELINATION



B. ALZHEIMER PATHOLOGY



C. PET-FDG METABOLISM

FIG. 3. Comparison of time of cerebral myelinization, cell loss in Alzheimer's disease and metabolic rate as determined by PET-FDG scanning. A Myelinization (Fleichsig, 1920). The lighter the shading, the later the myelinization. Note the retarded myelinization in the parietal, inferior temporal and midfrontal regions. B. Severity of cortical neuronal cell loss in Alzheimer's disease (Brun and Englund, 1981). The heavier the stippling, the greater the cell loss. C. Sagittal reconstruction of PET-FDG scan in an autopsy-proven Alzheimer case. The lighter the shading, the lower the metabolism. Blank areas in the most dorsal and ventral brain represent regions outside the scanning fields. Notice in the figure that the areas most retarded in myelinization are those most prone to neuronal loss in Alzheimer's disease. They are also the areas showing the greatest decrement in glucose metabolism in vivo.

companied by a deteriorating mental state. Such losses in a typical case are shown in Figure 4. This figure demonstrates the loss in metabolic rate in the left temporal lobe in a case where a PET scan was repeated 11 months after an initial scan, and where an autopsy was performed following death 9 months later. The figure shows the decline from the assumed normal rate of metabolism at the time of first clinical symptoms to the assumed rate at the time of death. From curves of this type, it should be possible to predict the number of surviving neurons and compare these with the actual levels measured. In Figure 4, the calculated metabolic rate for glial cells is taken from affected areas in stroke cases where it is presumed there are no surviving neurons. More reconstructions of the type shown in Figure 4 will become available over time. From them, it should be possible to make better correlations between functional deficits and neuronal losses than are now possible. However, PET is not sufficiently sensitive to assess the contribution of smaller areas such as the subcortical masses shown in Figure 1, or even larger areas such as the hippocampal formation, to deficits in function that are believed to be primarily neocortical.

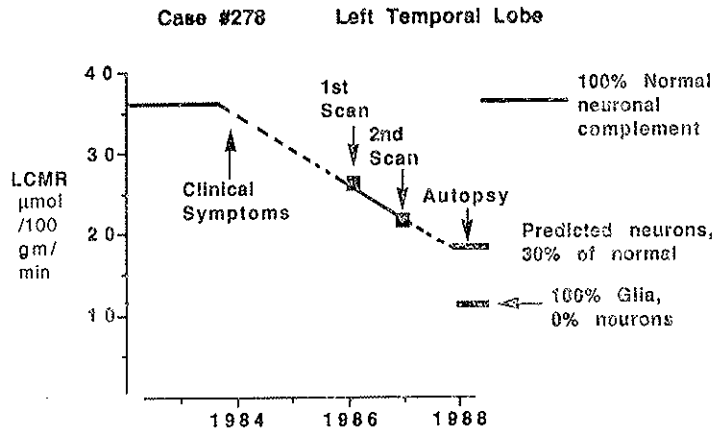


FIG. 4. Changes in cerebral metabolic rate with time in the left temporal lobe on serial PET-FDG scanning in an autopsy-proven case of Alzheimer's disease. The time of onset of symptoms is indicated on the graph. The assumed initial metabolic rate is the average for normal cases in an age-matched control group. The value assumed for metabolic rate at death is a linear projection from the values of the two scans. Minimal metabolic rates, which are presumed to reflect residual glial cells, are those obtained on stroke cases where neuronal tissue has been destroyed.

Etiology and the Role of the Immune System in Alzheimer's Disease Pathogenesis

The data in the preceding sections provide little insight into the actual cause of Alzheimer's disease. Different techniques will be required to cast light upon that problem. There are many theories as to the cause, including pathogens, toxins, an autoimmune disorder, or merely genetically programmed cell death. As yet, none of these interesting hypotheses can be discarded. However, if the disease is due to a pathogen, an autoimmune disorder, or even the widespread production of an abnormal protein, an appropriate response of the immune system might be anticipated.

As one approach to the pathogenesis, we have explored the response of the peripheral immune system to the Alzheimer process. We have identified in Alzheimer brain tissue the presence of large numbers of reactive microglia expressing the MHC class II glycoprotein HLA-DR (McGeer *et al.*, 1987). Some of these reactive microglia are apparently engaged in phagocytosis, and they are particularly congregated near the cores of senile plaques (Figure 5A). They are a different population from the reactive astrocytes, also shown in the figure, which congregate around the periphery of the plaque. The reactive astrocytes stain for glial fibrillary acidic protein (GFAP), and are presumably responsible for laying down the fibrous tissue which is the residuum of neuronal loss.

The function of HLA-DR in the reactive microglia is not known, but it is a surface glycoprotein expressed only by immunocompetent cells. One known function is to present foreign antigen to T-lymphocytes. We have also detected T-lymphocytes in Alzheimer tissue, both in post-capillary venules and in the tissue matrix itself (Figure 5B) (Itagaki *et al.*, 1988). The capillary in the figure is stained by an antibody to a common structural element of MHC class I (HLA-A,B,C) glycoproteins. In addition, we have found significant numbers of cells staining for common leucocyte antigen in Alzheimer brain tissue, as well as the interleukin-2 receptor (data not shown). Interleukin-2 is a lymphokine elaborated by activated T-cells, which stimulates the immune response. It is known to induce MHC class II expression in immunocompetent cells.

The schematic diagram of Figure 6 is a proposed interaction of brain tissue with the immune system in diseases such as Alzheimer's where there is a chronic inflammation. Many of the steps are yet to be established for brain, although the general scheme for presentation of foreign antigen

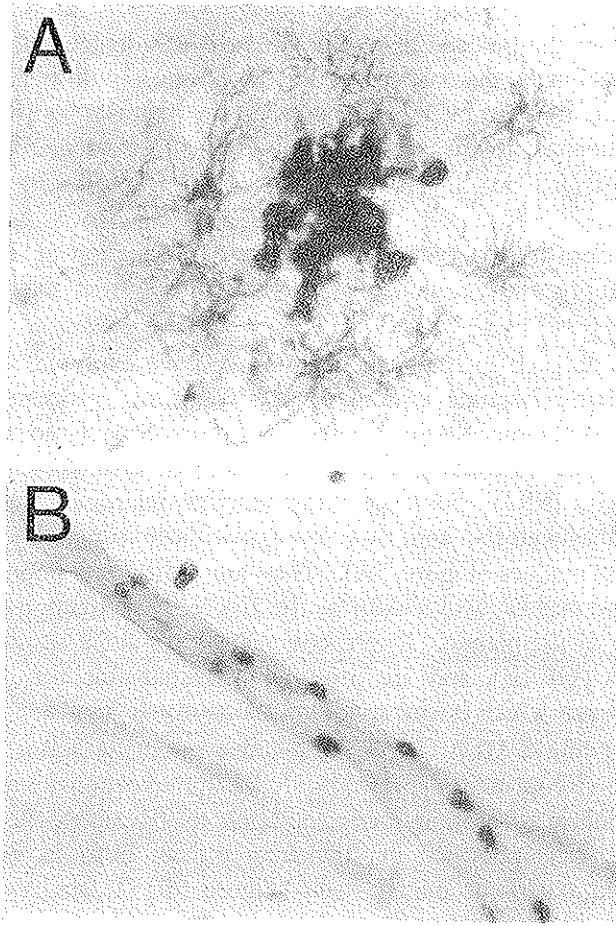


FIG. 5. Immune reactions in Alzheimer's disease. A. Hippocampus of an Alzheimer case doubly immunostained for HLA-DR and glial fibrillary acidic protein (GFAP). HLA-DR positive reactive microglia (macrophages) form conglomerates in the center of senile plaques. Reactive astrocytes, expressing GFAP, are arranged around the periphery. HLA-DR positive microglia are stained purple, while the GFAP-positive reactive astrocytes are stained brown on the original slide. B. Alzheimer hippocampus stained for T-8 cells and MHC Group I structural protein. On the original slide the T-8 cells are stained purple and the capillary is stained brown. T-8 cells can be seen both inside and outside the capillary. One cell appears to be on the border.

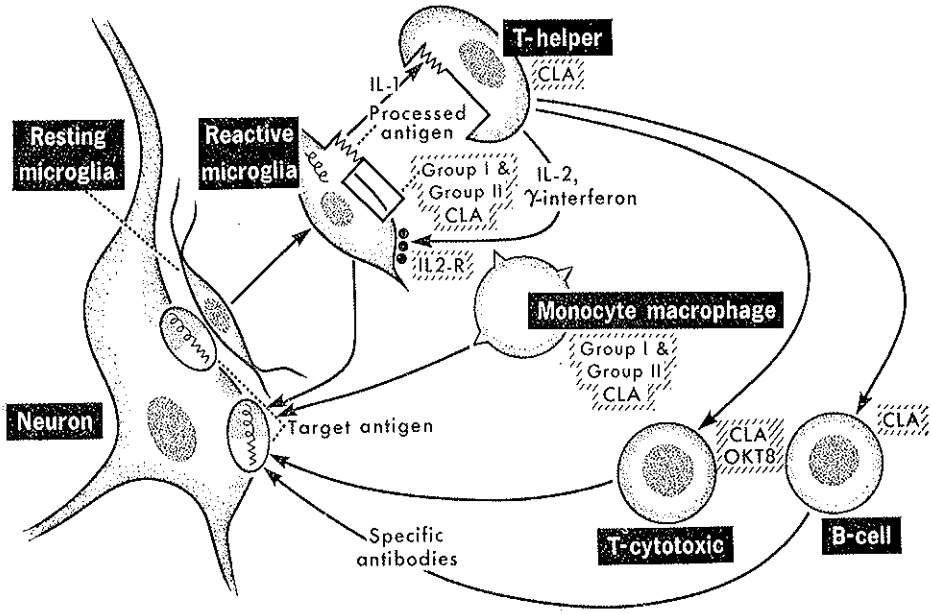


FIG. 6. Proposed interaction of brain and immune system. Abbreviations: IL-1, interleukin-1; IL-2, interleukin-2; IL2-R, interleukin-2 receptor; Group I, major histocompatibility complex A, B, C; Group 2, major histocompatibility complex D, including HLA-DR; CLA, common leucocyte antgen; T-helper, T-lymphocytes of the helper-inducer subclass; T-cytotoxic, T-lymphocytes of the cytotoxic-suppressor subclass (these lymphocytes carry a surface marker recognized by the antibody OKT8); B-cell, B-lymphocytes.

to the T-cell system and the method of stimulating an immune response has been established in the periphery. In Figure 6, protein which has the potential for stimulating an immune response is phagocytosed by microglia which are transformed from the resting to the reactive state so that they may go through the respiratory surge necessary for phagocytosis. In the process they display HLA-DR. Processed antigen is presented in conjunction with this group II glycoprotein to T-helper lymphocytes. The reactive microglia stimulate a lymphocyte reaction by elaborating interleukin-1, while the activated T-helper cells stimulate the reactive microglia by elaborating interleukin-2 and γ-interferon. The resident microglia of tissue can be assisted by monocytes from the peripheral blood which can become ameboid cells and mature macrophages in brain tissue. The T-helper cells, when presented with foreign antigen, begin cloning a response to that antigen. T-cytotoxic cells are produced which can then

directly attack neurons which present the same "foreign" antigen displayed by the reactive microglia. In addition, T-helper cells can stimulate B cells to produce specific antibodies against the antigen.

The occurrence of T cells in affected Alzheimer brain tissue, along with group II glycoproteins and evidence of lymphokine stimulation through interleukin-2 receptors, is consistent with either the presence of a pathogen, an autoimmune process, or an abnormal brain protein. Clearly, further investigation of the immune system response to Alzheimer's disease is warranted because appropriate intervention might be one route to effective therapy.

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DISCUSSION

INGVAR

I take this chance to continue the discussion that you gave after my talk, starting from your paper. You were talking about the correlation of these metabolic and blood flow changes and the psychological deficits. I think it is an important fact that blood flow studies have shown that there is such a correlation, namely that where the blood flow is the lowest, you have the most defects, for example in apraxia and in aphasia and in memory. So the morphological and the blood flow indices as well as the metabolic, which you showed, go together quite well.

Friends in Lund have studied over the years some 120 patients of Alzheimer, which they have followed for 5, 6, 8 years, until their death, and they have autopsied them also. There is a very nice correlation between the deficits in the flow landscape and the morphological changes. These are different in the Alzheimer cases from those with the multi-infarct dementias. So the blood flow studies may be used for diagnostic purposes. Prospective studies in these Alzheimer cases have shown that the blood flow pattern may tell you with good confidence the diagnosis.

MCGEER

I absolutely agree that the blood flow and glucose metabolism parallel one another. We recently found that the brain can be stained marvellously with MHC class 1 antibodies, and the capillaries are beautifully outlined in this fashion. When you compare that with neuronal stains, you find that each neuron almost has its own personal capillary. I think that the Sokolov model, in which you imagine that the blood flow is the same and that you are extracting a little more glucose out of the blood on demand, is really not the way you should view things. Rather, the production of CO_2 is causing that microvessel to relax, thus making available more blood from which oxygen and glucose can be extracted. The two are parallel measures while you are in a reasonably homeostatic condition. Of course if you go to extreme deprivation of either blood flow or oxygen, that's no longer going to hold. But when, on the same patient, we do blood flow and then glucose metabolism, the general pattern is the same. You can get a better resolution with glucose metabolism

because you can go in a higher resolution mode and accumulate your counts over a longer period of time. When it comes to activation studies, whether done with glucose or whether done with blood flow, the difficulty is when you give a single bolus. Then you are looking at a depreciating value in time as opposed to the activation which you want to be constant over time for your particular test.

DEECKE

The notion of the deficiency of the choline acetyl transferase which you presented triggered a number of therapeutic trials. The first trial was that one tried to give choline as such or lecithin, just to give a high amount of substrate in order to get some transmitter. The other is choline esterase inhibitors. One should not say that therapy in Alzheimer is absolutely useless. There may be some mild effects of recovery.

MCGEER

You have to remember that, even if there is a slight recovery, you're looking at a chronic inflammatory process in which the brain is quite literally being consumed. These cortical cells are dropping out at the rate of hundreds of thousands per day so that unless you have a way of arresting that process, over a period of time there is going to be a substantial cumulative deficit. In other words, the pharmacological approach is going to have very limited value, and what one really has to do is to get at the process which produces the inflammation, or if you can't get at the process, find some way of reducing the consumption of brain cells by this destructive but selective process. It's not just any neuron, there is a hierarchy of neurons that fall, and that's what's so exciting about the investigation of the cause.

DEECKE

What about the basal ganglia and the subcortical losses you mentioned?

MCGEER

The basal ganglia are relatively spared. The cell losses are minimal. If you look at the enzymes which are easy to measure and which therefore give you the first clue as to whether something significant is going on, they're unchanged. For

example, choline acetyl transferase levels in the basal ganglia of Alzheimer's are normal, but in the cortex they go down to 10, 20, 30% of normal. With noradrenergic cells you start with about 30,000 cells and the normal complement of an elderly person would be perhaps of the order of 20,000 but in the people with Alzheimer it may go down to 5,000 or 10,000. So you can lose in Alzheimer's disease 60 or 70% of the neurons in the locus coeruleus. The disease normally will last about 3,500 days, their retrospective recollection of when they first had symptoms to the time of death.

DEECKE

Is there any evidence so far that in Alzheimer's disease you have some leakage of the brain CSF barrier, as you have in other inflammatory diseases of the brain?

MCGEER

I think you have to distinguish between an acute inflammation where you'll have the capillaries releasing materials as in an acute infection or a vascular accident in the brain, and the chronic inflammatory process in which the specific T cells and the monocytes move in, starting in the post-capillary venules where they stick to the side of the wall and where you can actually see them crossing that wall and going into the matrix. Now these are the cells that participate with the microglia. These are the cells that are responsible for calling up the T cells, therefore being the local brain participants in the inflammatory process. Now that all takes place at the post-capillary level.

SINGER

I wonder whether one should call all these processes inflammatory, because during early development there is massive cell loss and reorganization of connections, and one would not call this inflammatory I guess, even though, there are phagocytes and there is removal of debris.

MCGEER

You are into semantics there because again the immune system is involved and of course what you are saying is that inflammation involves some foreign invader. But would you call it an inflammatory process if something caused destruction of tissue that had to be removed?

SINGER

No, I don't want that. If we call this inflammation we also have to call early development an inflammatory process.

MCGEER

I agree, because I think if you are cleaning up neurons that have been pruned and therefore have to be removed, you are calling in the same immune system that you would call in if a foreign invader were present.

ROLAND

You just said that there was a good correlation between the region's cerebral blood flow and the region's cerebral metabolic rate for oxygen in Alzheimer. But I would like to ask, is it really so, and how do you know that the rCBF and the rCMR glucose in Alzheimer's brain are actually correlated? As far as I can see, the only way to go is to study this inflammatory process, which is seen in the brain and which is dependent mainly on glycolytic activity and not on oxidation processes. Do you have any indication that would support this?

MCGEER

I suppose that the kind of inflammatory process that we are talking about would operate at such a low level that you wouldn't be able to detect it by the relatively crude techniques.

LEJEUNE

I would comment on the correlation you quoted between Alzheimer's disease and trisomate 21. It has been published repeatedly in the United States that in families in which a child with Down's syndrome was born, there was an increase of Alzheimer patients. We have checked that in France, and it does not happen. There is no excess of Alzheimer's disease in the parents and grandparents. What exists is that Down's syndrome patients themselves get Alzheimer-like syndrome around 20 times more frequently than normal people. What we did, was a trial every six months when they begin their regression. They stop talking and they begin going towards dementia. We have treated 50 cases with folinic acid. The result is extremely interesting because they are totally

cured of their pseudo-Alzheimer-like symptoms and they come back to their ordinary level of Down's syndrome. Now I don't know if this could be used at the beginning of the Alzheimer disease in normal persons, but at least it is interesting to know that, in a disease in which Alzheimer-like complication is so frequent, folinic acid is really doing something.

McGeer

One would assume that if it works in Down's, it ought to work in Alzheimer equivalently because, as far as people can tell, the lesions are identical both morphologically and biochemically. That should be published.

Lejeune

It is under publication. It will appear in the open literature next month.

McGeer

You see there is this enormous controversy at the present time because the Boston group found the four families that had genetic linkage to two markers on chromosome 21 and everybody immediately jumped to the conclusion of Down's syndrome, but then a whole series of studies came along in which a genetic linkage was not just negative but was absolutely excluded. That's why I think the possible correlation between Down's and Alzheimer's would be an important thing to bring forward right now.

ON IDEATION AND "IDEOGRAPHY"

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ABSTRACT. — The term "ideography" (Ingvar, 1977) has been introduced to denote regional circulatory (rCBF) and metabolic (rCMR) measurements of events in the human brain related to ideation. *Evoked* ideography denotes records of rCBF and rCMR changes coupled to cognitive phenomena following sensory stimulation or voluntary motor activity, including changes related to perception, or production of speech. *Pure* ideography records brain events during ideation which are not coupled to any ongoing sensory input or motor output. Simulated movements and silent (inner) speech are examples of pure ideational activities. They give specific cerebral ideograms with activity changes not only in the cerebral cortex, but also in subcortical structures and in the cerebellum. Ideographic paradigms appear to offer new approaches to study the physiological basis of the human psyche. Clinical ideography may be used to study mental disturbances in neurological and psychiatric disease.

Current imaging techniques of functional changes in the human brain permit studies with increasing spatial and temporal resolution of cerebral events which are related to mental activity (cf. Ingvar and Lassen, 1975; Ingvar, 1977; Ingvar, 1985; Risberg, 1980, 1988; Roland *et al.*, 1987). The ultimate aim of such studies is to describe and to quantitate, as well as to localize in two and three dimensions, the cerebral biochemical and/or circulatory "structure" of thoughts, concepts and ideas, i.e., the neuronal substrate of ideation. The term cerebral "ideography" has been suggested for this type of research (Ingvar, 1977).

From a simplistic neurophysiological point of view, two principally different types of ideation can be recognized:

1. *Evoked ideation*:

A. cognitive events evoked by perception of actually ongoing *sensory* stimulation, including perception of spoken or written language, or

B. cognitive events which pertain to the actual performance of voluntary *motor* activity, or to the production of spoken or written language.

Evoked ideation may be considered as an "on-line" activity of the brain.

2. *Pure ideation* is defined as cognitive events which are *unrelated* to any actual ongoing sensory stimulation (including speech perception) or to any ongoing motor performance (including speech production). Pure ideation may be divided into

A. pure *sensory* ideation, i.e., the conceptualization of sensory messages, including the imagination of speech perception, and

B. pure *motor* ideation, i.e., "inner" simulation of motor acts (motor ideation), or of speech (silent inner speech).

Pure ideation corresponds principally to an "off-line" activity of the brain.

There are indeed other forms of ideation which in the present context might be termed *complex ideation* in which it is not possible to identify a clear-cut "sensory" or "motor" component. Examples of such complex types of cognitive activity are the imagination of a promenade in familiar surroundings, recall of memories, problem solving, making theories and hypotheses, etc. The neurophysiological basis for such high levels of cognition and ideation is largely unknown. Hence, for the sake of simplicity the present review will be devoted almost exclusively to categories 1 A and B, *evoked* sensory and ideation, and to 2 A and B, *pure* sensory and motor ideation.

Events of the types defined above may indeed be studied by electrophysiological techniques (cf. Deeke and Freund, this volume). However, such studies lie outside the scope of the present review.

It will be claimed

— that cerebral ideography provides a unique approach to study in a concrete way the functional anatomy of some of the highest functions of the human brain and to identify some primary components of such functions.

— that cerebral ideograms, especially of pure ideational events, permit a mapping of brain structures which are selectively involved in the primary steps of the creation of ideas, concepts, memories, thoughts, plans, fantasies, theories, hypotheses, and cognitive events in general. Ideation related to speech and music should be included here. Cerebral ideography thus opens new approaches to the study — directly in the brain of unanaesthetized conscious humans — of the physiological basis of the highest functions of the brain, especially of cognition and language (symbol handling).

— that brain structures involved in pure ideation have a different localization from those involved in actual sensory and speech perception, or in the execution of movements or production of speech. A study of brain structures activated by pure ideation therefore appears to open a new approach to understand the human psyche.

— that clinical applications of cerebral ideography, at rest and during mental activation, may be used to analyze the cerebral defects which pertain to cognitive and language disturbances in neurologic and psychiatric disease. Already, several rCBF studies demonstrate that this is so.

Technical considerations

Cerebral ideography has in principle been possible since techniques were developed to measure regional cerebral blood flow (rCBF) clinically (Lassen and Ingvar, 1961; Lassen *et al.*, 1963; Ingvar and Lassen, 1975; Risberg, 1980). Quantitative rCBF values obtained with 133-Xenon clearance can be considered as indirect measures of the metabolic activity of the neurons in the regions in which the flow is measured. There is normally a close correlation between the neuronal metabolism and rCBF (Roy and Sherrington, 1890; Ingvar and Lassen, 1975; Raichle *et al.*, 1976).

The first cerebral records (ideograms) of more or less pure cognitive events in the human brain were carried out with simple rCBF techniques using only a few detectors (Ingvar and Risberg, 1965, 1967; Risberg and Ingvar, 1973). Currently, rCBF studies are made with high spatial resolution, using multidetector instruments and administration of 133-Xenon intravenously or by inhalation, both for two-dimensional measurements of cortical rCBF changes (Risberg, 1980; Roland, 1985; Ryding, 1986; Risberg, 1987, 1988) and with three-dimensional tomographic

techniques for the whole brain (SPECT; Stokeley *et al.*, 1980; Lassen and Friberg, 1988; Decety *et al.*, 1988, 1989).

The 14-C-deoxyglucose technique of Sokoloff *et al.* (1977) provided the experimental basis for clinical tomographic studies of man of rCMR with positron-emitting isotopes (PET; Reivich *et al.*, 1978; Raichle, 1979; Phelps *et al.*, 1979; Mazziotta *et al.*, 1982). Over the last years there has been an explosive development of quantitative PET techniques to measure the regional cerebral blood flow (rCBF) and the regional metabolic rate (rCMR) of glucose and oxygen, as well as different transmittor/receptor events in the brain. The spatial resolution of current PET techniques is only a few mm and the temporal resolution in some cases only seconds. However, so far PET techniques have been used only to a limited extent to measure higher brain functions (Kuschner *et al.*, 1987; Celesia *et al.*, 1982; Petersen *et al.*, 1988). There have been only a few PET studies of brain events immediately related to ideation (Roland *et al.*, 1987).

The resting conscious state

As in previous reviews of topics related to the present one (Ingvar, 1977, 1979, 1983, 1985), we shall here depart from the *resting conscious state*, i.e., from the distribution of neuronal function in the conscious awake human brain, not exposed to any deliberate sensory input (covered eyes, plugged ears), nor moving (performing motor acts), or solving problems. This state may be considered to represent a basic type of brain activity with an "idling" type of cognition. It has been well established that normal humans in this state have a stable EEG, and an overall mean cerebral oxidative metabolism of about 3 ml oxygen per 100 g brain per minute, and a mean blood flow (CBF) of about 50 ml/100 g/min (Schmidt, 1950).

Furthermore, as shown repeatedly in many laboratories, 2D-rCBF studies have demonstrated a stable *hyperfrontal* flow pattern in the resting state awake. The flow in premotor and frontal areas is about 10-20% above the mean, and the temporo-occipital flow about 10-20% below the mean (cf. Ingvar, 1979; Risberg, 1980, 1988). This pattern, the resting ideogram, is also evident, though not as clearly, in some PET-studies of the resting state (Mazziotta *et al.*, 1981, 1982; Phelps *et al.*, 1981).

As suggested by our group, the hyperfrontal rCBF pattern may also

be principally related to the classical resting EEG alpha-pattern (with closed eyes) which shows lower frequencies (alpha) in postcentral/temporal regions and higher frequencies in frontal regions (Ingvar *et al.*, 1979). The correlation between mean EEG frequency and rCBF as well as rCMR (Ingvar *et al.*, 1976 b) corroborates this juxtaposition of the hyperfrontal resting rCBF pattern and the hyperfrontal resting EEG. Both patterns show a marked stability.

It is claimed here that the hyperfrontal rCBF (and EEG) patterns recorded in the resting state with its "idling" cognitive activity, not influenced by any deliberate incoming sensory signals or production of behavioural reactions, represent *the resting cerebral ideogram* of wakefulness. Elsewhere it has been proposed, in part on the basis of introspective evidence, that resting cognition implies a "simulation of behaviour", which may include a low level rehearsal, refinement and optimization of cognitive, behavioural and speech programs (Ingvar, 1979). Such programs are by nature serial and organized on a temporal basis and highly dependent upon premotor and frontal cortical regions (Fuster, 1980; Ingvar, 1985; cf. Goldman-Rakic, 1988 and this volume). This view is supported by much clinical evidence. Patients with a poverty of motor/behavioural reactions, as well as a lack of a goal-direction cognition and behaviour (Parkinson's disease, schizophrenia, organic dementia, frontal lesions) show a resting rCBF pattern which is *hypofrontal* (Ingvar, 1980, 1985, 1987). There are also some observations that the normal hyperfrontality disappears in sleep when the serial and sequential type of cognition pertaining to wakefulness disappears (Ingvar, 1977).

In wakefulness, all forms of conscious cognitive activity, be they of the inner "silent" type, or directly related to sensory perception or to motor performance, have a temporal (serial, sequential) organization. The brain activity behind this normal "stream of consciousness" (Davidson and Davidson, 1980) has a time basis, and the "time arrow" of mental activity ("la flêche du temps"; Prigogine and Strengers, 1988) is irreversible. The underlying brain events, like biological processes in general, proceed continuously, and irreversibly, from the *past* through the *present* into the *future*.

The conscious state, e.g., the conscious awareness of the reader of these lines — in the present Now, when the lines are actually read — thus includes an awareness (Now) of 1) the memorized *past* (text above), 2) the *present* visual input of these very words, as well as 3) an expectation (idea, concept, hope) that the argument of the author may lead to

some conclusion or consequence in the *future*, on the next page, at the end of the article, etc.

In view of the time paradigm used here to analyze conscious awareness, it might be apparent that cerebral ideography in principle concerns conscious experiences in the *present*, pertaining to "Now". Experiences of the present may, however, be coupled to actual sensory perception or motor acts (evoked ideography), or be of pure "inner" nature (pure ideography). In both cases ideation contains components of the past (memories) as well as ideas about the future ("memories of the future"; Ingvar, 1985).

With the use of the time paradigm above, a review will now be given of some basic findings with cerebral ideography in the four main situations outlined above.

1 A. *Cerebral ideography of sensory perception*

Not unexpectedly, deliberate augmentation of the sensory input by, e.g., cutaneous electrical stimulation (Ingvar *et al.*, 1976a) or by increasing the visual input (e.g., Phelps *et al.*, 1981; Celesia *et al.*, 1982) augments the rCBF and rCMR in the appropriate primary cortical sensory areas. But not only this. Cutaneous stimulation in conscious subjects, especially if it involves pain sensation, also activates extensive frontal cortical regions. The resulting rCBF patterns (Ingvar *et al.*, 1976a) may be interpreted as ideograms of the cognitive consequences of sensory stimulation (Fig. 1):

1) *The ideogram of REST* shows the unstimulated idling brain, active mainly in the frontal lobe with its inner low level ("idling") resting cognition. This ideogram shows the hyperfrontal pattern (see above).

2) *The ideogram of TOUCH* (of the right hand) shows a slightly more marked hyperfrontality relative to rest, indicating that the cognitive consequences of the weak cutaneous signals are limited. The modest frontal increase suggests that the stimulus only evokes a limited mobilization of cognitive and behavioural programs since the weak stimulus can be supposed to have a low significance (meaning).

3) *The ideogram of PAIN* (induced by repetitive electrical stimulation of the contralateral thumb) shows, however, a markedly increased activation, mainly frontally. The experience of pain necessitates, as we all know, an acute mobilization of a great number of cognitive and behavioural action programs to deal with the pain situation. To use the

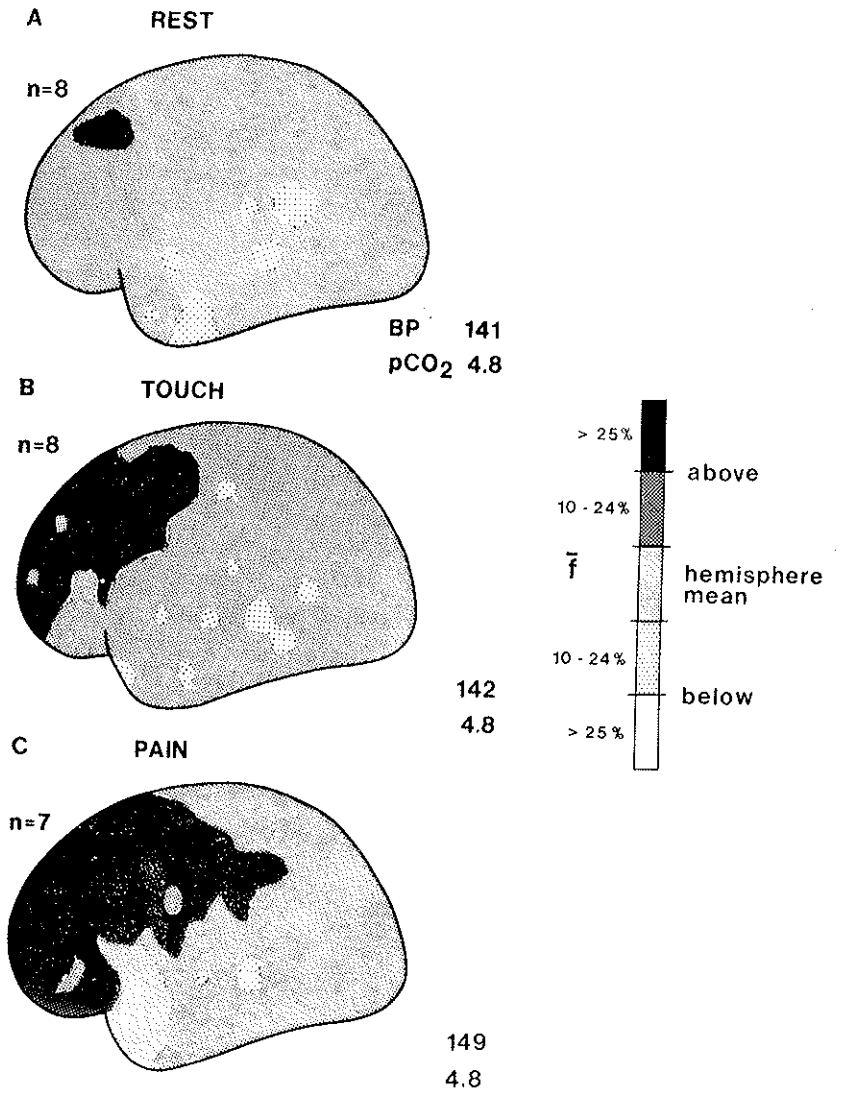

FIG. 1. *Evoked ideograms during Rest, and perception of Touch and Pain.* Intraarterial multidetector 133-Xenon rCBF measurements in the left hemisphere in eight subjects. Relative plots of flow changes with the resting hemisphere mean flow as reference. (A) *Rest*: Normal hyperfrontal flow distribution. (B) *Touch*: Electrical stimulation of contralateral thumb region at threshold. Note: Increase of hyperfrontality. (C) *Pain*: Stimulation 3 x threshold yielding moderate pain sensation. Note: Further increase of hyperfrontality and the involvement of larger, not only frontal areas. See text.

Adapted from INGVAR D.H. *et al.*, In: Y. Zotterman, Ed., *Sensory Functions of the Skin*, Pergamon Press, London, pp. 549-557 (1976). With permission.

time paradigm related above, a subject experiencing pain in the *present*, relates his actual sensations to previous memories and handling of pain in the *past*, and he mobilizes action programs to avoid and escape *future* pain.

This interpretation of the rest/touch/pain ideograms (Ingvar *et al.*, 1976a) is not only supported by common-sensical introspective evidence. There are also rCBF studies which might be invoked. We found early that any presentation of a problem to a subject, which requires serial sequential reasoning (complex ideation) also argumented the resting hyperfrontality, an augmentation which appeared proportional to the mental effort (Risberg and Ingvar, 1973; Risberg, 1980). Here it is of interest to mention that Risberg (1974) found some personality correlations in rCBF activation studies during psychological testing. This important finding has recently obtained solid confirmation in a study by Stenberg *et al.* (1989). In the resting state, "ready-to-act" extroverts show a more hyperfrontal rCBF pattern than "ready-to-contemplate" introverts. Using the time paradigm above, the hyperfrontal extroverts appear to have a larger inner production of programs for future actions than the less hyperfrontal introverts. Findings of this type suggest that cerebral ideography can be used to measure not only different cognitive structures and strategies, but also some of the underlying personality parameters.

Further support for the temporal interpretation for the rest/touch/pain ideograms is provided by findings concerning *anxiety*. Anxiety implies in principle an "overfuturing" (Melges, 1982), an abnormal concern for unknown and threatening future events. This state is accompanied by a marked hyperfrontality in alcoholics and demented patients who are exposed to cognitive stress (Ingvar and Risberg, 1967). In more advanced cases of dementia with low performance score, and no signs of anxiety in the test situation, the hyperfrontality reaction is reduced or absent (Ingvar *et al.*, 1975). The problem of anxiety has recently been further analyzed by Hagstadius and Risberg (1989) and by Hagstadius (1989) in high resolution rCBF studies. It was found that high levels of anxiety were linked to a marked hyperfrontality, especially on the right side. Cerebral ideograms may thus reveal personality traits as well as emotional aspects of cognition.

Speech perception

Listening to single sounds or spoken words represents another type of evoked sensory ideation (1 A above). As shown by Nishisawa *et al.* (1982), it produces a distinct bilateral rCBF activation pattern which involves regions outside the auditory and the classical speech areas, especially on the left side. An activation of mainly the left temporal and frontal cortex was demonstrated. This finding signals an involvement of frontal cortical structures in the perception of the semantic content of spoken messages. The ideogram of speech perception thus shows principal similarities with those evoked by touch and pain. In both situations the frontal activation may represent the general cognitive consequences of the perceived *serial* sensory input of language symbols. This interpretation has recently obtained solid support by the high resolution PET studies of Petersen *et al.* (1988). They showed that the semantic aspects of word perception gave regional frontal blood flow augmentations (see below).

In principle very similar results, including frontal activations, have been recorded during perception of music (Carmon *et al.*, 1975; Knopman *et al.*, 1983; Metter *et al.*, 1981). Using again the time paradigm above, the cerebral ideograms evoked by perception of linguistic and musical symbols demonstrate an activation of frontal structures. This finding provides direct ideographic support for the much adhered to "motor theory of speech perception" (Liberman *et al.*, 1967) which requires direct access to serial (frontal) speech motor programs for the perception of spoken words (Ingvar, 1983; Ryding *et al.*, 1987).

1 B. *Ideography of voluntary movements*

In 1971 Olesen showed that voluntary hand movements were accompanied by an rCBF augmentation in the contralateral rolandic region (sensory/motor hand area and adjacent fields). This finding was soon confirmed by Ingvar (1975) and extended by Roland (1982, 1984) who used a high-resolution multi-detector rCBF instrument. He also demonstrated that the supplementary motor areas were involved in temporally structured (sequential) movements, and that the basal ganglia took part bilaterally, even in unilateral movements (cf. Roland, 1984).

Highly complex paradigms (maze tests, proprioceptive tests, discrimination tests, etc.) have also been used to induce rCBF and rCMR changes (cf. Roland, 1984 and Roland, this volume). In several of these

studies, specific sensory/motor or cognitive components can not readily be identified, and an interpretation of the complex patterns recorded is difficult.

Speech production

Voluntary production of even a very simple series of words (week-days, series of numbers, etc.) gives rise to distinct bilateral cortical rCBF changes (Ingvar and Schwartz, 1974; Larsen *et al.*, 1978). The voluntary humming of a children's song, like automatic speech, also induces a bilateral, mainly rolandic and temporal, activation (Ryding *et al.*, 1987, 1989). A comparison of the rCBF patterns recorded from the right and left side during "Sunday, Monday, Tuesday ..." and those following "101, 102, 103 ..." shows several regional similarities and so they do with the ideograms pertaining to humming (Ryding *et al.*, 1987, 1989). Further studies will be required to identify the cerebral structures responsible for the ideational and semantic contents of certain spoken words (or melodies hummed), as well as to differentiate in the ideograms the output motor control of the articulation and the auditory feed-back effects (see Inner Speech, below).

Recently, Petersen *et al.* (1988), using a rapid high-resolution PET subtraction technique, have shown that the sensory, the motor and the semantic components in simple word processing have different cortical localizations. Their important study can be viewed as an exquisite model of "PET ideography" of language and cognition. The regional subtraction results provided support for the existence of multiple parallel routes between the visual input (reading, speech perception), the phonological, the articulation (speech production) and the semantic-coding areas. Of especial interest in the present context was the finding that the semantic processing of simple words activated frontal areas (area 47) rather than posterior-temporal (see above: speech perception).

To summarize, *evoked ideation* either by actual sensory stimulation (including speech perception) or by voluntary motor activity (including speech production) gives rise to cerebral ideograms in which two main components can be identified: 1) an activation of primary sensory, respectively motor regions and their immediate surroundings, and 2) activation of other, mainly frontal areas which in principle may be related to the cognitive consequences of the sensory input, respectively the volitional processes (planning) preceding the motor act. The ensuing

cortical activation patterns are often complex, and it is difficult to identify the specific regions in the brain which handle the ideational content of a simple sensory or speech input, or the ideational (volitional) background of a motor or speech output. Such a differentiation can only be made by cerebral ideography using pure ideation.

2. Pure ideation

2 A. *Pure sensory ideation*

Roland (1984, cf. Roland and Friberg, 1985) studied ideograms during expectation of (coming) sensory input such as a touch of a fingertip or of the mouth region. This type of selective attention induced a limited upper, respectively lower rolandic activation and, in addition, a substantial prefrontal increase of rCBF. They used the word "tuning" for the preparatory activation of centers involved in this type of ideation, but which were not activated by any actual afferent input at the time of the rCBF measurement.

2 B. *Pure motor ideation*

Ingvar and Philipson (1977; Fig. 2) were the first to record pure motor ideograms, i.e., cortical events in subjects conceptualizing a specific movement, a one-sided rhythmic hand-clenching. A contralateral activation of premotor and prefrontal regions was clearly demonstrated during this type of motor ideation, and so was the limited activation of the hand area which is so evident during actual voluntary movements (Olesen, 1971; Ingvar, 1975). Later, these findings have been principally confirmed (Roland *et al.*, 1980) and it has been shown that sequential movements activate the supplementary motor area bilaterally, as well as the basal ganglia on both sides (Roland, 1982, 1984).

Recently, Decety *et al.* (1988) have shown bilateral brain activations during simulation of a graphic task (Fig. 3). Not only did this ideogram differ from the one pertaining to actual graphic movements, but it also showed that both paradigms, writing and simulated writing, activated regions most likely related to the *cerebellum*. A cerebellar activation during motor ideation has recently been confirmed during simulated tennis movements during which the absence of peripheral EMG activity was controlled (Decety *et al.*, 1989).

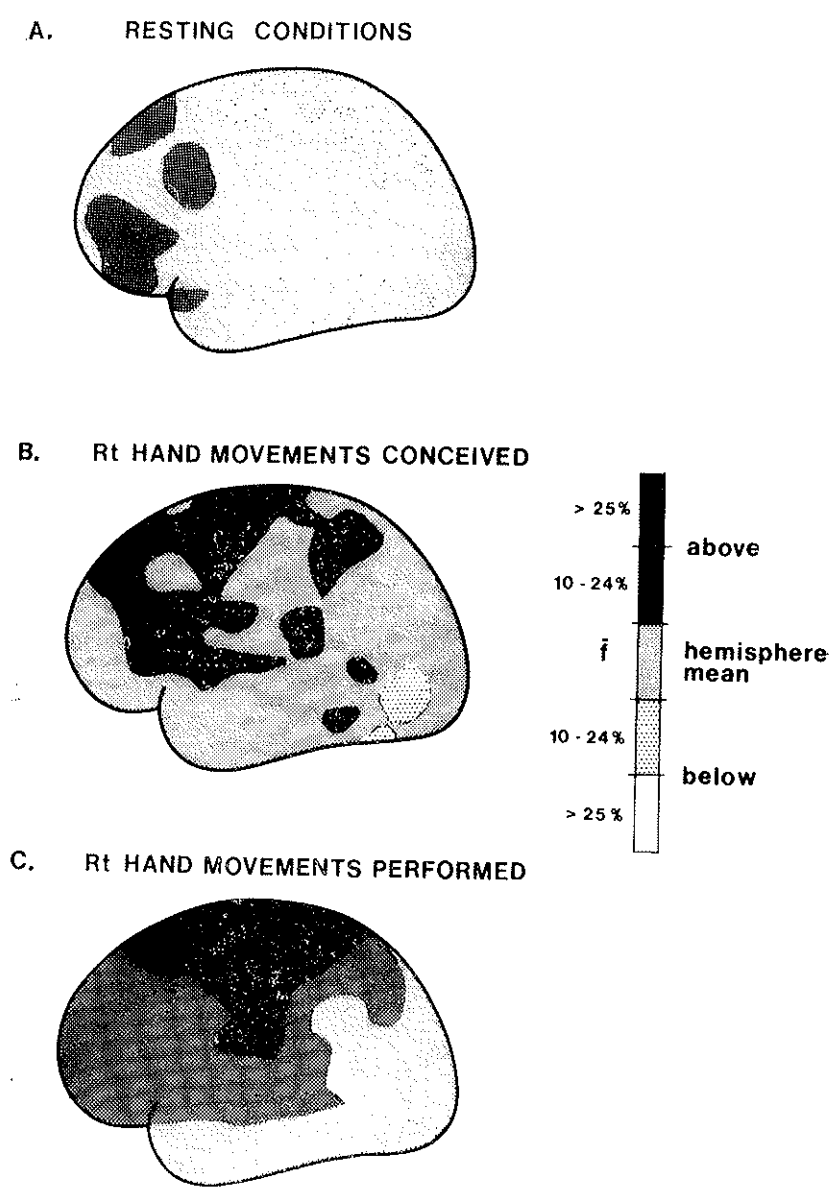

FIG. 2. *Pure and evoked ideograms during motor ideation* (B) *and motor performance* (C). Intraarterial rCBF measurements as in Figure 1. Mean of six subjects. (A) *Rest*: Note normal hyperfrontal pattern. (B) *Pure ideation*: Subjects thinking of rhythmic clenching movements of right hand. Note: Marked, mainly frontal, activation. Limited activation in Rolandic area. (C) *Evoked ideation*: During actual performance of voluntary rhythmic clenching of right hand. Note: Marked activation of Rolandic areas (confirming Olesen, 1971) in addition to frontal areas as in B. See text.

Adapted from INGVAR D.H. and PHILIPSON L., « Ann. Neurol. », 2, 232-237, 1977. With permission.

Pure speech ideation (inner speech)

Inner speech, e.g., counting silently "100, 101, 102 ...", and onwards, constitutes a pure form of a speech ideation lacking both actual sensory input and motor output. Both the auditory/proprioceptive sensory feedback is absent, and so are the motor/articulatory components.

In a study of 30 right-handed volunteers with a bilateral 2D-rCBF technique, Ryding *et al.* (1989) found that silent speech activated almost exclusively the *left* dominant hemisphere, and there in selective regions mainly. These regions showed a distinct relation to the Wernicke area and the upper SMA speech center of Penfield. A rolandic center was also identified, probably related to articulatory centers (larynx, mouth, tongue) and possibly also to Broca's area. On the right side a significant frontopolar activity was also seen during silent speech. Some diffuse frontal rCBF increase was also recorded like in preliminary studies of silent speech (Lassen *et al.*, 1978), but they did not reach significance. It should here be added that Decety *et al.* (1989) also found that silent speech activated the cerebellum, apparently in a symmetrical fashion.

The studies of silent speech illustrate clearly the value of *pure* ideography in analyzing the symbol functions of the brain. The findings of Ryding *et al.* (1987, 1989) are, it seems, the first studies which compare brain mechanisms perception and production of spoken words with mechanisms "behind" the concepts of words and speech. It appears of fundamental interest that the study of silent speech showed such a clear preponderance of cortical foci of activation in the left (dominant) hemisphere, and that these foci showed a direct relation to the classical speech centers. In contrast, speaking aloud confirmed a widespread bilateral activation, dominating on the right (sic!) side, mainly in temporal and rolandic areas (Ryding *et al.*, 1987, 1989).

Clinical considerations

So far, only a few studies have been made in patients with defective cognition and language in which ideographic principles have been applied. In organic dementia and chronic schizophrenia, abnormalities have, however, been found with evoked ideation (psychological testing). In both disorders, a defective activation of especially frontal association cortices has been recorded (Franzén and Ingvar, 1975; Risberg, 1980, 1988).

It is highly inviting to suggest here that pure sensory ideography,

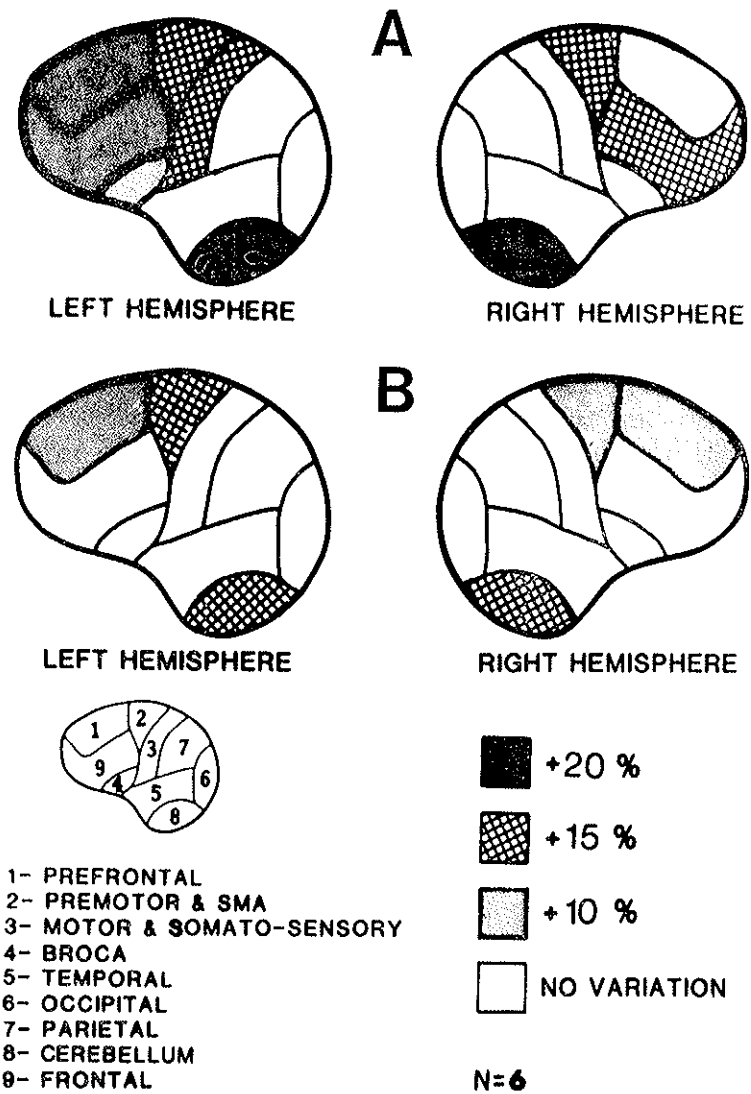

FIG. 3. *Motor performance* (A) *and motor ideation* (B). rCBF measurements with 133-Xenon inhalation using a rotating gamma camera in six subjects. Mean flow changes in relation to rest in regions indicate. (A) *Actual writing* (with right hand) of figures ("one, two" etc.) on a paper. Note marked flow augmentation especially in the *left* hemisphere including the Rolandic region. On the right side, premotor and prefrontal areas were activated. Note: Market bilateral flow increase in the cerebellum. (B) *Simulated writing* with right hand of "one, two..." etc., at the same speed as in (A). Note: Absence of left Rolandic activation, but retention of bilateral premotor and prefrontal flow increase — as well as some clearcut cerebellar activation. See text.

From DECETY J. *et al.*, « Eur. Arch. Psychiatr. Neurol. Sci », *238*, 33-38, 1988. With permission.

e.g., during expectation of a (future) sensory stimulus, listening to an "inner" recital or a melody, etc., might be profitably used in focal neurological disorders (aphasia), as well as indeed in mental disorders accompanied by cognitive and emotional disturbances. rCBF studies with evoked ideation have already proved that specific psychological testing in schizophrenics using, e.g., the Wisconsin Card Sorting Test, reveals clearcut frontal abnormalities in this disease (Franzén and Ingvar, 1975; Weinberger *et al.*, 1986; Warkentin *et al.*, 1989).

The ideographic approach may also be used to evaluate psychiatric therapy in patients with cognitive and emotional disturbances. Kullberg and Risberg, (cf. Risberg, 1988) have shown a frontal rCBF reduction following cingulotomy which alleviates anxiety. Psychopharmacological treatment (Haloperidol) also lowers the frontal activity lever, an effect coupled to therapeutic success (cf. Risberg, 1988). It does not in fact appear far-fetched to envisage that the ideographic approach might be used to measure the effects of classical psychotherapy. Examples have been given above of how, e.g., symptoms of anxiety as well as mental effort during problem-solving is reflected in cerebral ideograms. Therefore a diminished anxiety proneness during successful psychotherapy should, for example, lead to a reduced hyperfrontality (cf. Hagstadius, 1989).

Right-left differences

Several of the studies quoted have shown important side-differences in evoked or in pure ideograms. These differences are at present not well understood. Emotional factors appear to engage the right frontal region more than the left (Hagstadius and Risberg, 1989; Hagstadius, 1989). Silent speech activates, as mentioned, almost only the left (dominant) hemisphere, while speaking aloud gives rise to bilateral activations, which normally are more pronounced on the right side (Ryding *et al.*, 1987, 1989). Much further work, in which indeed ideographic techniques can be used, will have to be done in order to reconcile the many current theories on brain lateralization which arise from the abundant neurophysiological and electrophysiological findings available today.

Emotions

This large field should also merit a systematic consideration in future ideographic studies. Already it has been shown that the resting ideogram (the hyperfrontal pattern) correlates to anxiety proneness. "Over-futuring" (Melges, 1982) anxious persons are more hyperfrontal (more action- prone) than the less anxious ones (Hagstadius and Risberg, 1989; Hagstadius, 1989). Patients with brain lesions also show a greater frontal activation and clear signs of anxiety in a test situation than do normals, possibly due to the awareness of their handicap (Ingvar and Risberg, 1967; cf. Risberg and Ingvar, 1973).

Concluding remarks

This meeting on "*The Principles of Design and Operation of the Brain*" has an obvious goal: to review the state of the art concerning mechanisms related to the highest functions of the brain. The present contribution is based upon studies from the last two decades which have used multiregional two- and three-dimensional techniques to measure neuronal mass activity (blood flow; rCBF) or metabolism (rCMR) in circumscribed cerebral regions. These techniques for rCBF and PET haved proved very successful for localization and quantification of brain events related to different aspects of cognition, speech, volition, and also (to some extent) of emotions. However, the data obtained so far are indeed very limited in view of the complexity of the human psyche. Nevertheless the following conclusions appear warranted:

1) There is overwhelming evidence that mental events are coupled to an almost cosmic variety of metabolic and circulatory patterns in the human brain. (The important electrophysiological events are not included in this review).

2) In order to set aside multiregional rCBF and rCMR studies of *mental* events from other investigations of brain mechanisms, the term *cerebral ideography* has been introduced (Ingvar, 1977).

3) Using a simplistic neurophysiological approach, one may differentiate between (A) *evoked ideography*, i.e., a study of brain events (cognitive and others) directly related to sensory and speech perception, or to voluntary motor activity as well as to speech production, and (B) *pure ideography*, i.e., a study of brain events unrelated to sensory stimula-

tion or motor performance, including inner speech. There are, in addition, many other forms of complex ideation and cognition which have not been considered in this review.

4) *Evoked ideography* portrays the cerebral functional landscapes which are coupled with the perception of sensory messages and of speech, as well as the cognitive and emotional consequences thereof. It may also picture the volitional processes which accompany the execution of voluntary movements and speech.

5) *Pure ideography* includes selective measurements of "inner" brain events related to cognition, such as sensory and motor imagery, fantasies, expectation, planning, problem-solving, etc., in situations *without* sensory or speech input as well as *without* motor or speech output.

6) By comparing evoked and pure ideograms such as (1) the ideograms during cutaneous electrical stimulation vs. imagination of the same stimulus, or (2) the ideograms during speaking aloud vs. speaking silently, it is possible to some extent to outline the brain structures which are specifically involved in actual sensory perceptions or motor execution, in contrast to structures responsible for ideas, concepts, symbol handling, etc., as well as cognition in general.

7) Our studies of silent speech have demonstrated for the first time that ideas and concepts related to words and symbols activate almost exclusively the left (dominant) hemisphere, and there selectively a number of regions with clear relation to the speech centers (Ryding *et al.*, 1989). During aloud speech these ideational speech centers on the left side are apparently hidden by the substantial activations which are then induced in both hemispheres (Ryding *et al.*, 1987, 1989).

8) Motor ideation (stimulation of movements) gives clear-cut cortical prefrontal activations with a prominent bilateral component. In addition, the inner plans underlying concepts and ideas of movements — and silent speech — appear to activate the cerebellum (Decety *et al.*, 1989). Thus for the first time the cerebellum can be assigned a putative role in mental activity. The action plans which precede and which are a prerequisite for volitional motor acts, and the ideational component of speech, apparently include cerebellar mechanisms the nature of which are, however, still unknown.

9) Future clinical applications of ideographic paradigms appear highly promising. Already now significant ideographic changes have been

found (at rest) in organic dementia, chronic schizophrenia and anxiety states. These changes have aided the understanding of the cognitive abnormalities, including the disturbances of conscious awareness which accompany these disorders. A common denominator in these states is a disturbance of the temporal organization of cognition and/or behaviour, a function which has been localized to the prefrontal cortex. As described elsewhere, such disturbances may be coupled to, e.g., reduced abstract cognition in organic dementia, to the cognitive disturbances in schizophrenia, and to the abnormal concern and worry for future events in anxiety states.

ACKNOWLEDGEMENTS

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DISCUSSION

DEECKE

Dr. Goldenberg in our clinic also investigated imagery, by comparing sentences with low imagery, with visual imagery and with motor imagery. The highest activity we found in the brain was with motor imagery, e.g. visualizing how he ties his shoes and other complex motor tasks. But in visual and motor imagery we always saw a high activity in the visual cortex, although the eyes were closed.

INGVAR

We haven't specially studied the visual cortex. We can do it now with the tomographic techniques.

DESMEDT

Is the metabolic landscape really flat in sleep and paradoxical sleep? Don't you have valleys and geography in that?

INGVAR

We are studying sleep at the moment. One thing I can say is that the hyperfrontality goes away in deep sleep. This makes me wonder whether the cognition which pertains to sleep lacks the timetable, the temporal organization of wakefulness. But we are not ready yet.

POECK

I'd like to know to what extent the blood flow increase during your task is dependent on the complexity of the task. It strikes me that people always have to count one two, one two. Now if this patient would have to say hippopotamus or produce a word in a foreign language, would the activation pattern be more complex?

INGVAR

Yes. The activation of the brain correlates to the effort in general, to the complexity of the problem.

JEANNEROD

I was struck by your demonstration of the cerebellar involvement in the imagery of movements. Do you think it's a consequence of the prefrontal activation? How do you see it in the circuitry of movement?

INGVAR

I think we need all the circuitry that we know of. I cannot say the basal ganglia, the frontal lobe, the cerebellum. We simply don't know what is what here.

JEANNEROD

Was the involvement bilateral?

INGVAR

As it appears, yes, but our resolution is poor.

MCGEER

I would also like to say it's a remarkable demonstration of cerebral activation, especially given the technique. But positron emission tomography consistently shows that the occipital cortex has the highest metabolism. There was one slide where you had said it was the basal ganglia, but that almost looked to me like the thalamus, and I'll bet you find that the thalamus is involved in many of these activations as well as the cerebellum.

INGVAR

Yes, you are right. Now the occipital lobe and the occipital cortex, the visual cortex, has its own story, and I am not prepared to discuss it because the technique is not sufficient for it.

GOLDMAN-RAKIC

It seemed to me that the pattern of activation during rest was primarily an increase in activity in the premotor as compared with prefrontal. Would you comment on that? Does it make a difference and have you studied whether there is a difference in activation patterns in people who are at rest but either engaged in thinking about something or not?

INGVAR

The only evidence we have for such an analysis is in the schizophrenics when they have what the psychiatrists say is an empty type of rumination and they are hypofrontal. The second comment I have is that there are correlations with personality which I'll not go into detail about.

GOLDMAN-RAKIC

Is the premotor cortex the area which shows it primarily?

INGVAR

It appears so. Yes.

BAUMGARTNER

The cerebellum is always participating in planning for movements. If you record from neurons in certain parts of the cerebellum, they are activated before the movement. Do you see changes in cerebellar blood flow also during programming and planning which are not related to movements — for example expectation?

INGVAR

We don't know. We haven't done that as yet. With ideation you expect something to happen, and you expect what to do about what is going to happen, so there is a concept of movement in the expectation too.

CREUTZFELDT

Did I understand correctly that the parietal lobe is not involved in motor ideations? Does this mean that we should give up the idea of it being the highest command level, in Hughling Jackson's terms, for motor ideation and planning?

INGVAR

We have not as much information on that as Per Roland has, but I think that the movement in the extrapersonal space, the ideation of movements in extrapersonal and intrapersonal space, are related to the parietal areas. But to my mind, the structure of the movement, the programming of the movement takes place mainly in the frontal lobes, and part of this activation is rather diffuse and it's hard to get at because it's apparently widespread, and it's not always like little islands coming in and going out.

DYNAMIC REGULATION OF PERCEPTION IN THE LEFT AND RIGHT CEREBRAL HEMISPHERES

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University of Chicago

INTRODUCTION

Perceptual processes are highly constructive, under dynamic regulation and governed, from the earliest stages of stimulus encoding, by the ends to be achieved. These ends are inductive models or theories of reality that differ for the human left and right hemispheres (LH and RH), which organize, categorize, and elaborate sensory data in accordance with their representational aims and possibilities. Through attentional mechanisms, each hemisphere selects those aspects of stimulus information that are relevant for constructing a self-consistent perceptual model.

The consistency requirement leads to hemi-suppression of information in one hemispatial field when conflicting data are presented to the two hemispheres simultaneously. Moreover, the asymmetry of suppression is regulated by the nature of perceptual relations to be discovered, regardless of a hemisphere's ultimate success in finding those relations. Finally, as recent observations show, whether there is hemi-suppression or integration of bilateral information is determined by the outcome of a decision process regarding the consistency of data received directly and transcommisurally. In sections to follow, I discuss studies of split-brain patients and normal individuals that highlight the rather remarkable control dynamics of the human brain that govern our perceptual theories of reality.

Hemispheric Asymmetries in Perceptual Representations

There are multiple levels of stimulus realities, which are defined by the degree of relational integration among stimulus components and the interpretive enrichment that is added. The dot arrays, A and B, are identical in the number of elements and the characteristics of elements, and they differ only in their spatial relations. Unless those relations are computed, the arrays A and B are indistinguishable:

Nebes (1973) presented such arrays by tachistoscope in the left or right visual field (LVF or RVF) of split-brain patients, who judged whether arrays were aligned in columns or in rows. The RH was far more accurate than the LH, and its superiority increased as organizational demands increased (i.e., as the difference in relative dot distances along vertical and horizontal axes decreased). It is not that the LH's perceptions were less veridical than those of the RH, but rather that the LH represented the arrays as the dots they were, with much less organizational elaboration or enrichment than was imposed by the RH.

Some stimuli are interpretable either at the literal level or as symbols of a higher-order reality, and the Muller-Lyer figures are one example:

As two-dimensional drawings, the horizontal lines in A and B are identical in length. However, if the figures are read as symbols of a three-dimensional world, they consist of upper and lower planes that project forward from a more distant line of joining (figure A) or that recede back-

ward from a nearer line of joining (figure B), in which case, the line of joining in A is longer than in B, since it is more distant. Kumar, Zaidel and Bogen (1976), in an examination of split-brain patients, found that the RH perceived the lines to be of equal length only when the one with inward converging diagonals was 40% longer than the one with outward diverging diagonals, whereas equality was perceived by the LH when the disparity was only 10%. The RH, far more than the LH, interpreted the drawings as mere symbols of a three-dimensional world, which was modelled in the perception.

Whether one or the other hemisphere's perception is considered to be more veridical or illusory depends entirely on how we choose to define reality. This is especially evident in a study by Zaidel (1988). Split-brain patients were fitted with special lenses, which permitted unlimited exposure of visual stimuli to a single hemisphere at a time. Each hemisphere was shown a surrealistic painting of a human face, which, on closer inspection, is seen to be a female torso. Neither hemisphere experienced the surrealistic effect, since the RH perceived only a face, and not the conflicting torso features, and the LH perceived only the torso and its features, and not the conflicting relations that specified a face.

In order to construct a facial representation, the RH must extract global information from the picture, which can be integrated into relations that specify a face. Sergent (1982, 1984) flashed cartoon faces in the LVF or RVF of normal right-handers and found qualitative differences in how LVF and RVF stimuli were encoded. In particular, when faces were presented in the RVF (to the LH), attention was deployed sequentially from the top to bottom features, which indicates isolated encoding of features as separate elements. However, when faces were presented in the LVF (to the RH), attention was distributed over the whole face, which indicates encoding of the stimulus as an integrated configuration.

Although it is the RH that constructs the more elaborated and relationally unified visuospatial perception, the reverse holds with respect to linguistic perceptions. Consider the following stimulus:

At the most literal level, the stimulus consists merely of a collection of 27 line segments, and with further organization these are reduced to 10 lines, which are then placed in three perceptual groups. The groups are further interpreted as letters by those who can read the alphabet, and finally, phonetic readers synthesize the letters into a unified phonetic representation (sound code). Moreover, if the phonetic synthesis is possible, it is unavoidable.

The brain is compelled to integrate the elements of the stimulus into the most unified and meaningful perception possible, which for the LH is the phonetic representation. This unification is less complete for the RH, which has no capacity for phonetic representation (Levy and Trevarthen, 1977) but can organize the stimulus into alphabetic letters. The LH has a dual representation of the letters, both as individual elements and as part of the phonetic representation. However, it is the phonetic synthesis that governs how the LH extracts information from the stimulus, which supersedes letter representations, as shown by studies of normal people (Levy *et al.*, 1983a).

Levy *et al.* (1983a) flashed vertically oriented 3-letter nonsense syllables in the LVF or RVF of normal right-handers and asked subjects to pronounce the syllables. Although the LH always gives the verbal response, stimuli are initially encoded by the hemisphere contralateral to the stimulus. By an analysis of error patterns, Levy *et al.* found that, in exact contrast to Sergent's (1982, 1984) observations with face stimuli, the RH deployed attention sequentially, from the first to last letter, as each letter was encoded as an individual element, whereas the LH distributed attention more globally over the whole syllable, which was encoded as a phonetic unit.

The LH extracted partial information with respect to all letters in the syllable to construct the phonetic representation. It was from this representation that specific letter information was secondarily derived, as revealed by a correlated accuracy between first and last letters in the RVF but not LVF. First-letter accuracy for RVF syllables was much higher when the last letter was correct than when it was not. If the LH's phonetic mechanism was successful, the representation specified both first and last letters. If the last letter was missed, the phonetic mechanism had evidently failed, in which case errors for first letters were greatly increased.

It is not merely that the final perceptions of each hemisphere differ, but that the differing perceptual goals act downward to determine the encoding process itself, and probably at the first neural opportunity (i.e.,

beginning at sensory relay nuclei). Through this mechanism, perceptions become self-fulfilling prophecies that specify the processes that lead to their achievement. These prophecies gain even greater potency in governing perceptions when the two hemispheres receive input simultaneously. Under these conditions, non-existent realities may be created in the perceptual representation, whereas some stimulus realities may not be perceived at all.

Hemi-Completion and Hemi-Suppression

In a series of studies, split-brain patients were presented with rapidly flashed chimeric stimuli (see Fig. 1 for example), in which one half-stimulus, in the LVF, was joined to another half-stimulus, in the RVF (Levy, Trevarthen and Sperry, 1972; Levy and Trevarthen, 1976, 1977).

Whether chimeric stimuli were faces, line drawings of common objects, chain patterns of vertically arranged 3-element arrays of X's and squares, or words, patients perceived the perceptual completion of a half-stimulus in one visual field and nothing at all in the other. When patients were asked to name or describe the stimulus, they described the completion of the half in the RVF, presented to the LH (since the RH is mute). Even after intensive and leading questioning, patients insisted that there was nothing "peculiar" about the tachistoscopic stimuli. After describing or naming a stimulus, they examined an array of the whole stimuli from which chimeras were made and stated that the one they saw was identical to the whole stimulus. The perceptual system simply created a missing half and suppressed the half in the opposite visual field.

Only the LH can speak, but either hemisphere can control a pointing response of either arm. In one condition of tasks, patients were asked to match stimuli with free-vision choices according to identity or visual similarity (discovery of visuospatial invariants), semantic relations (words with their pictorial referents; pictures according to functional association), or phonetic relations (matching of pictures with rhyming names). Only a single choice was made on each trial, which shows that only one hemisphere perceived a stimulus. When instructions specified the discovery of visuospatial invariants, patients perceptually completed the RH stimulus (faces, line drawings of objects, chain patterns, words), which was matched to a choice, and perceived nothing in the RVF. When instructions specified the discovery of semantic or phonetic relations, patients perceptually completed the LH stimulus and perceived nothing in the LVF.

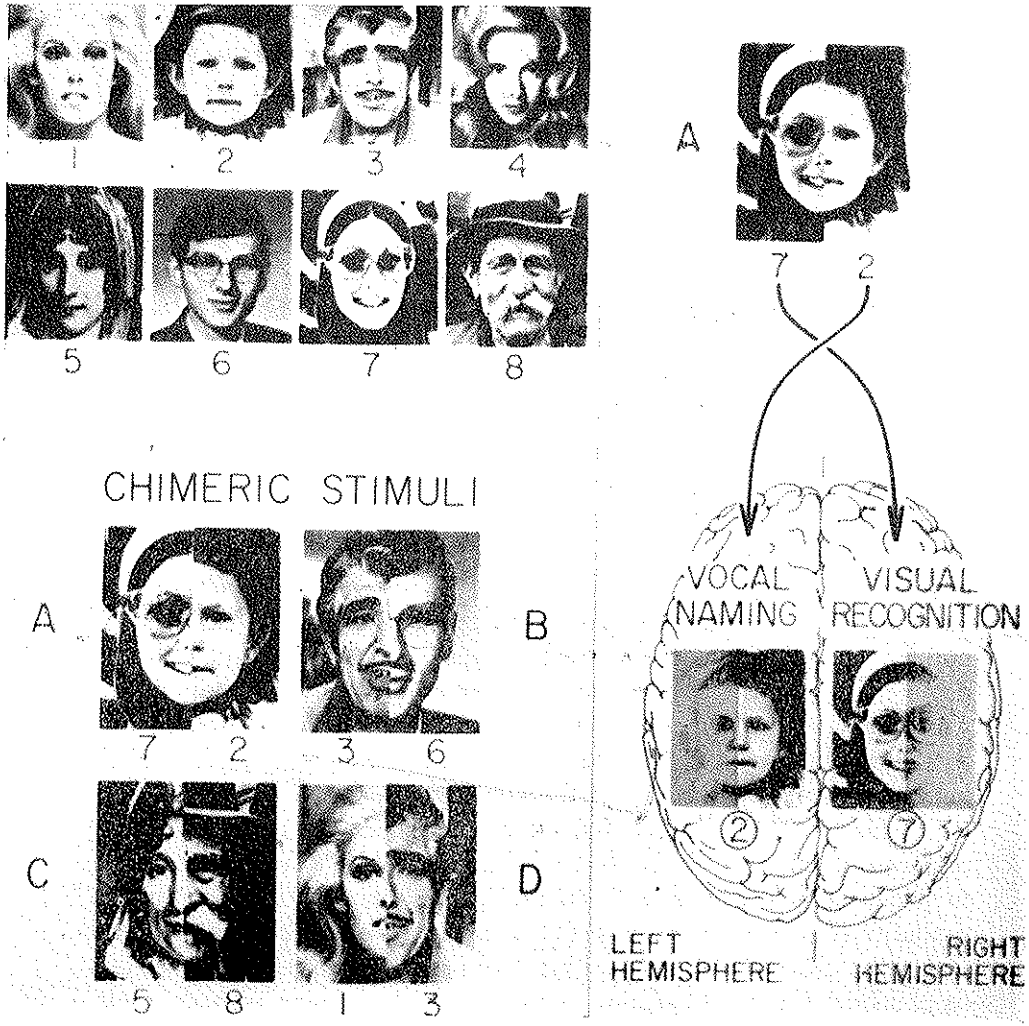

FIG. 1. An example of chimeric stimuli presented to split-brain patients by tachistoscope (from Levy *et al.*, 1972).

Although the RH is superior to the LH in representing faces, the LH is actually superior to the RH in representing the chain patterns, and the two hemispheres have equally accurate perceptions of common objects or words. However, whether the RH's superior visuospatial skills were of value or not for specific classes of stimuli, instructions to discover visuospatial invariants were sufficient to generate perceptions in the RH and suppress perceptions in the LH. Only the LH can match pictures according to rhyming names, but the RH is as accurate as the LH in matching simple nouns to their pictorial referents or pictures according to functional association. Nonetheless, semantic instructions were as potent as phonetic instructions in generating LH perceptions and suppressing RH perceptions.

The regulatory process that asymmetrically activated one hemisphere acted prior to execution operations and was not determined by the actual relative abilities of the two hemispheres in processing the specific stimuli nor even by their execution strategies. In all patients, instructions to match pictures according to visual similarity or functional association interacted strongly with the lateralization of the stimulus that was matched (RH or LH, respectively). However, under visual instructions, the RH often made functional matches, and under functional instructions the LH often made visual matches. Indeed, the patient C.C., with a single exception, made only visual matches, but to the RH stimulus with visual instructions and to the LH stimulus with functional instructions.

Each hemisphere of split-brain patients evidently evaluated task instructions with respect to the general nature of the perceptual discovery required and in relation to its general capacities. These metacognitive processes specified the behavioral or representational goal and led to hemi-suppression of input to one hemisphere and a perceptual elaboration of input to the other. However, once a hemisphere gained processing dominance, its actual executions depended on specific characteristics of stimuli, which could depart from general requirements of their class.

Although the hemi-suppressive function clearly acts prior to execution operations and the perception, this does not imply that the task instruction, prior to stimulus presentation, simply directs all attention to one visual field and removes all attention from the other. Split-brain patients can be induced, *following* stimulus presentation, to perceive the conflicting stimuli in the two hemi-fields (Levy *et al.*, 1972). If patients are suddenly interrupted in making visuospatial matching responses and are asked to describe the stimulus, they describe the perceptual completion of the

LH stimulus, and then proceed to match the RH stimulus. Similarly, if they are interrupted in making verbal responses and asked to match the stimulus, they match the RH stimulus and then proceed to describe the LH stimulus.

The interruption itself directs processing resources to pre-perceptual information, which is not processed to the level of a perception in the absence of the interruption. However, bilateral attention has been sufficient to extract all information necessary for perceptual constructions. The hemi-suppressive function therefore acts on the information extracted from one hemi-field to block its perceptual representation (which can be overridden by trial interruption).

Bilateral Consistency, Hemi-Suppression, and Cross-Integration

Since the hemi-suppressive function acts on pre-perceptual information that is fully adequate to be processed to the perceptual level, this raises the possibility that hemi-suppression may be secondary to the bilateral inconsistency of stimuli. Information relayed through brainstem commisures may be adequate to set off an "inconsistency alarm", which triggers the hemi-suppressive function.

Colwyn Trevarthen and I in unpublished observations examined vocal reaction times (RTs) of the patient N.G. to name common objects depicted in line drawings that were centrally presented by tachistoscope (half in the LVF, half in the RVF). Vocal RTs to name chimeric stimuli (i.e., the perceptual completion of the half in the RVF) were significantly slower than RTs to name bilaterally congruent stimuli (i.e., normal and complete stimuli), even though the LH had direct access only to the half-stimulus in the RVF for both classes of stimuli. N.G.'s performance implies that even the brainstem commisures are sufficient to relay information that can be checked for consistency with direct input. The difference in her vocal RTs in response to congruent and incongruent stimuli strongly suggests that a consistency check determines whether information in one hemi-field will be integrated with that in the other or suppressed.

If so, then normal people should manifest perceptual hemi-completion and hemi-suppression when presented with bilaterally inconsistent stimuli. Indeed, Milner and Dunne (1977) found precisely this in an examination of normal right-handers. Chimeric faces, masked at midline by a narrow strip, were flashed by tachistoscope for matching with faces in free vision. Subjects perceived only a single face, which was the per-

ceptual completion of the half-face in one visual field (more often the LVF than RVF). These observations do not, of course, prove that suppression and completion is triggered by an inconsistency outcome of a decision process. It is possible that only a single hemisphere would perceptually complete a half-face even if the half-face in the opposite visual field was its exact mirror image.

However, the question is testable. If a single hemisphere completes a half-face and the other half-face is suppressed, regardless of the congruency of the two half-faces, then single responses to congruent and incongruent half-faces should be equal in accuracy. One perceptually completed half-face would be matched in either congruent or incongruent half-faces.

My students (Evan Bouffides, Devin Shafron) and I are examining these issues in an ongoing study (9 subjects tested to date). Stimuli were constructed from the normal and mirror prints of the left hemiface of nine posers. The normal and mirror prints from the same poser were joined to make bisymmetric composite faces (B faces). Chimeric faces (C faces) were made by joining the mirror print from one poser to the normal print from another. All faces have a narrow strip down the midline that hides the line of joining. The choice array consists of the B faces of the nine posers with a smiling expression (one array) or a sad expression (another array). Half the stimulus faces are B faces with a neutral expression and half are C faces with a neutral expression (72 different chimeras).

Stimulus faces are flashed by tachistoscope at midline (72 C trials/subject and 72 B trials/subject, randomly intermixed). Subjects are told to select the person they saw from the array, and are told they have two chances (two choices) "since the task is so difficult". The purpose of forcing two choices was to determine the frequency of doubly correct responses on C trials. Although subjects were generally unaware that C faces had been included among stimuli, subliminal or "semi-liminal" information could guide responses to one half-face. The frequency of doubly correct trials, though low (12% of C trials), was above chance.

To compare accuracies for B and C faces (first-choice responses), it was necessary to correct for guessing, since the *a priori* probability of a match is only 1/9 for B faces and 2/9 for C faces (either half could be matched). Accuracy for B faces was 69.0% compared to only 37.5% for C faces ($p < .0001$), which were more often RH than LH matches ($p < .001$). Analyses show, moreover, that there was not only a lack of hemi-suppression for B faces, but an actual interhemispheric facilitation.

Where c is the probability of a half-face completion and match, derived from responses to C faces, independent hemispheric processing of B faces would predict that the probability, b, of a match of B faces equals $2c - cc$. However, the mean value of the latter was only 0.583, compared to $b = 0.690$ ($p < .05$, two-tailed).

Since the two halves of B faces were perfectly bilaterally redundant, an interhemispheric facilitatory effect would not be expected if each hemisphere merely relayed, in tape-recorded form, its input to the other hemisphere. Direct and transcommisural information would be identical, and b would simply be the probability that a half-face was encoded by the RH or the LH or both hemispheres — in any of the cases the B face would be matched. As previously discussed, however, the two hemispheres represent different aspects of stimulus information. An integration of the RH's facial code (relational) and the LH's facial code (featural) would lead to a representation more complete and richer in information than either hemisphere could achieve alone. This can explain why $b > 2c - cc$.

Given the significance of effects with only nine subjects tested to date, it seems evident that the hemi-suppressive function is engaged after direct and transmissural information has been compared and found to be inconsistent. If there is bilateral consistency, hemi-suppression does not occur, and, further, the differing, but consistent, RH and LH codes are integrated, which facilitates representational accuracy. The perceptual system evidently suppresses information that cannot be integrated into a self-consistent perception, yet is able to recognize different codes of the same stimulus as consistent and synthesizes these to construct a more complete representation than can be achieved by perceptual completion of one half-face.

Final Comments

Figure 2 shows one item from a set of 36 similar stimuli. The two chimeric faces are printed from the same negative and contain identical information. However, when right-handers are asked which of the pair of faces looks happier, the face with the smile to the left (smile-left chimeras) is chosen on the majority of trials by the majority of subjects (Levy, Heller, Banich and Burton, 1983b). Although the mean attentional asymmetry is to the left (due to differential RH engagement in processing faces), subjects vary widely around the group mean — some choose the

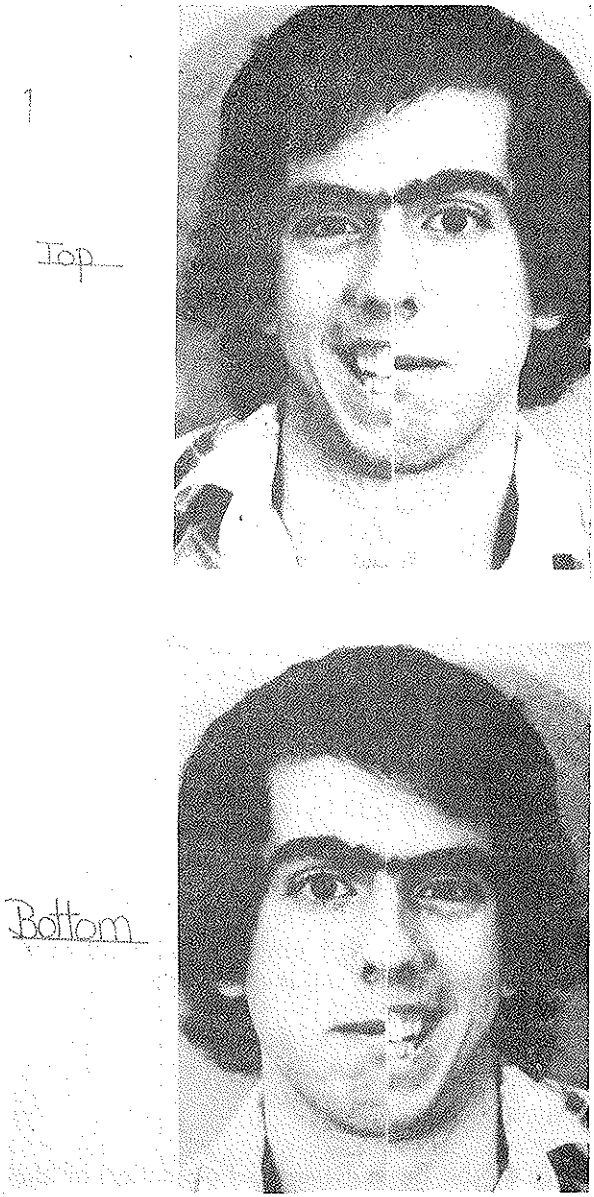

FIG. 2. A pair of smiling-neutral chimeric faces, both printed from the same negative. Subjects judge which of the two chimeras looks happier (from Levy *et al.*, 1983b).

smile-left chimera on every stimulus, and a few choose the smile-right chimera on every stimulus. These individual differences are extremely stable, as shown by strong correlations in attentional-asymmetry scores across repeated measures or on comparable tests with different specific items.

There is, however, one group whose attentional asymmetries are as different between repeated tests as the differences between separate individuals. Ten female patients of Dr. Bennett Braun (Levy and Braun, unpublished) with multiple personality disorder (MPD) were tested in each of four different personalities that Dr. Braun elicited. The personalities within patients varied in characteristic moods (e.g., flat affect, neutral, sad, happy, angry) and in handedness (in seven of the ten patients). The attentional asymmetry scores across personalities within patients were as variable as the scores of different patients. In dramatic contrast to normal individuals, there was simply no stability across the multiple assessments, each of a different personality.

The inference is that individual differences among normal people in attentional asymmetries, although strongly characteristic of the person and very reliable, are not due to implastic variations in brain anatomy, physiology, or chemistry, but arise from dynamic control processes that are very tightly regulated. The dynamics differ between people, but are potentially changeable, since they are changed, and very dramatically, as personalities shift in MPD patients. It is quite evident that the shifts in personalities and attentional asymmetries are not merely passive consequences of uncontrolled changes in neural activity patterns. A request by the therapist is sufficient to elicit the emergence of a personality. We are, of course, our brains, but this self-brain is powerfully self-regulating and self-creating, and in accordance with goals yet to be achieved. An eventual understanding of the neural mechanisms that underlie the regulatory dynamics may well give a scientific meaning to self-determination.

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DISCUSSION

ROLAND

As you correctly stated, it is quite a mystery why, in the normal brain, often homologous regions are activated, that is, they increase their metabolism or blood flow although people seem to be able to do the task with only one hemisphere. What do you think is the reason for this double innervation of both hemispheres in relatively simple tasks?

LEVY

I don't think that there is any human task that you can observe in normal behaviour which only one hemisphere will be involved in processing. I mean, speech is what people think of as the "be all and end all" of left hemisphere existence, but quite clearly studies have shown that the whole modulation of the speech output, the emotional intonation, the coordination with facial expression and gesture, all the communicative signals that we are giving in speech are a highly integrated outcome of both sides of the brain. It's not that the two hemispheres are doing the same thing, but they are making qualitatively different contributions to the task. If you remove the contribution of one hemisphere you can see the depletions in performance. We've emphasized this in the split brain patients. "Isn't it amazing that this isolated hemisphere can do this?" Yes, it is amazing that the isolated hemisphere can do that, but we've not really pressed these patients to the limit and I don't know how far they could go. Vernon Mountcastle asked me the other day, what about creative activities? I doubt very much that if you go beyond fairly well learned algorithms or built-in means of reasoning, these patients could actually make human creative leaps of the type that so impress us and that some of you have manifested already at this conference.

GOLDMAN-RAKIC

The idea of the top down control is very nice and I am not questioning it. I am just wondering whether self-regulation of the hemispheres is the correct terminology when it's really task regulation.

LEVY

Well, I don't like that terminology because task regulation impresses me as saying there is something out there and there is some output here and we go directly from task to muscle. Now, clearly any task effect is being mediated through properties in the brain. So I don't want to call it task regulation because the effect that this task is going to have on the output depends entirely on how this task is being interpreted and represented by the brain. I know you make this distinction, Pat, between memory regulation and task regulation, but I don't feel comfortable with that because it's all brain. It's a matter of what aspects of the brain. I don't think it's a task the brain is setting itself prior to presentation of any stimulus. In the split brain studies it was the nature of the instruction that turned on one or the other side, and I think we can get the same thing in normal people. You can mislead people, normal brains even, into doing funny things.

GOLDMAN-RAKIC

I was just thinking about the phraseology, and just wondering whether the instructions do set the pattern which hemisphere is going to react to the stimulus.

LIBET

I was interested also, above and beyond the behaviour responses, in what the subjective introspective experiences were in some of these cases — for example, the split brain patients that you described earlier on in the talk, seeing one half of a face.

LEVY

They didn't know they saw one half of a face. We questioned them.

LIBET

But you asked them about what they were aware of.

LEVY

Well, I can tell you this. We could talk to the left hemisphere about this thing, not to the right. But when we talked to the left hemisphere we said this

machine sometimes does funny things to the pictures. Do the pictures in that machine look different from these — (these being the whole stimuli and free vision) — do they look different? They would say no. I would say, sometimes, the machine distorts things and makes things look really peculiar. They absolutely denied that. They said, no, they look exactly like these pictures. The perceptual construction was complete. I mean the rules for world building are built in. There's a whole world out there. That's what evolution has said to us and if the stimulus happens to be depleted at mid-line, well, the brain is still going to build a representation according to rules that are built into it and it will take whatever available data there are at the receptors and mould them into a representation that's consistent. Colwyn Trevarthen and Roger Sperry in 1973 published a paper showing that brightness information gets cross-transferred by brain stem and so do certain parts of colour information, and motion information, and orientation information. If we presented orientation information, motion information, colour information, brightness information, then we could get cross-transfer between hemispheres, but not shape.

DESMEDT

I wish to congratulate you for bringing up this complex cognitive approach which I think is also very important in relation to the intact patient. When you emphasize the pre-preparation of the brain in anticipation, and at the same time the right parietal area role in the arousal control, what is the relationship that you see between the prefrontal that Patricia has been talking about and the parietal in relation to the setting of priorities and the decision about what is going to be the target?

LEVY

I think that in the next 10 years, there is going to be evidence coming in that this prefrontal region that Pat was talking about plays a special role in the left hemisphere in controlling preparation for motor action and that the right hemisphere parietal region is playing a special role in processing sensory input, and that these two regions specialized in opposite hemispheres are in fact playing a collaborative role in setting the brain at all stages from sensory input to motor output. We are beginning to investigate this question looking at the left hemisphere role in preparation for motor action.

DESMEDT

And the parietal lobe would support this in a more general and prolonged way, you think?

LEVY

Yes, because I think that when a particular motor act is being prepared, the facilitation for that particular set of motor outputs is not maintained over long intervals. It would be very maladaptive if we went into paralysis for 12 seconds waiting to move a finger. I think that the motor system is much more transient and dynamic in control. But very often in preparing for stimulus input, we do have to sustain this kind of focused alertness over fairly long periods. So I expect that we are going to see different properties.

DEECKE

Only a short comment. When you showed the chimeric faces in the beginning, you showed that the right face has a stronger emotional impact on the observer. This we take into account subconsciously. It has been shown that if you analyze or mimic facial expression or movement, that we do it a little bit stronger with our right side of the face.

LEVY

You mean left side of the face?

DEECKE

No, my right face as seen in the left hemisphere.

LEVY

True, but there are motor asymmetries too, and emotion is expressed more intensely on the left side of the face, which is a less attended field so that adults can hide, if they choose, emotions from the person they are communicating with. This facial asymmetry of emotional expression changes developmentally. In the infant, it's right asymmetric, passes through a period of symmetry and by age 7 reverses to the left asymmetry just when you need to start hiding emotions from the one you are interacting with.

SOME CONSIDERATIONS ON LANGUAGE AND THE BRAIN

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Introduction

Language is a species-specific system of signs or symbols and of rules that govern the concatenation of these symbols. The basic elements of language are words that are made up of phonemes and morphemes. Words are concatenated into sentences according to syntactic and semantic rules. Language is a supramodal system. It embraces oral expression and auditory comprehension and also secondary modalities, i.e., writing and reading. In some people it is expressed and understood by means of sign language (see below). Even though animals are capable of intelligent behavior, it seems to be the case that they do not possess representational and communicative systems comparable to language.

Systematic impairment in the use of language is called aphasia. By the term "systematic" it is intended to exclude deviations from standard language use that are due to defective motor processes (e.g., the variants of dysarthrophonia), to mental retardation, acquired mental illness or cognitive disturbances other than linguistic deficits.

Most, but by no means all of our knowledge on the relation between language and the brain stems from the study of aphasic patients. For purposes of diagnosis and treatment, to a large extent also for research projects, the language performance of aphasic patients is assessed by standardized psychometric tests. In our group we have developed the Aachen Aphasia Test (AAT) (Huber *et al.*, 1984) (Table 1). This test

TABLE 1

AACHEN APHASIA TEST (AAT)

PART OF THE TEST	Constituents		Scoring per scale/item
1. SPONTANEOUS SPEECH	6 scales		0 - 5
2. TOKEN TEST	5 parts	10 items each	0 - 1
3. SUBTEST REPETITION	5 parts	10 items each	0 - 3
4. SUBTEST WRITTEN LANGUAGE	3 parts	10 items each	0 - 3
5. SUBTEST CONFRONT. NAMING	4 parts	10 items each	0 - 3
6. SUBTEST COMPREHENSION	4 parts	10 items each	0 - 3

was produced for the German language. It has been adapted to the Dutch, Italian, English and French language, which will not only foster comparability of test results across research groups but also permit cross-cultural studies. With a view to studying also very mild language disturbances and special phenomena by psychometrically valid methods, we have further developed 4 supplements to the AAT that assess Multimodal Matching and Naming, Lexical Discrimination, Dyslexia, Understanding of Syntactic constructions (Poeck and Göddenhenrich, 1988). On the basis of test results, the majority of aphasic patients are allotted to one of the Standard or Non-Standard Syndromes of aphasia (Table 2).

Problems and Virtues of Aphasia Classification

Many researchers classify aphasic patients according to certain syndromes. The classification as Standard or Nonstandard is made according to frequency of occurrence (Nonstandard Syndromes are rare) and also to the greater or lesser coherence of the constituting symptoms. Table 3 gives the characteristic features of the Standard Aphasias.

The wisdom of classifying aphasic patients according to syndromes has been challenged by some researchers in the field of psycholinguistics and neuropsychology. They maintain that the aphasic language disturbance displays a large variety of individual differences across patients to the effect that what is described as aphasic syndromes is regarded as an artifact and the product of traditional preconceptions. It is felt that the grouping together of patients in broad categories tends to level out essential

TABLE 2

STANDARD APHASIAS (VASCULAR ETIOLOGY)
GLOBAL APHASIA
BROCA'S APHASIA
WERNICKE'S APHASIA
AMNESIC APHASIA
NON-STANDARD APHASIA (MIXED ETIOLOGY)
CONDUCTION APHASIA
TRANSCORTICAL APHASIA

features of the individual patient which might be the clue to a better understanding of the organization of language in the brain.

However, if one examines a large number of aphasic patients, it becomes obvious that these patients can be divided into certain groups. The patients within a given group share many important features of language behavior. Of course, not every patient in a group displays the whole set of symptoms held to be characteristic for the group, but sufficiently many symptoms can be assessed to assign the patient clearly to "his/her" group (Poeck, 1983).

The characteristic syndromes are found in about 75% of brain damaged patients with aphasia. Most of these are the patients with cerebrovascular accidents (CVAs) in circumscribed territories of the middle cerebral artery. Two of the standard syndromes are related to ischemic lesions in the territory of well-defined arteries. Broca's aphasia may occur when the prerolandic branch, and Wernicke's aphasia when the posterior temporal branch of the middle cerebral artery is affected. Global aphasia frequently indicates an occlusion of the main stem of the middle cerebral artery with total softening of its territory. There are observations, however, showing that the lesion in global aphasia can also be small (Poeck, de Bleser and Graf von Keyserlingk, 1984). There are exceptions to the expected lesion localization for the other syndromes as well (Basso *et al.*, 1985; de Bleser, 1988). The syndrome of amnesic aphasia does not have a distinct vascular correlate. It is a frequent aphasic syndrome when the etiology is not a CVA, e.g., in patients harbouring a brain tumor, in traumatic aphasia and in the initial stage of Alzheimer's disease.

TABLE 3 - *Classification and cardinal symptoms of aphasic standard syndromes.*

	Amnesic aphasia	Wernicke's aphasia	Broca's aphasia	Global aphasia
Language production	fluent	fluent	nonfluent	very much reduced
Articulation	usually undisturbed	usually undisturbed	often dysarthric	often dysarthric
Prosody	usually well preserved	usually well preserved	often flat, scanning speech	often flat, well preserved only in recurring utterances
Syntax	no disturbance	paragrammatism	agrammatism	only single words stereotypes
Lexicon	word finding difficulties with and without compensatory strategies, some semantic paraphasias	many semantic paraphasias occasionally wild paraphasic misnaming semantic jargon	restricted vocabulary few samantic paraphasias	reduced repertoire of automatized elements
Phonemic structure	some phonemic paraphasias	many phonemic paraphasias and neologisms phonemic jargon	many phonemic paraphasias	predominantly neologisms
Comprehension	mildly disturbed	severely disturbed	moderately disturbed	severely disturbed

These observations suggest that the existence of aphasic syndromes does not faithfully reflect inherent principles of language organization in the brain. Rather they suggest that we would not know of Broca's or Wernicke's aphasia as they are described in the literature if the vascularization of the cerebral hemispheres were different.

Also, the contemporary definition of syndromes is in expressive terms. There is no counterpart in language comprehension. Language under-

standing involves pragmatic and cognitive factors like situational knowledge, the arousal of semantic and association fields by words and the ability to draw inferences from the communicative context. Comprehension, in contrast to production, depends more on linguistic strategies than on regularities.

It follows that aphasic syndromes are, in a way, artifacts produced by the vascularization of the language area in the left hemisphere. They are, however, useful artifacts because the distribution of the branches of the middle cerebral artery shows only little interindividual variation. Patients with aphasia post stroke are clustered very strongly in well-defined subgroups. This is very useful if one conducts group studies which, again, are indispensable if one wants to know whether observations in single cases can be generalized: "In all sciences we are being progressively relieved of the burden of singular instances, the tyranny of the particular" (Sir Peter Medawar, cf. Watt W.C., 1988).

Localization Issues: The Role of the Nondominant Hemisphere

The relation of language performance to brain structure has been amply discussed in terms of left hemisphere localization and its development. I do not intend to reiterate here the well-known facts and hypotheses. Rather, it might be useful to consider the lesson that might be learned from the study of language functions of the nondominant hemisphere. These have been investigated along various lines: *hemispherectomy* in infancy, *hemispherectomy* in adult age, *surgical disconnection* of the two hemispheres, language disturbances after *circumscribed right hemisphere lesion*, and *recovery* in cases of severe aphasia after left hemisphere (LH) lesion. The results of dichotic listening experiments and of stimulation experiments will not be considered here. The various lines of evidence do not converge and there does not emerge a coherent picture of the linguistic endowment of the minor hemisphere.

Language after Dominant Hemispherectomy

Hemispherectomy evidence is scanty and controversial with regard to language functions. The main reason obviously is that dominant hemispherectomy has mostly been performed as surgical treatment for intractable epilepsy in patients with perinatal damage to the LH. These patients had either sustained the injury before acquiring speech or during

the process of speech acquisition. French *et al.* (1955) rightly note that "the hemisphere removed is always the nondominant since these patients suffered their loss of function many years previously". Also, hemispherectomy in children often results in decrease of number of seizures as well as improvement in behavior. It is hard to assess to what extent these two factors might influence overt language behavior. The situation is different in adults.

The largest series of hemispherectomy in infancy has been published by Basser (1962). Unfortunately, this author has investigated language functions only by means of the Wechsler Intelligence Test, and the report on the faculty of language is based on a comparison of the verbal vs. the performance scale of the Wechsler Test. This is, of course, a rather global method of assessing linguistic performance.

Gott (1973) reported on a 12-year-old girl who had developed a malignant brain tumor that probably had started growing by the age of 11. At 12 years of age this girl underwent left hemispherectomy. Postoperatively she was able to follow commands, to give proper "Yes" or "No" answers to declarative statements, and her verbal intelligence measured by the Peabody Picture Vocabulary Test was 70.

Dennis and Whitaker (1976) have studied the language development of three 9 and 10-year-old children who had undergone removal of one hemisphere prior to the manifestation of expressive speech. In other words, these children had acquired speech and language with only one hemisphere. None of the children had seizures. The authors found that in the two isolated hemispheres (one left, two right hemispheres) phonemic and semantic abilities were similarly developed. Syntactic competence, however, had been asymmetrically acquired. The right hemisphere (RH) was deficient in understanding spoken language, especially when meaning had to be extracted by syntactic operations. This syntactic impairment was demonstrated in production, repetition, comprehension, awareness of anomaly and judgements on relatedness of words. LH specialization for processing syntactic relations is more prominent than for other categories of language.

It emerges that the age beyond which speech functions cannot be satisfactorily acquired by the opposite hemisphere is variable and has not been sharply determined. Ogden (1988) has suggested that the time course after operation might be an important factor. She examined her two subjects 28 and 16 years after left hemispherectomy and found their language functions to be close to normal.

There are very few reports on hemispherectomy in adults, performed because of the presence of a large malignant brain tumor (Zollinger, 1936; Crockett and Estridge, 1951; Smith and Burklund, 1966; Smith, 1969). Receptive language functions were reported to be less impaired than expressive speech. Speech output remained limited to single utterances, to swearing and some degree of singing.

RH Language in Split Brain Patients

Evidence from Split Brain studies is more equivocal than would have been anticipated. There are too many variables in these patients that are ill controlled. The most important are the quality and duration of the brain lesion that necessitated the commissurotomy and the pattern of brain organisation prior to the operation. Given that the influence of these parameters remains obscure in most patients, there is a great degree of uncertainty as to what extent the findings can be generalized.

The first reports revealed a very limited language capacity of the isolated RH. The patients had some comprehension of simple nouns, very little ability to process verbs and short sentences. The ability of the RH to process syntactic structures appeared extremely limited.

Zaidel (1978), however, was able to demonstrate that the LH could analyze the spoken input into its phonemic components. At the semantic level, Zaidel found the RH to be inferior to the left but the difference was relatively small. The disconnected RH seemed to have access to a substantial auditory vocabulary. Very remarkable was the finding that the performance of both hemispheres showed the same dependency on word frequency that is seen by normal and aphasic adults and in normal children. Word frequency effects are taken to reflect the impact of linguistic experience.

Gazzaniga (1987) has recently expanded previous studies. He had observed that there are split brain patients whose RH possesses a remarkable degree of language capacity. He found that patients with right hemisphere language representation had a much more responsive right brain. The capacity to respond both to language and nonlanguage stimuli was surprisingly high. The patients made perceptual judgements, e.g., same/different judgements, in various modalities. In tests of facial recognition the RH in these patients was superior to the LH. The patients were able to establish within their RH subordinate and superordinate relationships between concepts presented as line drawings. However, the RH was

unable to make inferences, for instance, that pin and finger should result in the answer bleed. Also the RH was rather poor on simple mathematical problems. Gazzaniga has concluded that, even though the language system is not able to perform cognitive activities, language is a data structure called upon to label and express the computations of other cognitive systems.

Affective Language and the RH

The organization of affective components of language in the RH has been the object of recent studies. These functions are discussed under the heading of *prosody*. Prosody has two communicative functions. It gives an emotional blend to a spoken utterance, e.g., sadness or joy, and it conveys linguistic information, e.g., the distinction between a question and a command by means of the intonation contour of a sentence or the differentiation between noun and verb by word stress, e.g., cónvict and convíct. It has been proposed that the first aspect is associated with RH functions.

The concept of RH dominance for the emotional quality of language had been forwarded already by J.H. Jackson (1879). It has found support in dichotic listening studies suggesting that music and other nonlanguage sounds are mediated by the RH (see Kimura, 1967). Tucker *et al.* (1977) reported that patients with right temporoparietal lesions did have a comprehension deficit for emotional qualities of language but were also impaired in the ability to evoke affective tones.

In a series of papers, Ross (Ross and Mesulam, 1979; Ross, 1981; Ross *et al.*, 1981; Wolfe and Ross, 1981; Gorelick and Ross, 1987) has elaborated on these observations. He has even proposed a differential localization within the RH for the organization of distinct affective components of language. He hypothesized that the organisation of affective speech in the RH might be similar to the organisation of propositional speech in the LH.

Studying spontaneous prosody, prosodic repetition, prosodic comprehension and comprehension of emotional gesturing in 10 RH-damaged patients with varying loci of lesion, Ross described motor, sensory, global, conduction, transcortical motor, transcortical sensory, mixed transcortical and anomic aprosodia as well as pure prosodic deafness and ascribed a differential RH localization of lesion to most of these syndromes.

A patient with motor aprosodia who died did not show the proposed

pathology in the RH equivalent to Broca's area in the LH. Rather, he had bilateral lesions in the internal capsule, larger and more recent on the right side. To account for this discrepancy Ross assumed some kind of cortico-reticular formation disconnection. Another case showed clinically the so-called sensory aprosodia associated with left hemiparesis, though right hemiparesis is an unusual accompaniment of Wernicke's aphasia after left superior temporal lesion (Wolfe and Ross, 1987). On CT scan the patient had a recent infarction involving the right thalamus and the posterior limb of the internal capsule. This observation was interpreted as corroborating subcortical participation in the RH mechanisms of affective speech (but see the critique referring to PET studies as mentioned below). A recent paper of Gorelick and Ross (1987) reiterates the views advocated by Ross on the basis of 14 new observations.

These reports and theoretical considerations are attractive even though the strict correspondence of the varieties of aprosodia and the clinical syndromes of aphasia appears a bit too striking, as does the perfectly fitting localization. Also, the concept of RH dominance for the prosodic quality of speech is very much at variance with the experience on aphasic language disorders upon LH lesions. Reduced prosody, in fact, is a cardinal feature of Broca's and of global aphasia, in other words, in the great majority of patients with aphasia due to an ischemic LH brain lesion. What is missing are control studies comparing the effect on prosody of LH and RH lesions of homologous localization. Also, instead of bedside tests evaluated according to impressionistic criteria, objective phonetic measures of sentence contours are required.

Is Recovery from Aphasia Mediated by the RH?

The contribution of data on recovery from aphasia to the knowledge of RH language functions has remained purely speculative. Traditionally, there are two hypotheses on recovery processes in LH brain-damaged aphasic patients, i.e., reorganization of LH function or activation of an assumed RH language potential. For methodical reasons none of these two (competitive? complementing?) hypotheses has been supported by factual observation.

Some authors have maintained that the inborn language potential of the RH is constrained by a tonic inhibitory influence of the LH (Moscovitch, 1976; Poeck, 1979; Hartje, 1982). If this inhibition is abolished

by a LH lesion, by hemispherectomy or by commissurotomy, the RH language potential is liberated.

Loss of reacquired language after a second infarction in the territory of the right middle cerebral artery or following a right-sided Wada procedure (Kinsbourne, 1971; Czopf, 1972) is an ill chosen example because acute RH damage, in addition to chronic LH damage, might produce some kind of decerebration syndrome over and above effects on language functions only.

All these considerations leave out the possibility that hemispheric specialization might be quite variable across individuals, which would introduce an uncertainty that could not be overcome by experimental settings.

The Role of LH Subcortical Nuclei

There is general consensus that processing of language has some degree of functional localization at the cortical level. Also, it has to be expected that lesions of associative pathways produce language disturbance by disconnecting cortical areas. Before discussing this level I should like to briefly highlight the problems involved in the premature description of subcortical aphasia due to lesion of the basal ganglia and thalamus.

The idea that the deep nuclei participate in language functions is not new. As early as 1965 Krayenbühl *et al.*, on the basis of stimulation experiments, asked the question "Is there a dominant thalamus?". In recent years, disturbances of speech and language have been described upon lesion of thalamus and basal ganglia. Basically, these were quite similar to the syndrome that Luria has described as "dynamic aphasia". Many of these patients are mute or nearly so. Yet, they comprehend even complex sentences. When they are asked to repeat, they speak without effort, with good articulation and prosody, and they are able to repeat quite long sentences. One has to suspect that the underlying deficit is one of motivation and drive rather than of linguistic functions, similar to cases of "dynamic aphasia" after lesions of the SMA.

There are, however, patients who do have a linguistic deficit. Some authors, e.g., Naeser *et al.*, 1982 have gone so far as to distinguish various syndromes of aphasia due to basal ganglia lesion, e.g., a more nonfluent anterior and a more fluent posterior putaminal aphasia.

An important review is published by Cappa *et al.* (1983). The authors refer to work on aphasia associated with lesions in the putamen, the

caudate nucleus and the anterior limb of the internal capsule. They warned, however, that the significance of these findings must be evaluated with caution. This warning is fully justified if one considers the data published by Mazziotta and Phelps (1986) and Perani *et al.* (1987). These papers give examples where on the CT scan a deep thalamic or basal ganglia infarction is visualized, whereas metabolic studies show extension of the functional lesion to the entirety of the ipsilateral basal ganglia and a part of the cortical language area. Also in our personal experience 4 out of 9 patients with ischemic infarction in the lenticular nucleus and basal ganglia had hypometabolism extending to the cortex when examined with the SPECT technique. Three of these patients were aphasic.

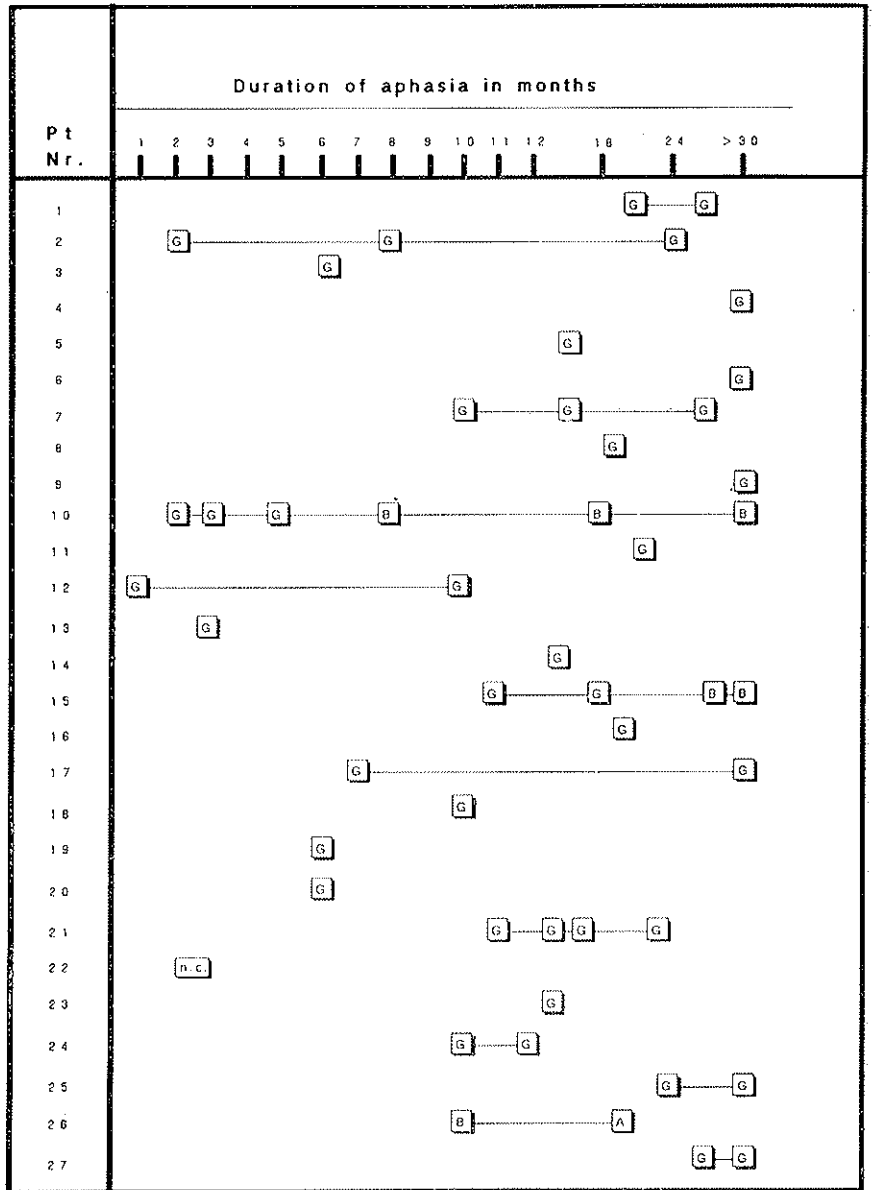
What is Established about LH Cortical Organization of Language

I am not going to review the abundant number of studies on this topic that are based on static imaging methods (CT scan and Magnetic Resonance Imaging). The findings are most controversial and the more it was attempted to demonstrate "the typical underlying lesion" the less the findings were supported by other researchers.

The many discrepancies in this field have induced us to study the thorny localization problem by further considering an aspect that has been widely neglected so far, i.e., time post onset. This time period reflects the spontaneous and/or therapy monitored evolution of the aphasia syndrome. So far we have analyzed only the data for Global, Wernicke's and Broca's aphasia (Thyssen and Willmes, 1988). It was found that initial presentation of an aphasic patient with the syndrome of Broca's aphasia is a very rare event. Rather, Broca's aphasia emerged several months post onset in patients that had originally been classified as global aphasia, and the CT lesion in these cases included the anterior branches of the MCA with or without affection of the basal ganglia (Table 4).

Is it reasonable to expect that language functions are precisely localized? In contrast to the expectations voiced with the advent of imaging methods, that these might permit the *in vivo* localization of brain lesions also for research purposes, progress in this area must be viewed with caution. Certainly, there is some localization of function, and the concept of a holographic representation (Pribram, 1971) has not been supported. On the other hand, there is no distinct localization in the sense that one and only this one lesion gives rise to a particular syndrome. Also, it has not been possible to localize certain symptoms within a

TABLE 4



Evolution of Global to Broca's aphasia in 27th pts with large infarction in the entire territory of the MCA .

syndrome which might give some suggestions for the brain localization of certain language functions.

This is not surprising if one envisages a network organization of psychological functions as it has been described for motor or sensory functions. Performing, e.g., a linguistic visual naming task does not only involve simple visual and verbal functions, both considered as unitary in the first disconnection concept (Geschwind, 1965). Rather, it requires the interplay of complex chains of events including attentional, motivational, cognitive, nonverbal as well as verbal memory functions with semantic and phonological processes. This is even more true in communication situations where the task is not, like in a formal aphasia test, to identify more or less isolated linguistic units but rather to process long pieces of discourse. Here, in addition to linguistic performance, pragmatic knowledge and insight, and processes of inference, deduction and problem solving are called upon. In other words, the communicative use of language requires linguistic and nonlinguistic cognitive performance.

Today, neuropsychological research is less interested in numbers of errors. These just provide the material for further investigation that is focussed on quality of errors and underlying processes and on the relation between aphasic language and modern theories of normal language. This shift of emphasis has somewhat attenuated the interest in the localization of psychological function. The basic principle governing the relationship of language and the brain in my view is operations and not localizable elements. Distinct localization of partial processes is not expected in the near future.

The association of language disturbance with LH damage and the differential pattern of linguistic deficit related to different loci of brain lesion in many (but not in all) patients raises the question: what is the nature of the processes that are lateralized and to a certain extent localized?

The linguistic functions in question are certainly supramodal. They involve spoken as well as written language and also sign language acquired by congenitally deaf people. Poizner, Klima and Bellugi (1987) have analyzed the way linguistic elements, including syntactic structure, are expressed and understood on the basis of hand, arm and finger movements in threedimensional space in American Sign Language (ASL). Users of ASL display almost all the features of spoken language, phonology, inflectional and derivational morphology and complex syntax. The authors have also studied the effect of lateralized and circumscribed brain lesions, 3 in the LH, 3 in the RH, on sign language, on praxic movements, and

on visuo-spatial performance in users of ASL. To this end, they have adapted test procedures taken from the Boston Diagnostic Aphasia Examination (Goodglass and Kaplan, 1983) and other standard neuropsychological tests. They have found that right-sided brain damage produced the deficit in nonverbal spatial processing that is known when brain lesions afflict speaking individuals. However, notwithstanding the important spatial component in ASL, there was no ASL aphasia in these patients. In contrast, LH damage made ASL users aphasic. There was even an association of an anterior lesion with laborious nonfluent, agrammatic sign language in the presence of good comprehension and of a posterior lesion with fluent paraphasic, even neologistic and paragrammatic expression and severe comprehension deficit. These deficits could not be accounted for by spatial disturbance or apraxia.

From these observations it may be concluded that what is organized in the LH is linguistic operations, independent of the modality where these are processed.

For a study on the structure of language processes it is worthwhile to consider further the interdependence of linguistic and cognitive operations. Are language and the various aspects of cognition potentially autonomous domains? Do both domains just provide the input for the actual operations the result of which we call language performances? Is the language area the place in the brain where these operations are computed? Tho what extent are cognitive processes dependent on linguistic operations? What is the effect of a semantic memory disturbance on language production and comprehension (see Poeck and Luzzatti, 1988)? Can a disturbance in working memory adversely influence certain linguistic modalities, e.g., repetition, but also spontaneous production and comprehension? Considering the complex wiring required for the interplay of these and other reciprocal processes, the question must be asked again what the functions are that are expected to be localized in the language area. One candidate might be syntax, including word morphology.

If chances are poor on the whole to elucidate the relation of language and the brain on the basis of lesion localization, this is certainly not unique for language. It has been proposed (Mesulam, 1981) that attentional processes are subserved by a cortico-subcortical network connecting the following structures: frontal cortex, thalamus, basal ganglia, parietal cortex. Also, spatial orientation or praxis have no distinct localization,

even though, similar to language, hemispheric specialization and gross intrahemispheric localization are known. My prediction is that insight into the organization of language functions will be gained by functional investigations. In particular, the possible interdependence of linguistic and other cognitive operations might be a central issue in future brain and behavior research.

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DISCUSSION

INGVAR

I'd like to emphasize the point that you made, namely that the lesions that you see in the morphological superposition techniques of MR and CT are usually much, much smaller than they are on Pet or on CBF studies. It is the functional defect that we have to base our analysis of speech defects upon.

The second comment I had was on aprosodia. I follow you indeed when you criticise Ross for his wild systematization of the aprosodias into sensory and motor aprosodia, and so on. We have just completed a study of single or solitary right-sided lesions and studied with new and sensitive tests the ability of people to understand words and tonal actions and emotional expressions. There is no question that you need quite some sensitive tests to pick up these things. But most of our right-sided lesions showed positive findings in these tests. We could not find any evidence for the Ross idea of motor and sensory aprosodia, but to us there's no question that the right hemisphere has something to do with the intonation and also the emotional comprehension.

POECK

Effects of right hemisphere lesions on prosody were described more than a hundred years ago. I only objected to a too extensive differentiation.

INGVAR

Yes, I may add that it's especially the posterior part of the right temporal lobe that seems to be involved in comprehension of these messages.

FREUND

We have recently studied two patients with hemispherectomies that had been performed at the age of 21 and 23. In one patient, the right, and in the other, the left hemisphere was removed. What struck us was the fact that in both patients, from everyday observation, you could not recognize a language disturbance whatsoever. The excised hemispheres, which had been investigated

by neuropathologists, had shown only relatively small lesions which gave rise to intractable epilepsy. So I wonder whether small lesions in the dominant hemisphere can give rise to the shift of large functional faculties to the other hemispheres. I might add that deficits on the cognitive and performance level in these patients were also amazingly well compensated.

POECK

I can only speculate on this, and this speculation points again in the direction of the difference between the anatomical and functional lesion. You have a small anatomical lesion, but if you do a PET scan, you may have a hypometabolic state over the entire hemisphere, and this may remain so for the rest of the person's life.

SINGER

There was recently a report in "Nature" (Warrington) on a very selective loss of semantic fields where the whole animal kingdom was gone and the rest was very well preserved.

POECK

I have some problems accepting that semantic fields are organized in little boxes, as much as I am sceptical about the results in electrical stimulation experiments by Whitaker and Ojemann where stimulation of one part of the brain abolished naming in French, and of another adjacent part, abolished naming of the same object in English. It's a bit against my philosophy of how the brain might work, but this might be a wrong idea.

JONES

One of the things that has always puzzled me somewhat is that it is relatively rare to find descriptions of aphasia following thalamic lesions. This has always seemed counter-intuitive in view of the close couplings between thalamus and cortex, and in view of the parallelism that occurs in cortical specialization and cortical differentiation in parallel with thalamic specialization and differentiation. One might imagine that the disconnection of a piece of thalamus from its relevant piece of cortex, in Broca's or Wernicke's area, ought to deactivate that cortex. Now I have always figured out that probably

this means that we have just never had very good thalamic lesions. A pure thalamic lesion is very rare, and small ones are even rarer. So it seems not very surprising that this has not been uncovered. You are a little dismissive of the thalamus, I think, perhaps not quite as dismissive as you were of the basal ganglia. But really I think what you gave to me was another idea on what the thalamus might be doing here, because in introducing this concept of thalamic regions creating a dynamic aphasia, you may well have put your finger on what it really is that the thalamus is doing in relation to the cortex. It may well be recruiting the cortex under particular conditions.

POECK

I would fully subscribe to that.

CREUTZFELDT

Can you be somewhat more specific about the extent to which the temporal and parietal speech areas depend on their input from the thalamus? If you can produce the same type of functional defect by a thalamic lesion as after a cortical lesion, then this could indicate that the thalamic input is necessary and that of association fibres is not sufficient. What is the thalamic contribution, and what is the association fibre contribution? Can you distinguish between these?

POECK

I answer with a question. Would you expect to find a patient with an appropriately placed thalamic lesion with aphasia and who in metabolic studies does not show insular and cortical involvement? No I wouldn't, and you wouldn't either. So if we consider the complex wiring, and you can consider a very simple wiring, back and forth, then it's not surprising at all that we find aphasia after thalamic lesions, in those cases where the appropriate nuclei are damaged.

ROLAND

This is a little bit along the same line. I was very impressed once with the experiments of Ojemann where they stimulated for instance the po-nucleus and found amnesic aphasia, which subsided as soon as they cut the current

off. Of course I totally appreciate the fact that the po does actually project to the motor cortical areas, and to Broca's area as well, and that might be the cause of the effect. Now still I cannot get away from the idea that the thalamus is involved in the production of normal speech, and there are studies from Heiss' group in Cologne which showed that the thalamus is actually active during normal production of speech, and so are the basal ganglia. Then, what is the role of these structures? I don't think that you can claim that the basal ganglia are recruiting the cortex. If they are doing so, they are doing it via the thalamus. So what is the role then in speech?

POECK

In speech you have activation even of right motor areas, which is quite natural because you have bilateral input to the articulators and entire areas of the motor system have to be activated when you start speaking, even prior to speaking.

ROLAND

Did you ever observe any size principles in studying pure cortical lesions, so that a small lesion only affecting the Broca area would be co-existent with totally normal performance in your aphasia tests? Did that ever occur? As you know, the lesion in Broca's case involved the whole inferior frontal gyrus.

POECK

Well, this is a controversial issue. In his paper on the brain of demented old people, Tom Linson and collaborators said that if you lose 150 cc of your brain then you are demented, and if you lose 60 cc of your brain then you are very likely to be demented and Alan Rubens *et al.* maintain that if you lose 60 cc of your left-sided area of the middle cerebral artery then you will be very severely aphasic. It might be. I can only say it has been claimed. It is a little bit in contradiction to our findings on global aphasia. I showed this slide where there were very small lesions associated with very severe aphasia. So all these considerations appear a little simplistic to me. It might not be important how much brain tissue is gone, but which brain tissue, and which are the pathways it is going through.

ANDERSEN

I wonder whether you would comment upon the fact that you had rather variable involvement of cortical lesions in these aphasic patients, and correlate that to the finding of Gschwind from Boston on eight patients who were dyslexic. He found a large amount, about 100 small patches spread across the whole cortex and usually confined to the upper cortical layers with completely disorganized neuronal tissue and pial ectopias, which sort of suggests a developmental disorder. They were predominantly located on the left side, and mostly in the Broca and Wernicke areas, but also outside.

POECK

I realize that this is an important question but I am unable to give a decent answer because we have never studied dyslexic children, let alone their brains. So I can just trust Gschwind and say, if he says so, probably it is that way. I have no personal experience and it has not been studied by others as far as I know.

NEURONAL RESPONSES IN THE HUMAN LATERAL TEMPORAL LOBE TO SPEECH

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INTRODUCTION

The lateral human temporal lobe receives thalamic afferents from the medial geniculate body and the pulvinar, and association fibres from the prestriate cortex and the frontal lobe. The primary auditory cortex is located in its most dorsal parts, while the more ventral aspects are considered as auditory and visual association areas. The caudal perisylvian cortex on the language dominant hemisphere is part of Wernicke's area and necessary for a variety of linguistic functions such as understanding of spoken language, naming and speaking. The function of the rostral portion, the temporal pole, is not known. The intermediate portion, below the motor and somato-sensory cortex, contains auditory and visual association fields (for details and references see Creutzfeldt, 1983). The auditory association cortex is thought to be confined to the superior temporal gyrus (Galaburda and Sanides, 1980), while the middle and inferior temporal gyrus are considered as visual association areas, homologous to the infero-temporal cortex of subhuman primates.

During temporal lobe surgery under local anesthesia in conscious humans, who gave their informed consent to this investigation, we had the opportunity to record with microelectrodes the activity of single neurons or groups of neurons in various locations of the right and left

temporal lobe convexity during auditory, visual and linguistic tasks. As microelectrode recording is an invasive technique, it was restricted to brain tissue which, after electro-corticographic and functional exploration with electrical stimulation, was subsequently to be resected. This, of course, precluded recordings from Wernicke's language area, *sensu strictu*, of the dominant hemisphere. With these constraints, our analysis included microelectrode recordings predominantly from the lateral surface of anterior, superior, middle and inferior temporal gyri, with a few recordings from the posterior third of the superior temporal gyrus of the non-speech dominant hemisphere (fig. 1 A, B).

Details of the methods for recording, stimulation and other circumstances have been described elsewhere (Ojemann *et al.*, 1988; Creutzfeldt *et al.*, 1989). Formal auditory stimuli consisted of 20 to 30 words or short sentences which were presented from prerecorded tapes by a studio cassette recorder placed about 1-1.5 m in front of the patient's face at an interval of 3-5 sec between words. The loudness was adjusted so that it corresponded to the loudness of a normal speaker (60 dB sound pressure). In addition, activity was recorded during conversation such as specific instructions, information exchange between the surgeon and other persons. Noises and conversations not related to the tests were kept to a minimum, but could not be avoided completely. They were recorded as well and were often useful as control stimuli.

Results

Single units in the lateral temporal lobe usually do not respond to inadverted noises in the operation room, but conspicuous activity changes related to speech were frequently observed either during listening to the tape-recorded words or sentences, to informal speech (instructions) or when a patient spoke himself.

All *superior temporal gyrus* recordings clearly showed such speech related responses to words or sentences presented by a tape or informally, and when the patient spoke himself (see fig. 1 C). An exception were some rostrally located sites in or near the *temporal pole*, of which only one showed a significant excitatory response during informal speech and patient speaking. Responsiveness of *middle temporal gyrus* neuron activity to speech sounds was much less conspicuous. In fact, only one recording showed a clear excitatory response to tape-recorded words,

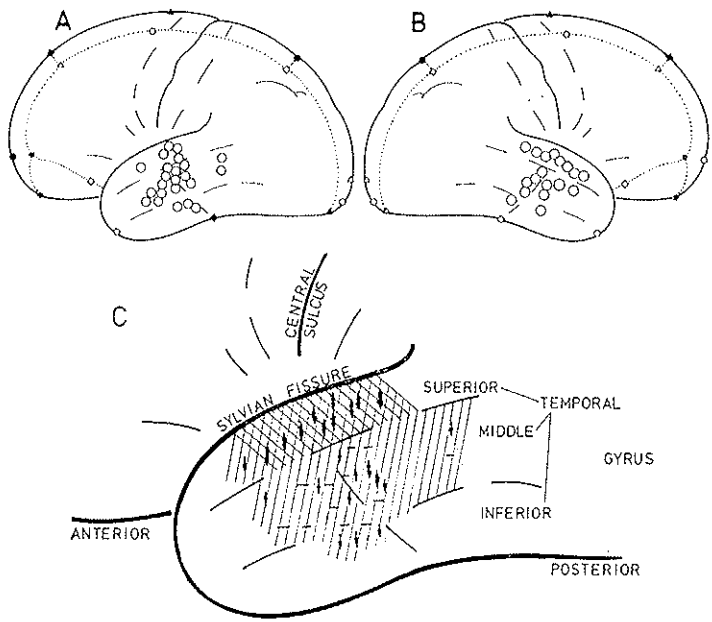

FIG. 1. A, B: *Schematic drawing of the left and right hemisphere.* Sites of microelectrode recordings are marked by circles. The number of recording sites (41) is larger than the number of patients (34), because in some patients recordings from different sites were taken in succession (e.g., middle and superior temporal gyrus, respectively). Successive recordings or simultaneous recordings of several units with one or two microelectrodes at one site are represented as one site. C: *Schematic representation of response distribution over the temporal lobe to auditory language signals.* Data from right and left hemisphere are drawn into one (left) temporal lobe. Symbols indicate the predominant response at one recording site, independent of whether only one single unit, multiunit activity, or several units were recorded simultaneously or successively. Recording sites in which auditory responses to language were not tested or where units could not be sufficiently discriminated are not included. *Symbols*: ↕ strong and specific modulation of activity by spoken language (for details see text). ↓ only suppression of spontaneous discharge rate, ↑ only slight activation, — no response. The region with predominantly strong responses is cross-hatched, that with weak responses is marked with diagonal lines.

two showed a slight excitatory and six a slight inhibitory modulation of discharge rate. In ten middle temporal gyrus recordings (60% of the sites with successful recordings), the unit activity was unresponsive to speech signals from outside. When the patients spoke themselves (repeating words, naming, answers) middle temporal gyrus recordings were more frequently affected. Three of the five *inferior temporal gyrus* recordings showed a slight suppression during speech, while two responded with a

slight suppression and one with a slight activation, when the patient spoke himself.

Some units in the superior temporal gyrus appeared to be specifically responsive to certain phoneme categories. An example is shown in fig. 2 A, from the right superior temporal gyrus of a female patient. This unit substantially discharged during some words of the list (words 1 and 7 in this figure), only during some syllables in others and did not at all respond to the remaining words (4, 6, 8). These responses were repeatable as the same pattern of responsiveness was seen when the word list was presented two minutes later in A, when the patient was asked to repeat each word. With some variations, the activation pattern was similar during the first and second presentation of the same words. Closer inspection shows that the responses were related to certain sounds. Activation typically appeared after the guttural closure consonants *k* and *g*, especially when these were combined with another consonant such as *r* (*cr*, *gr*) or *s* (*s*, *sk*), and after the fricative *s*, in combination with another closure consonant (*st*, *str*). The activation often continued throughout the vowels following these consonant sequences.

The responses of other neurons clearly *distinguished between long multisyllabic and compound words*, such as the example in fig. 2 C. It was also recorded in the right superior temporal gyrus but of another patient. A burst of activity appeared during the second part of compound words, in which the second syllable changed the semantic meaning conveyed by the first syllable (Ba, c), but this activation was less or completely absent during the second or third syllables of polysyllabic words of similar length, in which the first syllables were non-words with no semantic meaning (Bb, Cd). The time that elapsed between the beginning of the first vowel of the second word component and the neuronal activation was between 60 and 100 ms. However, the activation lasted longer than the first syllable of the second word component and could continue throughout following syllables. Neuronal responses of this type may have a function in composition of word segments to word entities probably largely based on temporal features, but without specific semantic coding, since the activation was seen in all compound words of this series.

Other neurons only distinguished between short and long words, and tended to respond more to long polysyllabic than to short monosyllabic words, irrespective of whether the long words were compound or not.

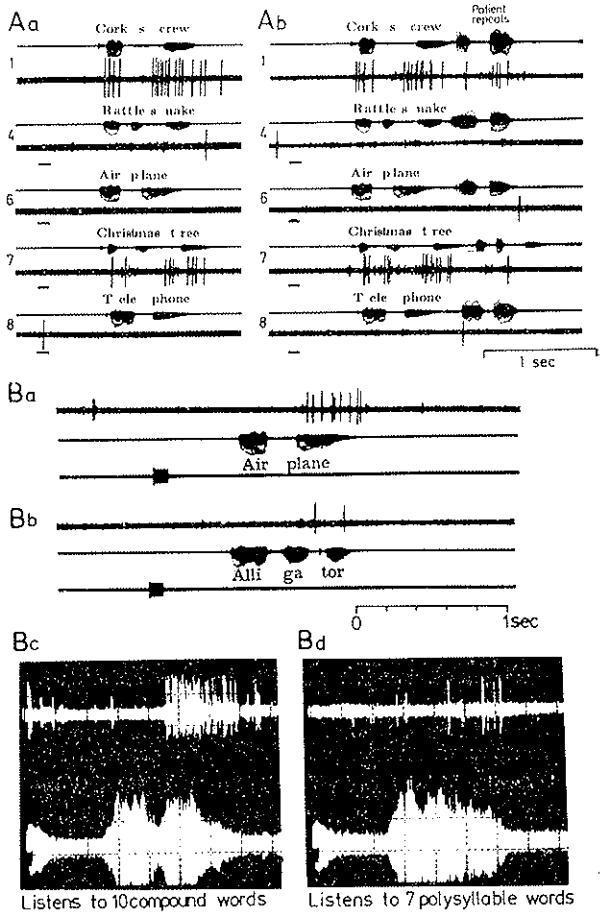

FIG. 2. A: *Responses of a neuron in the right superior temporal gyrus to a restricted class of phonemes* (8512, female). The words were tape recorded and played to the patient in an open field situation with 5 seconds between words. The numbers to the left of the records refer to the sequential number of the respective word in the word list. Not all words are shown in this figure. Aa: The patient was asked just to listen to the words. Ab: 3 min later, the patient was asked to repeat each word. In each record, the audio signal is recorded on top and the single unit activity below. The short line at the left below each record indicates the appearance of the 1000 Hz tone which preceded each word. B: *Selective responses of a neuron in the right superior temporal gyrus to the second part of compound words* (8424, female). Ba: Example of a response to a compound, and Bb: to a 3-syllable word. The single unit recording is on top, the audio-signal in the middle and the 1000 Hz tone in the third line. Bc: Superimposed responses to all ten compound words, and Bd: to all seven polysyllable words of the word list.

Such responses may be significant for prosody of speech, integrating a syllable into a word, i.e., speech functions that have been particularly related to the nondominant hemisphere (Ross, 1981).

Some units demonstrated both enhanced activity towards the end of compound words and activation specifically related to certain phonemes. Suppression of activity during certain parts of words was also seen, but was less conspicuous, partly due to the low spontaneous discharge rate of lateral temporal lobe neurons. The activity of some active neurons or neuronal populations may be suppressed throughout words or sentences, usually followed by a rebound at the end of speech.

The responses of some neurons varied with attention. Thus a neuron could respond strongly to speech addressed to the patient, but only slightly to speech not directly addressed to him. Excitatory responses to word presentation were sometimes enhanced or diminished, or a slight suppression changed into excitation when the patient was asked to repeat the words instead of just listening to them. This could represent increased attention directed to the stimulus or preparatory activity related to the overt response. However, such task-related changes of responsiveness were not seen in all neurons, probably in less than 50%. Task-related changes of responses were again most obvious in some *superior temporal gyrus* recordings. An example is shown in fig. 3 A, B. This unit occasionally discharged towards the end of the words when the patient just listened to them (A). This response was much stronger when the patient was asked to repeat each word (B). Some units of the superior temporal gyrus decreased activity (down to 50-70%) when listening to words that the patient had been instructed to repeat compared to the same words presented without the instruction. In *middle temporal gyrus neurons* such changes of responsiveness were less obvious but could be recognized occasionally.

Neuronal responses to the patient's own voice: Neuronal activity in the lateral temporal lobe is differently affected by the patient's own voice and by the voice of others. The neuronal populations affected by speaking have a slightly wider distribution over the lateral temporal lobe than those affected by only listening to language sounds, and also in this situation, neuronal responses in the superior temporal gyrus were more specifically related to the voice elements than those elicited in other parts of the temporal lobe.

In the *superior temporal gyrus*, neuronal activation during overt

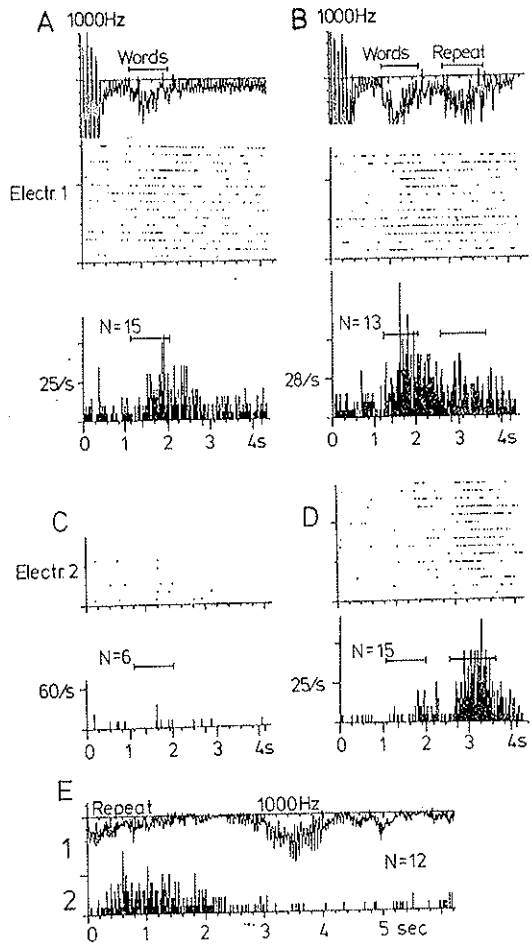

FIG. 3. *Differential responses of two simultaneously recorded neuron activities in the right superior temporal gyrus to hearing and repeating the same words.* (8603, female). The tips of the recording electrodes were about 3-4 mm above each other. Averaged audiograms on top of dot display of unit discharges and averaged discharge rates during each condition. A and B: The unit activity in electrode 1 (essentially from one single large unit) is activated by some words (especially longer words) (A) but this activation is enhanced when the patient is asked to repeat words (B). During phonation of the word the unit is only sometimes activated (see dot display). C and D: The activity recorded by electrode 2 (one single unit) does not respond to words during listening (C), but is activated at the end of some words when the patient had to repeat them. The unit responds strongly to the patient's voice, however, when she repeats the words (D). This activation during repeat has a definite latency after the beginning of the patient's vocalization as shown in E, where the averaging is started by the patient's voice. The undulations of the averaged 1000 Hz tone are due to sampling and do not correspond to the tone frequency.

speech could, in fact, be quite specifically related to single elements of phonation. These are auditory responses as the definite latency of activations after onset of the respective speech sounds indicate. Examples of this are shown in figs. 3 C-E and 4. We have, so far, no indication of activations appearing before phonation. This excludes input from motor control regions of speech production, in the sense of a corollary discharge. It appears to be rare, on the other hand, that the same phonemic combination which elicits a response during listening to language would also elicit a response during speaking. We saw it clearly only in two recordings.

A typical finding was that an individual neuron responded predominantly to listening or speaking, or that the response to one was much stronger than to the other. An example is shown in fig. 3. The activities in A/B and C/D, E were recorded simultaneously with two micro-

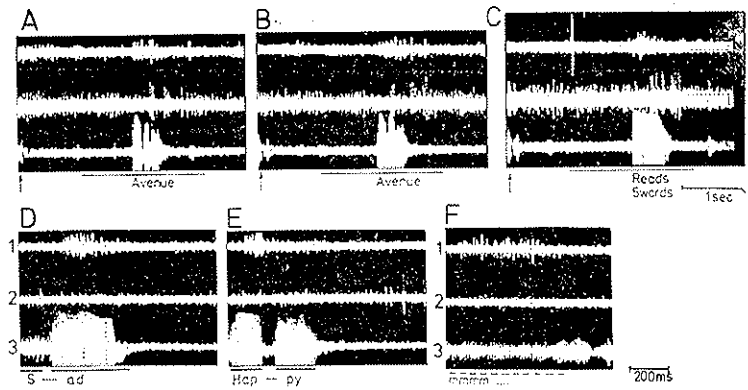

FIG. 4. *Responses of single neurones in the right superior temporal gyrus during overt reading and naming* (male patient 8533). Simultaneous recording with two microelectrodes, the tips of which were 3-4 mm above each other (records 1 and 2). 3: Audio-record. A-C: The patient was shown a word on the projection screen and was asked to read it aloud. Vertical arrows below the audio-record indicate the noise produced by the slide falling into the frame. The horizontal lines indicate the time of shutter opening. The words pronounced by the patient are written below the speech records. In record 1 only small multiunit activity can be recognized, while in record 2 one unit with large and several with small action potentials can be distinguished. D-E: The patient was shown the photograph of an actor expressing a certain emotion and had to name that emotion. Records at higher time resolution. The multiunit activity in record 1 can now be better distinguished and the long delay between speech onset and activation of the unit can be recognized. The large unit in record 2 is not activated during these words. The multiunit activity in record 1 is increased also during the humming of the patient while he ponders about the expression on the face he is shown (F).

electrodes 2-3 mm above each other in the right superior temporal gyrus. The single unit activity picked up by electrode 1 was affected only by words played to the patient from the tape (A, B), though with different responsiveness in the two situations (see above), while that recorded by the second electrode responded only to the patient's voice (C, D, E). Consequently, *the local distribution of activated neurons within the responsive region of the superior temporal gyrus becomes a distinguishing characteristic of representation of language sounds from outside or from the subject himself.* We must leave it open at this stage whether acoustic features of heard and self-produced language determine as such that one neuron responds more or less to one or the other type of language, or whether the responsiveness of the whole local cortical circuitry is changed by inputs from other speech-related areas, so that different sets of neurons are set free to respond to one or the other type of speech input. We hesitate to conclude, at this point, that there are neurons in the superior temporal gyrus, which exclusively respond to one's own or to outside linguistic sounds, although within the framework of our tests some neurons may indeed respond quite exclusively to one or the other.

Middle and inferior temporal gyrus: In contrast to the little responsiveness of neurons in these regions to language spoken by others, about 2/3 of our recordings revealed clear excitatory or inhibitory neuronal responses during phonation. Yet the excitatory responses were much less specifically related to phonemic or temporal aspects of the words than in the superior temporal gyrus and were more of the unspecific type. In 1/3 of our population and in about half of the responsive units in the middle and inferior temporal gyrus, spontaneous activity was strongly suppressed during speaking, however. Like in the superior temporal gyrus, this *suppression* often preceded the actual phonation by up to a few 100 ms and outlasted it by up to a second. This could indicate that the activity is turned off not so much or not only by the auditory signal itself but by other inputs more closely related to speech command. The purpose of such a widespread suppression of activity in regions not directly related to language analysis or speech command is not clear, but one may speculate that spontaneous activities in these regions could interfere with speaking and therefore have to be cut down during speaking.

In addition to the different local activity pattern, the extent of cortical surface involved in speaking and listening to speech differs. This is already indicated by the fact that middle and inferior temporal gyrus activity is slightly more affected by the subject's speaking than by listening

to speech. It is more obvious from the distribution of evoked potentials. Fig. 5 shows the averaged surface potentials from five different sites. These recordings are from a patient with a frontal glioma the outlines of which are indicated by the broken line. When only listening to words (A), the evoked potential, i.e., a broad positive wave with a peak latency of about 300 ms, was essentially restricted to the medial part of the superior temporal gyrus. When the patient was asked to repeat the words (B), the potential evoked by the words was now also recorded over the posterior part of the superior temporal gyrus. During the repeat, potential

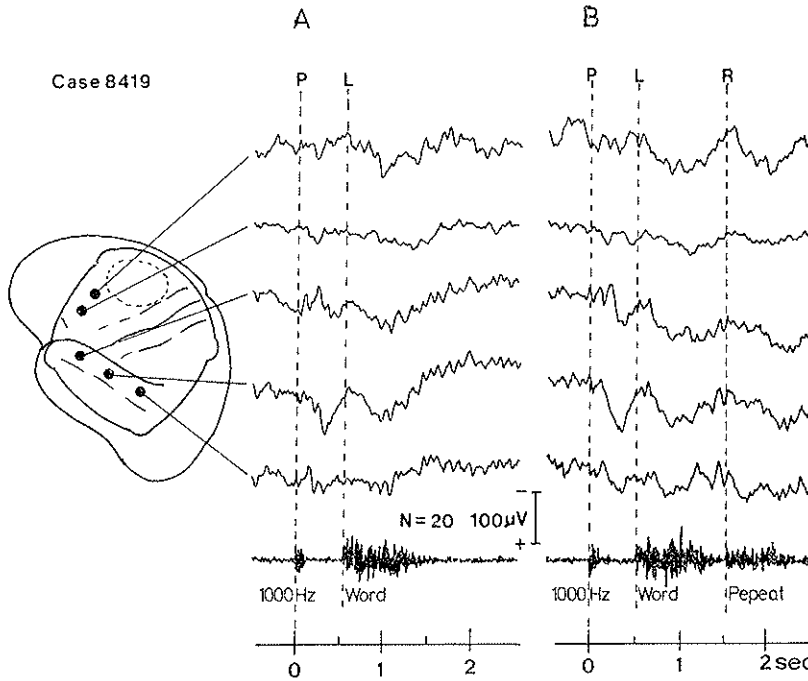

FIG. 5. *Auditory evoked potentials recorded from five corticographic electrodes on the left frontal and the superior temporal lobe as indicated* (8419, male). A: Listening to words, B: Listening and repeat. The potentials are averages from 20 runs. The vertical broken lines indicate the onset of the 1000 Hz tone (P), the word presentation from the tape (L) and the beginning of the patient's voice (R). There was a slight time jitter of up to 15 msec between the beginning of the tone and the beginning of the word presentation, and an even larger jitter (up to 200 msec) to the beginning of the word repeat. Note different amplitudes and distribution of evoked activities during listening and word repeat (see text).

variations of different amplitude and time course appeared over the whole superior temporal gyrus, as well as over the frontal cortex in the region of Broca's area, where a negative motor potential preceded the phonation. A more widespread involvement of various cortical regions in the frontal, prefrontal and temporal cortex is also evident from measurements of regional cerebral blood flow during overt speech (Ingvar, 1983; Ingvar and Schwartz, 1974; Ryding *et al.*, 1985) and of cerebral event related potentials (Desmedt, 1977; Hillyard and Picton, 1987).

Conclusions

A) *Topographical distribution of responses*

The responsiveness to auditory speech signals of the lateral temporal cortex does not show obvious differences between the *right and the left hemisphere*. This in itself could indicate that the neuronal signals which we recorded do probably not represent, as such, the semantic elements of the spoken language since otherwise one would have expected clear lateral differences. The detailed analysis of individual responses also in other tests (see Ojemann *et al.*, 1988) do not give any indication that semantic meaning as such is represented in the activity of neurons in the middle and anterior segment of the lateral temporal lobe including the superior temporal gyrus.

It is furthermore clear from our recordings that the superior and the middle temporal gyrus and the anterior temporal cortex are differently affected by spoken language. All neurons in the *superior temporal gyrus* lateral to the sensory and motor cortex showed activity modulations closely related in one way or the other to different aspects of spoken language, including the subject's own voice. Excitatory responses were strong event-related bursts of discharges at a mean rate of 20-50/s and peak rates reaching 70-100/s. In contrast, *middle temporal gyrus* neurons were either not at all or only little affected by spoken language with mean rates below 5-10/s. Thus, the superior temporal gyrus is clearly more involved in the representation of auditory linguistic signals than the middle temporal gyrus as shown in fig. 1 C. This is consistent with the observation that phoneme recognition may be impaired by electrical stimulation of the superior temporal gyrus lateral to the sensory and motor fields (Ojemann, 1983). It is also in line with the definition of the superior temporal gyrus as an auditory association cortex (see Creutz-

feldt, 1983). The lack of obvious pitch or noise sensitivity of its neurons, and the loose — if any — coupling of their activity to harmonic elements of speech signals such as formants (vowels) indicates that this area is not part of the tonotopically organized auditory cortex.

The region in which we recorded phoneme-related responses in the superior temporal gyrus corresponds approximately to the internal and external parakonio-cortex as defined cytoarchitectonically by Galaburda and Sanides (1980), which may correspond to the nontonotopically organized lateral or ventral auditory association cortex of other mammals such as the rhesus monkey (Merzenich and Brugge, 1973), cat (Merzenich *et al.*, 1979), or guinea pig (Redies *et al.*, 1989).

As to the pathways which carry activation and inhibition into this auditory association area, we cannot say much from our data. Whenever an activation can be related to a well defined phonemic event, the response latency is between 60 and 100 ms. At the sound pressure used, this long latency suggests several relays. It must be considered, however, that the sound pressure of voiceless consonants is much lower than that of the vowels so that long latencies can be explained by the low intensity of such phonemes. The long-lasting activations during and following words and often across phoneme boundaries indicate that activities in this region are not just a feature-related selection of primary auditory cortex activities but represent additional "labels" related to acoustic signal. They contribute rather than extract specific information to the multiple parallel representation of auditory linguistic signals in the brain similar to what we see in other sensory systems (Creutzfeldt, 1983, 1985). To what extent these additional informations reach the brain via a separate thalamo-cortical projection system (through the pulvinar) or whether they result from a combination of pulvinar-thalamic and transcortical-association inputs must be left open at this stage. Yet it should be noted that neuronal activities in the thalamus and other subcortical structures are also affected by spoken language in a specific manner (Bechtereva *et al.*, 1979), and that electrical stimulation or lesions in the pulvinar may lead to speech disturbance (Ojemann, 1976).

Neurons in the *middle temporal gyrus* were as a whole much less responsive, but not all were completely unresponsive to auditory language signals. No specific features of our auditory stimuli could reliably be related to activity changes of units in this area, however (see below). Visual stimuli, written language, pictures or faces also did not modulate the

activity of these neurons in a prominent and reliable manner, although modification of discharge rate may be revealed in some of them during various tasks involving memory (see Ojemann *et al.*, 1988). Possibly other variables which were not included in our exploration have to be linked to the auditory (or visual) stimuli in order to affect the middle temporal gyrus neurons more consistently. Yet, as auditory responsiveness, including responses to the subject's own voice, was found in nearly 50% of the recording sites on the lateral surface of the middle temporal gyrus below the sensory and motor cortex but no visual responses, this region may still be considered as part of the auditory rather than the visual association cortex, if one wants to connect it to one of these two senses at all.

The functional topography of the lateral temporal lobe with respect to the analysis of speech as derived from these single unit studies is consistent with some, but not with other conclusions based on observations with other methodological approaches. The changes of RCBF and metabolic rate are distributed more widely over both temporal lobes during listening to speech and during conversation, although — in some studies — heaviest in the region over the superior temporal gyrus (Ingvar, 1983; Lassen and Larsen, 1980; Raichle, 1987; Reivich *et al.*, 1983). Our single unit studies indicate that during listening to speech only the superior temporal gyrus is specifically activated, but during overt speech of the subject we have noted a slightly stronger involvement of the middle and inferior temporal gyrus. During silent reading and naming we have seen only little if any systematic changes of activity over the whole lateral temporal lobe (Ojemann *et al.*, 1988). Also RCBF changes during silent reading appear to be restricted to the posterior perisylvian cortex, in addition to patches of increase in the frontal and occipital cortex, while during silent speech changes of RCBF are restricted to the dorsal frontal cortex (Ingvar, 1983). When comparing results of the two approaches, one has to keep in mind also the differences in the experimental situations in which the measurements were taken. RCBF and metabolic measurements are integrated over long time and the tasks may involve more attention and mental concentration over longer periods, whereas during the single unit studies, temporally restricted activity changes related to short linguistic signals are tested. Both approaches agree on the bilateral participation of the temporal lobes in speech perception, except for the minor and apparently variable lateral differences in RCBF and metabolic studies. Evoked potential studies also demonstrate a bilateral involve-

ment of both temporal lobes in speech analysis but without further dorsolateral differentiation (Hillyard and Picton, 1987).

B) *Significance of responses*

As mentioned, responses of some neurons in the *superior temporal gyrus neurons* may be specifically related to certain temporal and phonemic aspects of spoken language, such as the length of a word (longer words may elicit a stronger excitation than short words), some neurons may be excited only by the second part of a compound word, or responses may be restricted to only one phoneme combination or syllable of a word. Some of these responses could help in *categorization* of certain classes of phonemes. This applies mainly to consonants. With respect to formants, we have not found one neuron that responded exclusively to only one vowel, although one of our word lists was specifically designed for vowel detection. Some units were activated during certain vowels when the patient spoke, however (see fig. 4). But the same neurons were also activated when the patient just hummed (fig. 4). This indicates that it may be just the resonance of the basic frequency which activated this neuron.

The long activations elicited by voiceless consonants usually reached across the phoneme boundary into the vowel phonation and it may therefore be that the consonant/vowel combination or coarticulation (Pols and Schouten, 1982) as such was marked. In any case, neurons appear to be relatively broadly tuned to phoneme classes and their activation pattern can therefore only code for broad phonemic and linguistic categories within words.

Other neurons in the *superior temporal gyrus* may carry information on segmentation of phoneme sequences within words and spoken language, on coherence of phoneme sequences in long polysyllabic and in compound words and on the presence of language altogether. This information appears to be distributed across different neurons or sets of neurons each of which is not tuned to just one of these various aspects, and activation patterns elicited by the various triggering elements overlap in time. It is quite possible that in different linguistic contexts neurons may show different patterns, and it is probably the ensemble of activities going on in this cortical network which determines its contribution to the representation of speech signals rather than the specific activation pattern of one single neuron.

In the *middle temporal gyrus*, suppression of activity was the only response to words or speech in the majority of those recordings which showed any activity changes. In half of the recordings, the neuronal activity was not at all affected by language. In all responsive recordings, the excitatory or suppressive effect of language was weak and activations never went above 10/s, usually less than 5/s discharge rate. In several units the activity was suppressed during the words and showed a slightly increased discharge rate only following the word. In others the activity was slightly depressed following the word. Yet these responses did not appear to be just unspecific auditory responses, as noises or the 1000 or 500 Hz tones did affect such neurons much less or not at all. These observations indicate that some recording sites in the middle temporal gyrus may be affected by spoken language but there are no clear indications that they contribute an important signal about phonetic, temporal or semantic aspects of speech. The prominent suppression may even suggest that activity is being tuned down during listening to speech, as it might interfere with comprehension of spoken language otherwise. This is even more so if the patient speaks himself.

C) *Task-dependent changes of responsiveness and activity*

Responses to words or short sentences could be stronger or weaker when the task or the situation demanded specific attention to them. Less than half of our recordings were affected by attention, however. In the *superior temporal gyrus*, response variations related to attention were essentially quantitative, i.e., more or less of the same type with only larger or smaller amplitude. To what extent the increased responsiveness reflects gating of afferent signals in the thalamus controlled by reticulothalamic circuits (Singer, 1977) or at the cortical level through prefrontal mechanisms (Roland, 1982) via association fibre connections, must be left open at this stage. Increased as well as decreased responsiveness may indicate that the total excitation pattern in the neuronal network is not only generally elevated or lowered during directed attention, but that the distribution of relative excitations may also change. Response variations depending on attention paid to the task have also been observed in monkeys even in the primary auditory cortex, but also here only a minority of neurons showed such effects (Beaton and Miller, 1975; Hocherman *et al.*, 1976; Benson and Heinz, 1978). Also in humans, language and other auditory-evoked potentials may change, depending on

the attention paid to the stimulus (Hillyard *et al.*, 1973; Näätänen *et al.*, 1981; for further references see Hillyard and Picton, 1987).

The non-specific activation or suppression of ongoing activity by speech, which we observed in the *superior* as well as in the *middle temporal gyrus,* may be interpreted as a more general arousal, however, indicating that more extended cortical regions are temporarily alerted by language. These may be reduced again if their contribution is not needed or may be even disturbing for a detailed representation of the signal.

D) *Concluding remarks*

Our data indicate a specific involvement of the superior temporal gyrus in the analysis of speech. Neuronal activities in this region may add to the multiple representation of acoustic language, in parallel with other predominantly acoustic and predominantly semantic representations in nearby areas. Lesion of the superior temporal gyrus on both sides produces auditory agnosia, which disables the patient to recognize sounds and to distinguish between language and other sounds (Kleist, 1934; Luria, 1966). Unilateral resections that included those sites in many cases, including all resections in nondominant hemisphere, were followed by no lasting language disturbance at all. Resections on the speech dominant side occasionally were followed in comprehending or repeating long words. This defect may last for some time (up to several weeks) and thus outlast the anomia seen during the first days following the operation due to post-operative local edema. Our observations are consistent with the suggestion that this intermediate part of the superior temporal gyrus belongs to perisylvian language cortex and thus plays a role in the mental composition of acoustic noises to a linguistic code but without major lateral specialization. The relatively small deficits after unilateral removal indicate that this region is at least unilaterally disposable and thus not essential for language functions. The different involvement of neurons in the lateral temporal lobe, especially again in the superior temporal gyrus, when the subject hears linguistic sounds or when he speaks himself, indicates that this region also contributes to the distinction between one's own speech and that of others.

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DISCUSSION

INGVAR

I have a brief question. Did you observe any form of emotional reactions in these neurons? Were there neurons that reacted to laughing, or when you said funny things, or the opposite?

CREUTZFELDT

No.

INGVAR

You didn't say anything funny, perhaps?

CREUTZFELDT

We did say something funny during conversations, but did not see anything special in our recordings. Not even when the patients laughed.

BAUMGARTNER

What you call phoneme specific neurons — are they dependent on frequency, in high pitch or low pitch, or is this completely separate?

CREUTZFELDT

We tried to investigate frequency tuning in some neurons. But none of the neurons responded to pure tones. Apparently it is not the frequency content as such which turns them on.

ZEKI

I think that there are interesting parallels between the visual system and the auditory system and I am surprised, to hear you say that the temporal cortex is analyzing acoustic signals when all the evidence that you have

given us actually shows that the acoustic cortex is constructing these signals. You see, there are 20,000 hair cells in the cochlea. I think there are about 20,000, it could be 30,000, but they are limited, and from that you've got to construct all the sounds and introduce a sound constancy. This is not very dissimilar to what you do with colour. The evidence that you have given us today, I think, speaks forcibly in favour of it. Don't you think that that's perhaps a wrong way of looking at your cortex if you think of it in terms of analysis? And do you not think, moreover, that this is perhaps one of the main reasons why work on acoustics or the auditory cortex has been so poor over the past 30 years?

CREUTZFELDT

In comparing the visual and the auditory systems, a basic similarity is the segmentation of our visual and auditory environment into meaningful entities (Gestalten), which differentiate them from the rest, and give them meaning. Segmentation is partly done in the sensory periphery, but meaning is given to it in the cortex. Here I agree with you. I therefore prefer to speak of "extraction" of segment boarders and representation of complex signals. The question is how the machinery is made to extract these things.

ZEKI

It's extracting information from which it is constructed. You are speaking in terms of representation, and in fact the phonemes are not representations. They are constructions. There is a big difference there, a fundamental difference.

CREUTZFELDT

Well, they are not constructions.

ZEKI

What is the outside nature of a phoneme?

CREUTZFELDT

Our machinery interprets certain sound compositions as phonemes. I would not call this a construction of the cortex, but restricted and selective

representation of our environment in the cortex. Giving semantic meaning to a signal may be a construction, because here the stimulus is brought in relation with a stimulus independent store of possible meanings.

DEECKE

The most surprising thing for me was that you twice said that there was no side difference. Did this mean that the neurons which coded the last part of a compound word, for instance, were also found in the right temporal lobe?

CREUTZFELDT

The one I showed to you actually was in the right, non-dominant temporal lobe. The bilateral representation simply indicates that the machinery for presenting complex auditory signals to the "brain" singles out certain phonetic aspects already at a pre-conscious, pre-analytical and pre-semantic level. I wouldn't be amazed if one would find a lot of these phonemic representations also in monkeys or cats and there are, in fact, indications of that.

THE CONSTRUCTION OF REALITY

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INTRODUCTION

Questions concerning how it is that we apprehend objects and events in the world around us and how those things are represented in our brains have long been central themes in man's endeavour to understand himself. What the nature of these representations may be is an ancient and difficult but still rich and rewarding research program in Brain Science.

A sensory stimulus evokes a distributed ensemble of nerve impulses in primary nerve fibers that is projected into a primary sensory area of the cerebral cortex. Certain features of sensory stimuli are signalled by some sets of neurons within that ensemble, other features by other sets. Only rarely are even first-order representations truly isomorphic with physical reality; often certain stimulus features are not encoded at the peripheral interface, while others are accentuated.

These early, quasi-isomorphic representations in primary sensory cortical areas are from thence projected into and transformed along parallel pathways in the distributed systems of the brain, particularly in those of the homotypical neocortex. Each of these imposes its own set of transforms upon the initial representations. Some channels lead to motor output, executing the spatial, co-ordinate transforms linking sensory input to motor response. Input representations along other channels are surmised to be complexed with stored records of experience and lead to perception — the original model of Helmholtz. Transformations in different channels differ qualitatively, but they have in common that in each succession they

become less isomorphic and more abstract. In all of these there is a flow-through from one neural ensemble to another: neither grandmother cells nor pontifical modules exist.

I contend that the neural representations within the brain vary along a continuum from those relatively isomorphic with physical reality to those I term central constructions. These latter are produced by the complexion of transformed and abstracted afferent input with the neural correlates of life experience derived from memory, with those of central control states, and with those of cognitive and affective sets. Central constructions are determined both by the microstructure of brain systems and by the dynamic patterns of neuronal activity within them. The macrostructural relations of brain systems are largely set by genetic factors. Microstructural relations, by contrast, are dynamic and changeable, and are influenced by epigenetic and experiential factors selective and degenerate in nature (Edelman, 1987). The microstructural relations in the primary somatic sensory cortex of the monkey can be modified by changing peripheral afferent input: by amputation of a finger (Merzenich *et al.*, 1984), by section of a peripheral nerve (Merzenich *et al.*, 1983), or by excessive local sensory stimulation. This explains the fact that the pattern of representation of the body form in the somatic sensory cortex of non-human primates varies so greatly among individuals of the same species, sex and age (Merzenich *et al.*, 1987).

My major theme is that central neural representations can be studied directly in waking, behaving, non-human primates. Evidence from studies by a number of investigators has established what I regard as one of the central dogmata of neuroscience: that representations of material reality are instantiated in patterns of neural activity within the brain, and that these representations are essential components of the mechanisms of mind.

Data Base and Methods of Study

I shall now describe the results of three studies of representations. Two are taken from my own work, the third from that of my colleagues in the Philip Bard Laboratories in Baltimore. The three are arranged in sequence to illustrate the transition from relatively isomorphic images of physical reality to those that are clearly neural constructions. Experimental arrangements details are given in the original papers. More generally, the three had several things in common. All included experiments made on

the neocortex in waking monkeys as they executed behavioral tasks. Thus each dealt with the dynamic aspects of neuronal activity recorded in behaving brains. Recordings were made simultaneously of behavioral performance and of the activity of single neurons in areas of the neocortex known on other grounds to be essential for correct execution of the task behavior. The method of single neuron analysis was used, combined with *post hoc* reconstruction of the actions of neural ensembles. Correlations were sought between neural and behavioral events on the grounds of simultaneous variation, and also from the effects of brain lesions on behavior and from the patterns of anatomical connections. Each investigation was aimed in the long run at study of "higher functions", at those levels of the nervous system where we can expect to see abstracted and constructed images of the sensory world, and the operation of the processes of perception.

Temporal Order: the Sense of Flutter-Vibration

Flutter-vibration is a dual mechanoreceptive sense, for the subjective experience differs with frequency. Low-frequency mechanical sinusoids (5-50 Hz) delivered to the glabrous skin of the hand evoke a local fluttering sensation. Sinusoids of higher frequency (50-400 Hz) evoke the widely spreading and poorly localized sensation we call vibration. Frequencies above 500-600 Hz are perceived as stationary. Monkeys and humans possess virtually identical capacities to detect mechanical sinusoids (Mountcastle *et al.*, 1972) as well as to discriminate between those of different frequencies or amplitudes (LaMotte and Mountcastle, 1975). The identity of the psychometric functions of man and monkey at 30 Hz are given in Figure 1, together with the detection function across the full frequency range. These identities lend some validity to the assumption that at levels of first-order input and early cortical representations neural events observed in monkeys resemble those evoked in humans under similar circumstances. Over the range of frequencies monkeys can detect, stimulus frequency is encoded in a periodic sequence of nerve impulses in the relevant sets of afferent fibers innervating the hand: in the Meissner afferents for the range of flutter (Figure 2), and in Pacinian afferents for the range of vibration (LaMotte and Mountcastle, 1975; Talbot *et al.*, 1968). The tuning points at different frequencies for these two populations of first-order fibers shown in Figure 3 blanket the monkey detection function. Thus for

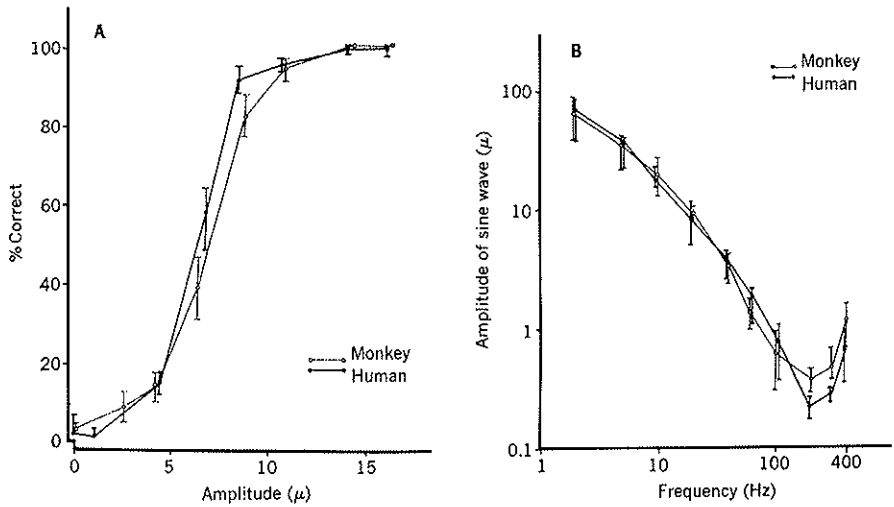
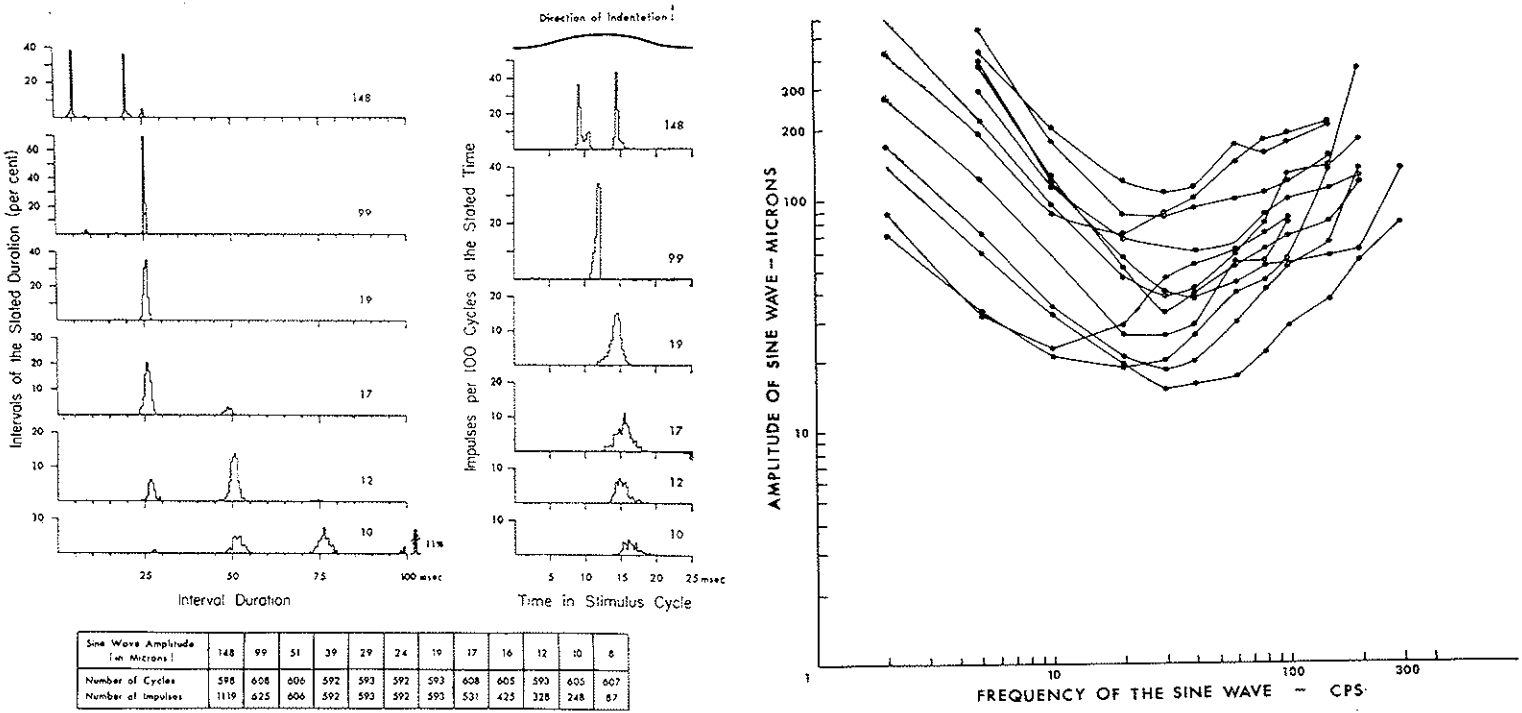


FIG. 1. A: Averaged psychometric functions for groups of human and monkey subjects required to detect a 40 Hz mechanical sinusoid delivered to the glabrous skin of a finger tip. B: Frequency-threshold functions for groups of human and monkey subjects who repeated the experiment of Figure 1-A at a number of different frequencies. Vertical lines = ± 2x SEM. (From Mountcastle, 1984).

this sensory mode the peripheral neural apparatus delivers to the central nervous system an isomorphic representation of the temporal order of peripheral events.

The Cortical Representation.

The major classes of large mechanoreceptive afferent fibers innervating the glabrous skin of the hand project over the dorsal column — medial lemniscal pathway to the somatic sensory cortex of the postcentral gyrus. They do so with little sign of cross-convergence between the mechanoreceptive sub-modalities (for review, see Mountcastle, 1984). This segregation appears to be produced by the specificity of linkage at each synaptic level, but dynamic processes may play a role in this restriction. Regardless, one regularly observes that many columns of neurons in the somatic sensory cortex are activated exclusively by impulses in the Meissner afferents. This allowed us to examine the form of the cortical representation of the frequency of peripheral stimuli; i.e., of their dynamic, time-dependent properties. We did this first in inactive, waking monkeys



Sine Wave Amplitude (in Microns)	148	99	51	39	29	24	19	17	16	12	10	8
Number of Cycles	598	608	606	592	593	592	593	608	605	593	605	607
Number of Impulses	1119	625	606	592	593	592	593	531	425	328	248	87

FIG. 2. Left: interval and cycle histograms for responses of rapidly adapting mechanoreceptive afferent fiber innervating the glabrous skin of a monkey's hand to 40 Hz mechanical sinusoids delivered to the center of the receptive field via 2 mm probe tip. Numbers = amplitude of the sine waves. Histograms: 0.5 msec bins for interval histograms to the left; 0.25 msec for cycle histograms to the right. For stimuli weaker than that which produced perfect tuning (19 μm), the impulses which did occur were phase-locked to the stimulus, and appeared at nearly integral multiples of the stimulus period. Right: tuning curves for a number of such fibers, determined by measuring the tuning points at a number of frequencies, for each fiber. (From Talbot *et al.*, 1968).

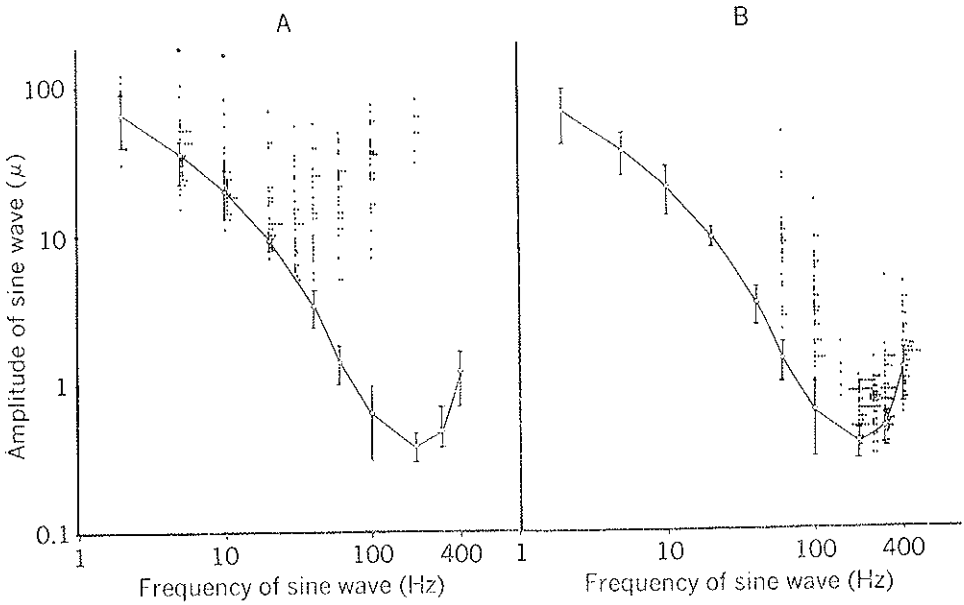


FIG. 3. Solid lines = the detection function for monkeys, from Figure 1-A. The dots on the graph to the left are the tuning point for a number of Meissner afferents innervating the monkey hand; those to the right are tuning points for Pacinian afferent fibers. All fibers studied across the full frequency range from 5-400 Hz. The frequency detection function can be accounted for only in terms of the sensitivities of both sets of fibers; thus flutter-vibration is a dual sense. (Adapted from Mountcastle *et al.*, 1972).

(Mountcastle *et al.*, 1969), then in behaving monkeys as they executed detection tasks yielding psychometric functions like those of Figure 1 (Carli *et al.*, 1971; Mountcastle, 1984). Typical results and the simple forms of analyses used are shown in Figures 4 and 5. The salient feature of the transformations between periphery and primary sensory cortex is evident, for at no stimulus amplitude is the discharge of cortical neurons entrained to perfect periodicity, as is the case for the first-order Meissner afferents. The periodic signal at the input level has been transformed at the cortical level to a code of frequency modulation. This code depends upon the sequential order with which impulses occur, for it is destroyed when that order is destroyed by a random re-shuffle, as shown by the renewal density analyses. The peripheral and the initial cortical representations of the stimulus parameter of frequency differ in the degree of isomorphic relation.

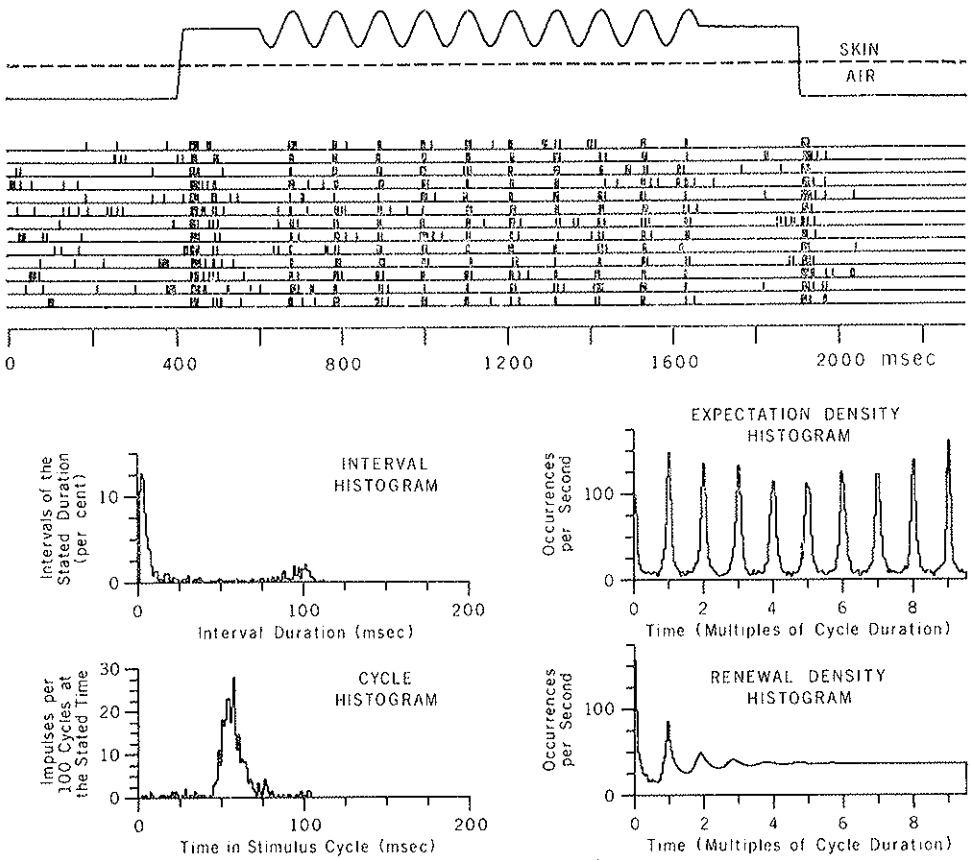


FIG. 4. The records above show the stimulus pattern at 10 hz and replicas of impulse discharges evoked by that stimulus from a neuron of the postcentral somatic sensory cortex of a waking monkey. The nerve impulse replicas (each short upstroke = 1 impulse) show sharp on and off discharges when the mechanical probe indents and leaves the skin, and a frequency modulated discharge evoked by the mechanical oscillation. Interval and cycle histograms are shown lower left; the latter indicates the strong linkage of impulse discharge to a particular phase of the stimulus cycle. Entrainment shown in detail by the expectation density function to the right. That pattern depends upon the sequential order of impulse intervals, for it is virtually destroyed by a random shuffle, as shown by the renewal density histogram. (From Mountcastle *et al.*, 1969).

The Ensemble Representation of Spatial Pattern

The glabrous skin of the hand possesses the most acute sensory capacity of any part of the somatic afferent system. This capacity is shown by blind humans trained in reading Braille type, for they achieve rates of 600 letters/min, and information flow rates of 60 bits/sec, the latter reduced by the serial dependencies and redundancies of language. Johnson and his colleagues have now carried out a brilliant series of studies of the neural mechanisms in tactual spatial perception (Phillips *et al.*, 1988). They sought to learn how stimuli such as embossed letters resembling

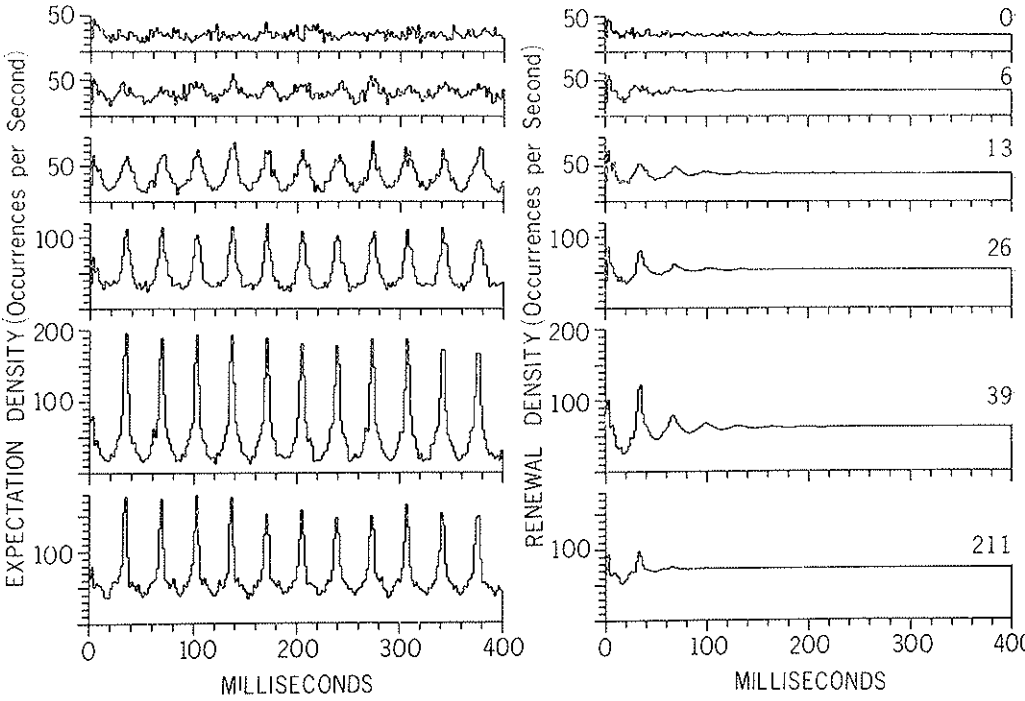


Fig. 5. Analysis of the responses of a postcentral somatic sensory neuron studied in a manner similar to that of Fig. 4, but at 30 Hz. The expectation density histograms to the left show that cyclic entrainment is first visible at 6 μm stimulus amplitude, about the monkey threshold at this frequency. The power of the entrainment grows with further increases in stimulus amplitude, but is destroyed by the random shuffling of impulse interval sequences as shown by the renewal density histograms to the right. Numerals to the right indicate peak-to-peak amplitudes of the mechanical sinusids, in μm. (From Mountcastle *et al.*, 1969).

those of Braille type are represented in the first-order afferent inflow from the hand, and how that representation is reflected or transformed at the level of the primary sensory cortex. Their method was to sweep embossed letters across the receptive field of a nerve fiber innervating the glabrous skin, or of a cortical somatic sensory neuron, to shift the line of passage of the stimulus by 100 μm, and sweep again. They repeated this stimulation until the receptive field had been traversed. They could then re-construct the pattern of afferent input in the population of afferents of the median nerve engaged by a single passage of the stimulus. The results obtained are shown in Figure 6. The panel to the left shows the results for four passes of the letter "K", to illustrate the method. The horizontal lines trace the stimulus movement, and each upstroke the discharge of an impulse in the fiber under study. The reconstruction for the letter "K" in the monkey's median nerve is given in the middle panel of Figure 6, and reconstructions for a number of letters in the upper row of Figure 7. Study of all large mechanoreceptive afferent fibers innervating the glabrous skin showed that the slowly adapting Merkel afferents provide the best transductions of the stimulus patterns. The patterns in the neuronal ensembles are remarkably isomorphic representations of the stimulus pattern, yet no inkling of the pattern can be detected in the evoked impulse discharge in any single fiber!

Johnson and his colleagues then translated their site of study to the postcentral gyrus of the waking monkey. The results of study of a neuron of area 3b are shown to the right in Figure 6. This neuron was linked to slowly adapting Merkel's afferents innervating the glabrous skin. Results are given in the lower row of Figure 7 for a number of letters, for two other neurons of area 3b. Two points are worth emphasizing: the patterns are discernible only in the ensemble reconstructions, and the representations are a bit fuzzier at cortical than peripheral levels. Further studies have now revealed that these representations are less isomorphic at the next cortical processing level, in area 1 of the postcentral gyrus. The inference is that what has been seen are the first steps in a series of transformations that lead to non-isomorphic and more efficient representations at the levels of perceptual processing, the flow-through to motor action, and storage in memory.

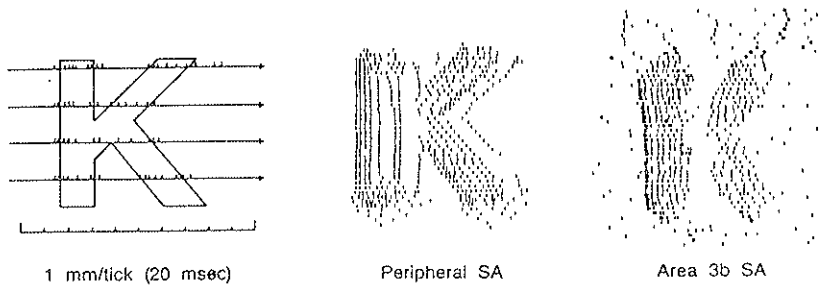


FIG. 6. *Left*: each horizontal line shows the direction of movement of an embossed letter K across the peripheral receptive field of a slowly adapting mechanoreceptive afferent innervating the glabrous skin of a monkey's finger. Each upstroke = 1 nerve impulse. Only four traverses are shown, to illustrate the method. *Middle*: the same stimulus is moved across the receptive field many times, and indexed in the second dimension by 100 μm between traverses. Each dot = 1 nerve impulse. By the reciprocal interpretation described in the text, this figure illustrates the pattern of discharge in the population of median nerve fibers activated during a single stimulus presentation. *Right*: results of a similar experiment made on a neuron of the postcentral gyrus of a monkey. This cell was linked to slowly adapting afferents innervating the hand. (From Phillips *et al.*, 1988).

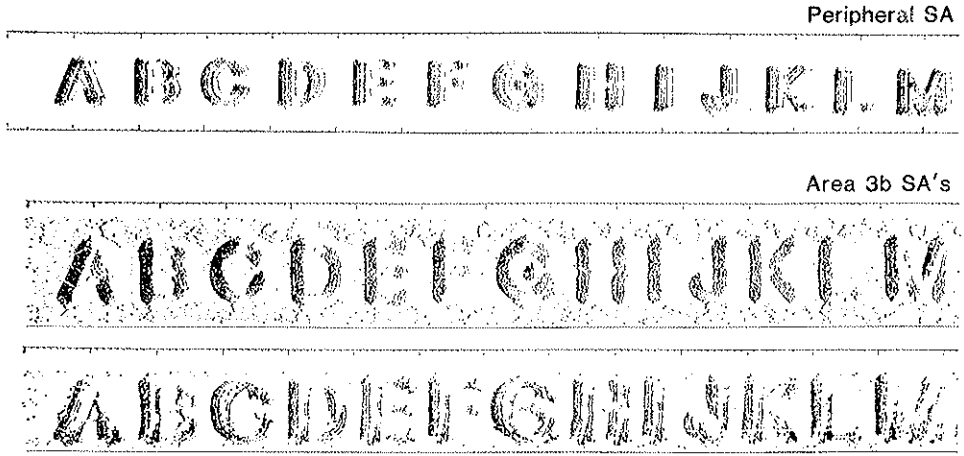


FIG. 7. Upper: results of a study of a peripheral slowly adapting afferent, in the manner of *Fig. 6 middle*, now for the different letters shown on the upper row of reconstructions. Those of the two lower rows are for two neurons of area 3b of the somatic sensory cortex of the postcentral gyrus, studied in a waking monkey in the manner of *Fig.* 6, right. (From Phillips *et al.*, 1988).

The Sense of Surrounding Space

The representations I have described are of simple sensory attributes, temporal cadence and two-dimensional pattern in tactual sensibility. The initial transductions and encoding of these sensory qualities at the level of peripheral nerve fibers innervating the hand are discernible in the primary sensory cortex, though important transformations occur between the periphery and the postcentral gyrus. These primary cortical representations are further transformed at still more central levels of brain operations.

The final example of representations I describe differs greatly, for it is a central construction, with no representational counterpart at either peripheral input or primary cortical level. I refer to the central neural representation of surrounding space as we are thought to carry in our brains, and particularly of the flow of the environment by us during locomotion, and of objects moving in the periphery of the visual fields.

It is at this level in the study of the neural mechanisms of perception that the experimentalist takes his lead from the defects in perception and the behavioral abnormalities produced in humans by lesions or disease of the brain; particularly, those of the neocortex and its linked distributed systems of the forebrain.

The syndrome of the parietal lobe system is one of the most dramatic and widely known of these disorders. Lesions of the posterior parietal cortex are followed by defects in spatial perception, particularly in the visual localization of objects; errors in projection movements of arm and hand and in smooth pursuit movements of the eyes; difficulties in map reading and in finding the way, even in familiar environments. The most striking of these defects is that such a patient neglects the contralateral side of surrounding space, and of his own body. It is clear that these abnormalities should be attributed to defects in function of the parietal lobe system, not of parietal lobe cortex alone. The posterior parietal cortex is heavily and reciprocally interconnected with the frontal lobe, with both cingular gyri, with the pulvinar, with the superior colliculus, and with its homologue of the opposite hemisphere, etc. Indeed, lesions at several different loci in this widely interconnected system produce effects resembling one or another feature of the parietal lobe syndrome.

Studies of the Parietal Lobe System in Non-human Primates.

My colleagues and I chose the parietal lobe system as for direct study of the higher functions of the brain (Mountcastle *et al.*, 1975; Lynch

et al., 1977), for the defects in humans characteristic of the parietal lobe system may occur without defects in the primary aspects of sensation, or in the control of movement. We first studied a number of monkeys in whom we produced lesions of the posterior parietal cortex. We found, as had others before us, that such lesions produce a syndrome similar to that in human subjects, if less dramatic in our non-speaking subjects. The animals showed a profound contralateral neglect, defects in the visual localization of objects, and errors in reaching to targets in the immediately surrounding space. We trained monkeys in a series of behavioral tasks designed to depend in a critical way upon the function of the parietal lobe system, and then recorded the activity of neurons in the parietal cortex as the animals performed these tasks (for methods, see Mountcastle *et al.*, 1975; Motter and Mountcastle, 1981). The general result is that the functional properties of neurons in the posterior parietal cortex appear as positive images of the defects characteristic of the parietal lobe syndrome. Here I wish to describe only the results dealing with certain aspects of visual perception, for they provide an example of central construction.

Spatial Perception and the Visual Flow Fields.

It is now well known that the cortical visual system consists of a number of areas sequentially and reciprocally linked by a stepwise, trans-cortical projection system (Livingstone and Hubel, 1988; Zeki and Shipp, 1988). Reciprocal connections between areas at different levels create a distributed system with both hierarchical and parallel arrangements. There are two major and partially divergent trans-cortical components of the system. The first projects into the temporal lobe, with its target area TE; this component is known to be essential for the perception of the shape and color of objects (Ungerleider and Mishkin, 1982). The second system projects into the parietal lobe with its ultimate target area PG (area 7a) of the inferior parietal lobule. This latter is essential for the perception of the location and movement of visual stimuli, and of the spatial relation of objects in the environment. There is a disproportionate projection of the foveal visual field into the temporal lobe system, and of the visual periphery into the parietal system.

We found in our very first experiments that many neurons of area PG respond to visual stimuli (Mountcastle *et al.*, 1975). These parietal visual neurons (PVNs) have several unique features (Motter and Mountcastle, 1981; Mountcastle *et al.*, 1981; Motter *et al.*, 1987; Steinmetz *et al.*,

1987). Their receptive fields are large and frequently bilateral, and in the limit a PVN may respond to a moving stimulus anywhere in the visual field, even from the monocular rims, though often the peri-foveal region is unresponsive. Figure 8 illustrates the directional sensitivity and organization of one of a major class of PVN's; the cell responded to any stimulus that moved into the visual field from the periphery towards the central line of gaze (Motter *et al.*, 1987; Motter and Mountcastle, 1981). A second class of PVNs has the opposite pattern of directional sensitivity to that shown in Figure 8, responding only to stimuli that move outward away from the central line of gaze towards the visual periphery. There is no sign of these unusual properties at the input level of the visual system, nor in any of the visual cortical areas projecting over the multi-staged transcortical system from V1 to PG. These properties depend upon integration of intra- with inter-hemispherically projected activity. The inference is that the final representation of movement of the surrounding world is constructed within the parietal lobe cortex.

The results of a series of experiments aimed at the neurophysiological mechanisms of opponency are summarized by the model of Figure 9. Each PVN is related to large, superimposed excitatory and inhibitory receptive fields that are *constructed within the parietal cortex itself.* When the excitatory field is larger than the inhibitory, as in Figure 9, the "all-in" pattern of directionality like that of Figure 8 results. In this case movement of the stimulus inwardly from any point in the periphery towards the central line of gaze first engages the excitatory field, evoking strong responses in the PVN. With further inward movement the stimulus begins to engage simultaneously the inhibitory field, and the delayed but powerful feed-forward inhibition evoked by that continued movement suppresses responses on the outward movement of the stimulus along the meridian. The inference is that for PVNs with "all-out" directionality, the inhibitory field is larger than the excitatory.

The Population Signal of the Direction of Stimulus Movement.

Few PVNs have receptive fields as perfectly symmetrical in the circular dimension of the visual field as that of Figure 8, or as required for the model of Figure 9. More commonly, the receptive fields are asymmetric in such a way that the intensities of the responses evoked by stimuli moving inwardly (or outwardly) with respect to the central line of gaze, along different meridians, are adequately described by a circular sinusoidal

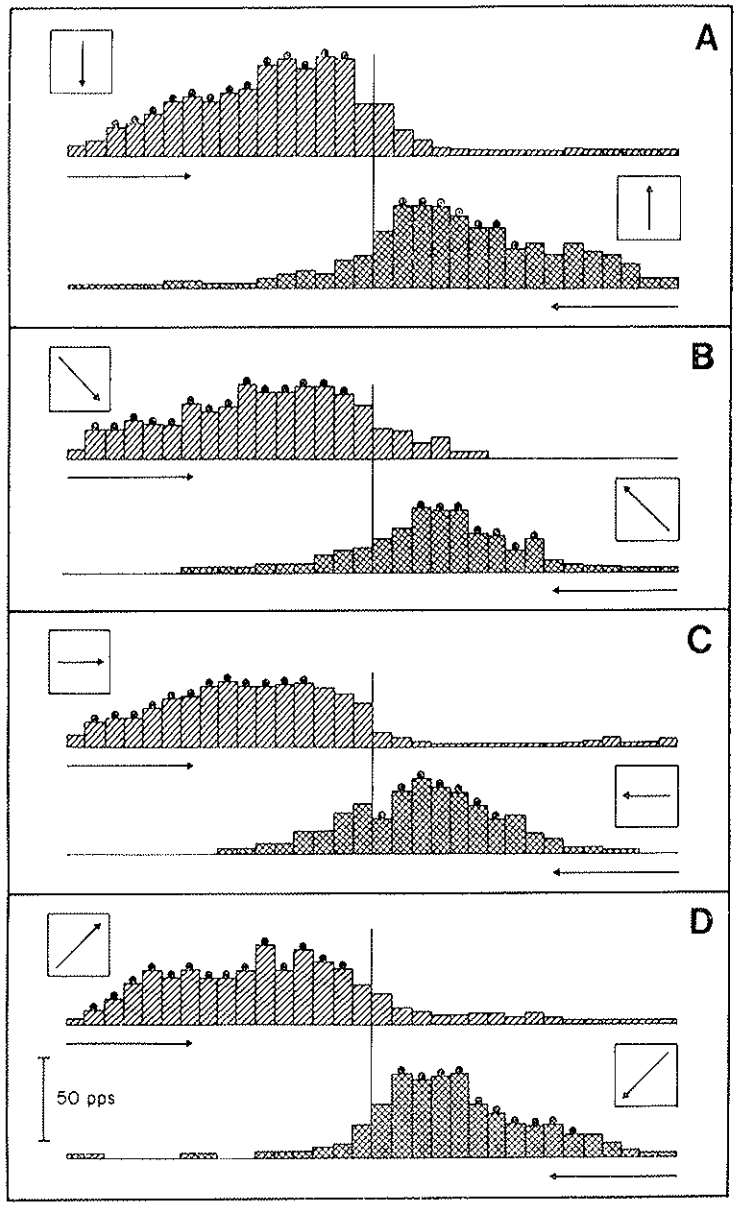


FIG. 8. Histograms of the responses of a parietal visual neuron to stimuli moving for 100 degrees along each of two directions along four meridians through the visual field, centered on the central line of vision: A, vertical; B, diagonal up right 45 deg; C, horizontal; D, diagonal up 45 left 45 deg. Each bin of the spatial histograms = 3.125 deg. Stimuli were 10 × 10 deg squares of light about 1 log unit above ambient background light of 1-2 Cd/sq m., back-projected upon a tangent screen at 34 cm viewing distance, and moved at 60 deg/sec. Trials in the eight directions were randomly sequenced. Directionalities significant at the 0.05 level are marked by dots. The central vertical line is the point of fixation. The zone of transition from one significant directionality to its opposite along each meridian occurred in a space no greater than 6.2 deg for A and D and 9.3 deg for B and C. The response patterns of this neuron give an example of strong and balanced inward opponent organization of directionality along each axis tested. (From Motter *et al.*, 1987).

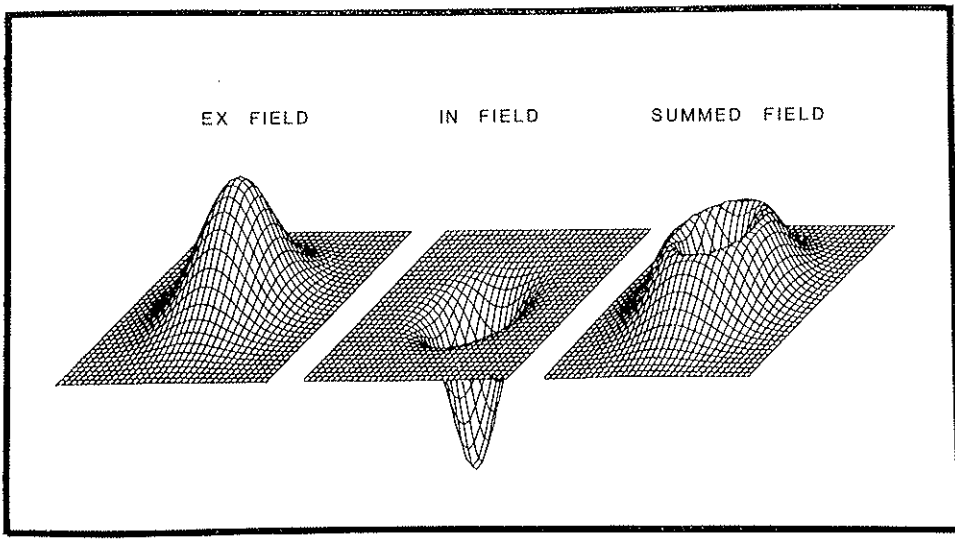


FIG. 9. Three-dimensional, double gaussian model representing the responses of a parietal visual neuron sensitive to inward stimulus motion. The horizontal and vertical dimensions of the visual field are represented on the X- and Y-axes, respectively, and response amplitudes on the Z axis. Left, the excitatory receptive field; center, the inhibitory receptive field; right, a summation of the inhibitory and excitatory influences produces strong responses only on the inward limbs of stimulus motion. (From Motter *et al.*, 1987).

function (Steinmetz *et al.*, 1987). An example is given in Figure 10 for a neuron with a strong inward directionality. This raised the question of whether such PVNs could signal the direction of motion of objects with any useful accuracy, even though the sinusoidal fit specifies a best direction for each neuron. The indeterminate signal of stimulus direction provided by each individual PVN contrasts with the accuracy of primates in perceiving the direction of movement of objects in the periphery of their visual field, and reacting to them. We therefore examined the possibility that a more accurate signal of stimulus direction might be embedded, i.e., constructed, in the activity of the total population of PVNs driven by the movement of a stimulus in a single direction.

We applied to this problem the analysis of linear vector summation. There are several assumptions: (1) that when a PVN discharges in response to any visual stimulus, it always transmits a signal of stimulus movement in its own best direction, the assumption of the labelled line; (2) that the PVN population is related to a neural network able to sum

the activity of all active PVNs in a vectorial manner; and, (3) that when a PVN is suppressed by a stimulus, it provides a positive signal of a stimulus moving in a direction opposite to its best direction. The analysis proceeds as shown for one stimulus movement in Figure 11, which illustrates a vectorial summation constructed from data obtained in a study of 90 PVNs with outward directionality. The discharge of each cell is shown by a vector indicating by its length the intensity of the response of that particular cell, and by its direction the best direction of that cell. The summed population vector (dashed line) is a powerful and accurate signal

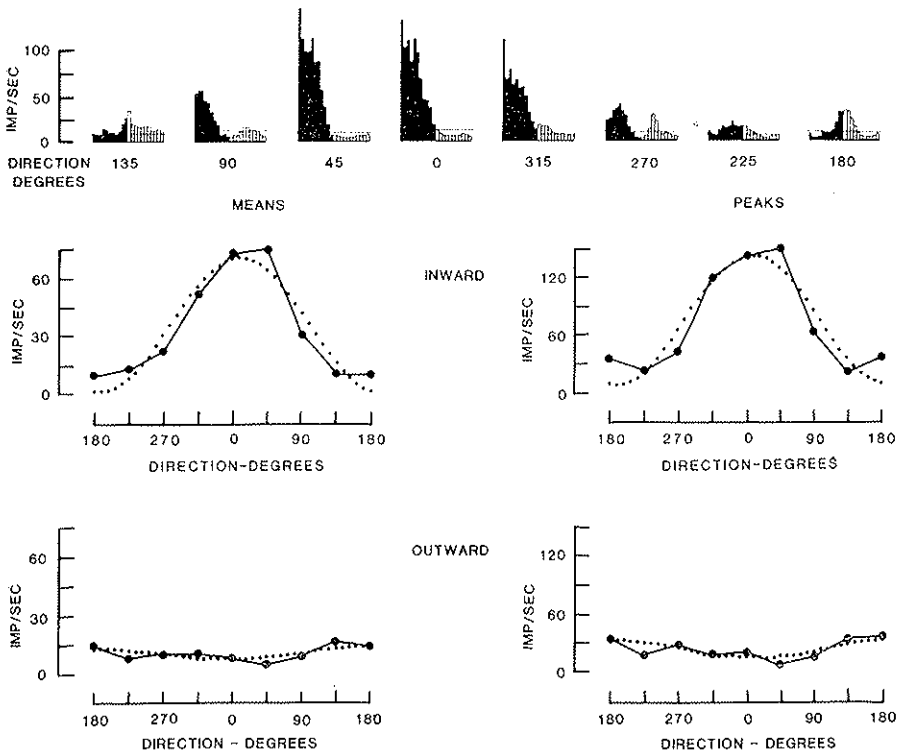


FIG. 10. Sinusoidal variation in the amplitude of the responses of a parietal visual neuron to moving stimuli. The histograms at the top show the time courses for the inward (dark shading) and outward (unshaded) 100 deg stimulus movement in each of the 8 directions indicated. The mean (left) and peak (right) responses are plotted as functions of the direction of stimulus movements for both the inward (middle) and outward (bottom) halves of stimulus movements. Solid lines connect data points; dotted lines show sine waves fitted to the data by periodic regression. (From Steinmetz *et al.*, 1987).

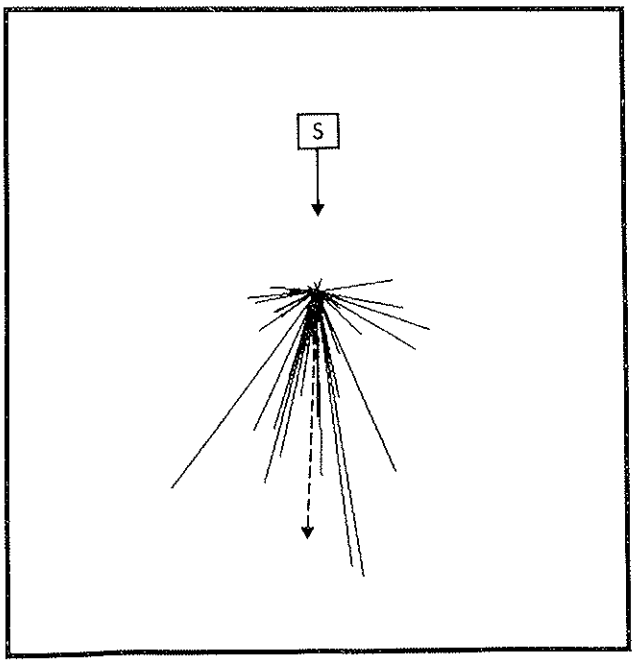


FIG. 11. A model to illustrate the application of the linear vector summation analysis to the responses of parietal visual neurons to moving stimuli. Description is given in the text.

of the direction of stimulus movement. We made a similar analysis for the population of neurons for each of the eight stimulus directions tested, for both inwardly and outwardly sensitive PVNs. The results are shown separately for the two populations in Figure 12. They suggest that the inwardly sensitive PVNs can provide a strong and accurate signal of the direction of a stimulus moving from any angle across the periphery of the visual field and towards the central line of gaze; and similarly for the outwardly sensitive PVN population. How accurately such a population signal might, on this analysis, reflect the true directions of stimulus movement is shown by the graph of Figure 13.

Thus the parietal view of the surrounding world is a special one, a central construction of the visual flow-by, one for which there are no counterparts in the quasi-isomorphic representations of the visual world at the levels of optic nerve or striate cortex. The head of a mammal is surrounded by a halo of marked sensitivity to the movement and to the

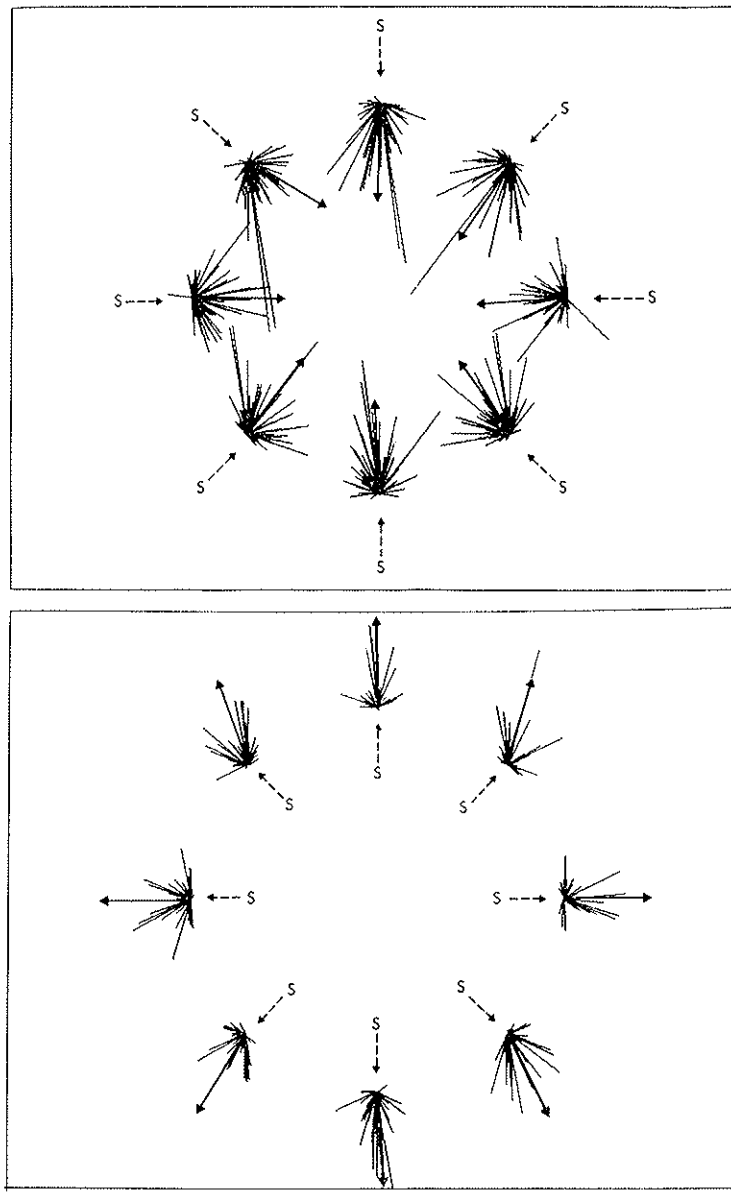


FIG. 12. Individual response vectors and the resulting population vectors (arrows) for the populations of parietal visual neurons studied in each of the 8 directions of stimulus motion along meridians through the visual field, centered on the central line of gaze. Above, for cells responding to inward stimulus motion from the periphery towards the central line of gaze; below, for cells responding to outward stimulus motion. S = stimulus direction, in each case; lines with arrowheads = calculated population vectors. (From Steinmetz *et al.*, 1987).

direction of movement of objects into or out of his visual fields, particularly in the periphery. The parietal lobe system provides a continuously updated image of the apparent movement of the surrounding environment during forward or backward locomotion, or during head turning. It is important to emphasize that we use information from the flow fields in a *pre-conscious mode of processing*, for the control of posture and locomotion and, by a lucky adaptation, in driving high-speed vehicles and landing airplanes.

When a primate is engaged attentively in foveal work, or fixates a target dead ahead during walking or running, there is a drop in his capacity for the conscious processing of contour or color in the extrafoveal visual fields — the function of the temporal lobe system. We discovered, however, that attention has a completely paradoxical effect upon the sensitivity of the parietal visual neurons (Mountcastle *et al.*,

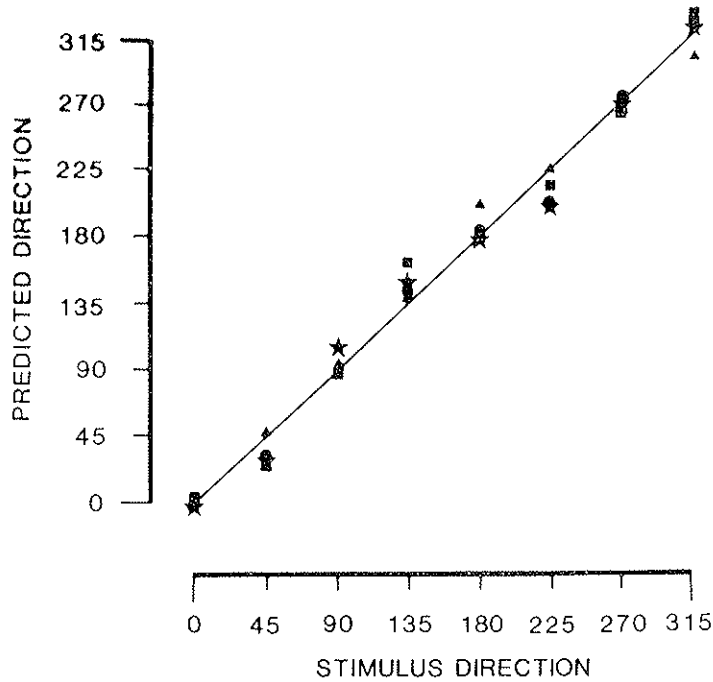


FIG. 13. Population vectors (predicted directions) shown as function of the actual stimulus directions for the populations of parietal visual neurons studied. The near identity relation indicates the accuracy of the population signal derived by the vector summation analysis, in contrast to the signal of a single neuron, shown in *Fig. 12*. (From Steinmetz *et al.*, 1987).

1981). During interested fixation of the target light as the monkey attentively awaits its dimming, there is a 3 to 4-fold *increase* in excitability in the parietal lobe system. The adaptive value of such a facilitation is obvious, not only in guiding locomotion, but as an early warning system, for a primate engaged in closely attentive foveal work is at risk to the predator's strike across the periphery of his visual field.

Summary and Conclusion

Each of us lives in the center of his own perceptual space, and from that central position each experiences the functioning of his own brain. That capacity for internal self-conscious experience is surely one of the most perplexing phenomena in all of biological science. Through your sensory systems you gain some abstracted images — representations — of what is outside. Complexing these with stored expectations and memories, you construct in neural space and time a continually updated image of the surrounding environment, of objects and events within it, of your movements through it.

You construct — that is my central theme. Only rarely are our representations of the external world at central neural levels isomorphic with physical reality. Indeed the majority of representations are central neural constructions, and for the more interesting cases of which we know they cannot be derived directly from the peripheral afferent input upon which they of course depend. Let the visual flow fields, or stereognosis, or the concept of body image stand as examples.

Our concept of how we construct reality as expressed by representations at the neural level includes the successive and parallel transformations imposed by the microstructure of sensory systems and cerebral cortex. The cerebral microstructure is in the first instance set genetically, but it is maintained dynamically, and is continually modified by life experience. Thus each of us constructs, stores, and recalls his own uniquely private image of the world and events within it. Your images and my images may at times be identical and viridical as regards physical reality. More often they are constructions that differ between individuals, differences determined by the different microstructures and dynamic processing mechanisms within each of our own brains. Thus we glimpse even at these rather primitive levels of brain function neural mechanisms that contribute to the uniqueness of each human personality.

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DISCUSSION

ZEKI

If these cells are constructed in the parietal cortex itself, there are substantial similarities between what you describe and the properties of the colour cells constructed in V4.

In V4 there is good evidence of a massive amount of intrinsic connections that is able to accumulate information from a large part of the field of view. Is there any evidence for a quasi topographic input into the parietal cortex and then a massive set of internal connections which could do the topographic erosion, so sacrificing topography for constructing the property?

MOUNTCASTLE

All of my evidence suggests that there is no retinotopic representation, and no evidence for a retinotopic input.

ROLAND

We published a model of reconstruction of three-dimensional objects in the "Brain Research Review" in 1987. In those experiments we had human beings having their own fingers sliding over objects that they were supposed to discriminate. In texture discrimination and shape discrimination, the subjects automatically chose a velocity of manipulation which will secure the maximum information transformation up to the somatosensory cortex. Is that a general principle that you would think would apply also when you look at floating vector stimulation or other types of stimulation?

MOUNTCASTLE

The evidence is as follows: the parietal visual neurons are sensitive to moving stimuli over a velocity range from 50 to 500 degrees per second. The curves are very flat. Concerning the movement of the receptor sheet, it is interesting to point out that it isn't movement of the sheet by the subject that matters but just that interaction. The sensitivity is just as good if the object is moved over the finger. I should add that about 15% of the parietal visual

neurons do not respond at all unless the stimulus moves. One only discovers them by testing with moving stimuli.

ROLAND

Next, is that you showed the letters. In areas 3B there are so-called slowly adapting neurons and we can discuss afterwards what that really means, but the representation seems to be more accurate in area 3B, whereas if you come further posterior it becomes less accurate.

MOUNTCASTLE

The statement that area 3B is dominated by slowly adapting afferents is not true. Modules that are both quickly and slowly adapting exist side by side. But here I am talking about a different type of construction. This is a population construction, still preserving some semblance of isomorphism to the periphery. I used it as a transition from the purely isomorphic input for temporal order to the flow fields.

ROLAND

The last thing is, where are the many modules that are active in the posterior parietal cortex, each constructing a population vector, where is that summed, where is that added up?

MOUNTCASTLE

In my opinion it is never summed. I think the idea of convergence towards summation points is wrong. There are no grandmother cells, there are no pontifical modules.

ROLAND

But there is an output.

MOUNTCASTLE

There is an output to all those regions that Patricia Goldman-Rakic talked about yesterday, but I think that output is an ensembled matching, no summation points. But that's just an idea.

SINGER

Are the neurons with the anisotropic directionalities the same as the set field neurons, which detect movements in the set axis?

MOUNTCASTLE

I have not tested for that.

SINGER

Now if this were the case, and since they seem to require callosal connections in order to do this, people studying callosal section in patients should look for these disturbances, because there must be something wrong in the way in which these patients perceive space.

MOUNTCASTLE

Absolutely. They shouldn't be allowed to drive cars.

BAUMGARTNER

Do you have any idea where spatial coordinates come in in this system?

MOUNTCASTLE

I have looked very hard for that. I think your question is aimed at a fundamental problem. Where do we transit in spatial coordinates from sensory to motor space? I don't think that these cells do it. You know that there is an effect to the angle of gaze, such that the excitability of the cells is affected by the change of the angle of gaze which Andersen described some years ago. I don't believe that the theoretical construct of that meets the requirement. I think there will be some other set of cells somewhere which does that. It's too simplistic, this deviation of gaze effect, but I might be wrong on that. But I looked, and never have observed sets of cells that were disjunctive from the retinotopic coordinates.

GOLDMAN-RAKIC

I'd like to make the comment that the peripheral field of the parietal neurons fits with the projection observed in several laboratories, including

ours, major from area PO which has the highest peripheral representation. This is a very nice correlation with anatomy.

ZEKI

In PO, which I call V6, the cells do have peripheral fields, but they do respond to contours. They are selective for contours.

JEANNEROD

Did you say where these visual neurons are located, in area 7?

MOUNTCASTLE

Yes, they reside in modules that are distributed through area 7, including the posterior bank of the anterior parietal sulcus, where one can see them in single concentrations interspersed with modules containing projection neurons, high movement neurons, etc.

JEANNEROD

So don't you think that contradicts somehow the effect of lesions because as I understand from the Michigan groups and other groups too, the lesions which produce the mismatching, for instance, are not the same as those which produce the visual disorientation.

MOUNTCASTLE

That may be true. The lesion experiments which I have studied indicate that the whole inferior parietal lobule is not differential in nature.

THE MIND-BRAIN PROBLEM REVISITED: THE MICROSITE HYPOTHESIS

JOHN C. ECCLES

1. *Introduction*

Mind-brain dualism demands primarily two authentic orders of existence with completely independent ontologies. As has long been recognized, this dualism necessitates transactions across the mind-brain interface in both directions (Fig. 1). Such formidable problems have led to various types of evasions, which are exemplified in Fig. 2 by the 4 materialist theories of the mind.

The only one of present interest is the identity theory, according to which the mind-brain problem is resolved by the proposed "identity" of mental events with neural events in the activities of the higher centers of the brain (Feigl, 1967), which is essentially a materialist hypothesis (Popper and Eccles, 1977).

The alternative hypothesis (dualist-interactionism), (Popper and Eccles, 1977) has been severely criticized for its alleged violation of the conservation laws of physics. However, by following up a suggestion of the quantum physicist Margenau (1984), it was possible to develop the microsite hypothesis (Eccles, 1986) according to which mental events can effectively act on neural events by selecting for exocytosis vesicles of the presynaptic vesicular grid (Fig. 3) by a process analogous to a probability field of quantum mechanics. In this way a mental event of intention could bring about appropriate neural events, for example on the supplementary motor area (SMA), for instituting the intended movement (cf. Fig. 4; Roland *et al.*, 1980).

The key concept is that in mind to brain interaction, in intention for

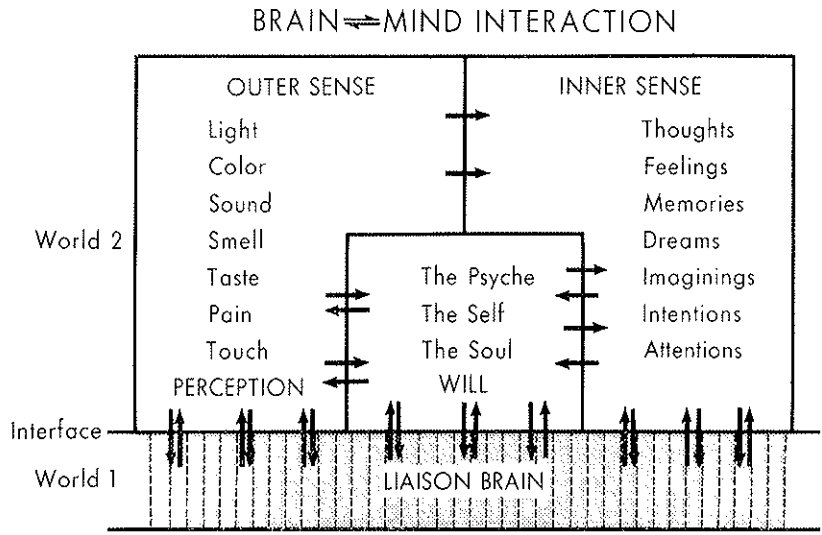

FIG. 1. Information flow diagram for brain-mind interaction. The three components of World 2 — outer sense, inner sense and the psyche of self — are diagrammed with their connectivities. Also shown by reciprocal arrows are the lines of communication across the frontier between World 1 and World 2, i.e., from the liaison brain to and from these World 2 components. The liaison brain has the columnar arrangement indicated. It must be imagined that the area of the liaison brain is enormous, with open modules probably numbering a million or more and not just the 40 here depicted. Note that memories lie in the inner sense of World 2 as well as in the data banks of the modules of the liaison brain.

example, the mental event has no initiative in bringing about an exocytosis in the presynaptic vesicular grid (PVG). All it can do is to select a vesicle of the PVG for exocytosis when there is a neural activation of the PVG that could lead to its exocytosis (Fig. 3A). In this selection the mental event operates by a process analogous to a probability field of quantum mechanics (Margenau, 1984) and so does not violate the conservation laws.

In the original formulation of the microsite hypothesis there was concentration on the manner of operation of the downward arrows across the interface — from mental events to neural events. The reverse arrows, from neural events to mental events, would imply that, when a mental intention successfully selects a vesicle of the presynaptic vesicular grid (Fig. 3) for exocytosis, this is recognized as a mental success. For example,

there would be a mental follow-up of every intended movement before it could be recognized physiologically from the motor response. So, according to the microsite hypothesis of mind-brain interaction, all transactions across the interface of Fig. 1 are reciprocal even at an elemental level, as shown by the arrows in Fig. 1. This proposed reciprocity will be discussed below in relation to special problems of perception.

2. *Mini Columns, the Units of the Neocortex*

Mountcastle (1978) defined the basic modular unit of the neocortex as a minicolumn. It is a vertically oriented cord of cells formed by the migration of neurons from the germinal epithelium of the neural tube along

DIAGRAMMATIC REPRESENTATION OF BRAIN-MIND THEORIES

World 1 = All of material or physical world including brains
World 2 = All subjective or mental experiences
World 1_P is all the material world that is without mental states
World 1_M is that minute fraction of the material world with associated mental states

Radical Materialism: World 1 = World 1_P; World 1_M = 0; World 2 = 0.

Panpsychism: All is World 1-2, World 1 or 2 do not exist alone.

Epiphenomenalism: World 1 = World 1_P + World 1_M
World $1_M \rightarrow$ World 2

Identity theory: World 1 = World 1_P + World 1_M
World 1_M = World 2 (the identity)

Dualist - Interactionism: World 1 = World 1_P + World 1_M
World $1_M \Leftrightarrow$ World 2; this interaction occurs in the liaison brain, LB= World 1_M.
Thus World 1=World 1_P+ World 1_{LB}, and
World $1_{LB} \Leftrightarrow$ World 2

FIG. 2. Schematic representation of the various theories of brain and mind relationship. World 1 is the world of matter-energy, World 2 is the world of conscious experiences. Further description on the figure and in text.

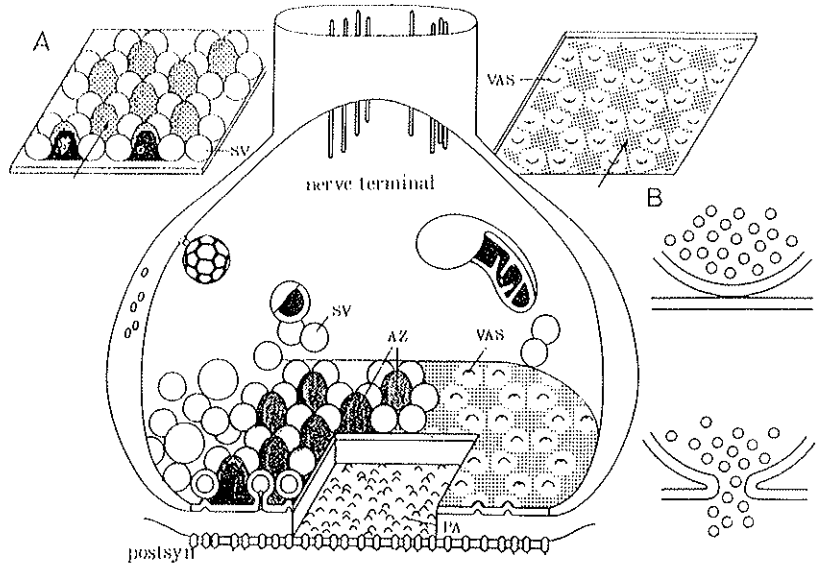

FIG. 3. A) Schema of the mammalian central synapse. The active zone is formed by presynaptic dense projections (az). The postsynaptic aggregation of intramembraneous particles is restricted to the area facing the active zone. sv = synaptic vesicles, pa = particle aggregations on postsynaptic membrane (postsyn.). Note synaptic vesicles (sv) in hexagonal array, as is well seen in the upper left inset, and the vesicle attachment sites (vas) in the right inset. Further description in text (Akert *et al.*, 1975). B) Stages of exocytosis with release of transmitter into the synaptic cleft (Kelly *et al.*, 1979).

the radial glial cells to their destined locations in the cortex, as described by Rakic (1972), and as illustrated in Fig. 5. Already Fleischhauer *et al.* (1972) had described bundling of apical dendrites of the cortical pyramidal cells (Fig. 6A) that can be recognized in a tangential section of the rabbit parietal cortex at Lam IV level (Fig. 6B). These original observations were developed in a series of investigations by Fleischhauer and colleagues and also by Feldman and Peters (1974). Fig. 7 illustrates a tangential section of the rat visual cortex with bundles clearly recognizable, one being defined by the open arrows (Feldman, 1984).

A definitive study has been made by Peters and Kara (1987). In Fig. 8A a Golgi stained preparation shows many Lam. V pyramidal cells, two large, numbers 1 and 2, and four medium, 3, 4, 5, 6, but of course the low frequency of Golgi neuronal staining makes it unsuitable for demonstrating apical bundling. Bundling is well seen in the tangential

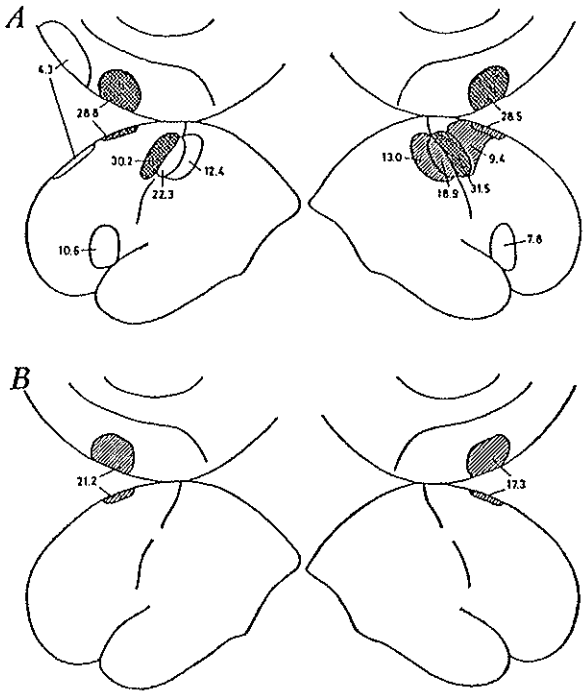

FIG. 4. A) Mean increase of the rCBF in percent during the motor-sequence test performed with the contralateral hand, corrected for diffuse increase of the blood flow. Cross-hatched areas have an increase of rCBF significant at the 0.0005 level. Hatched areas have an increase of rCBF significant at the 0.005 level, for other areas shown the rCBF increase is significant at the level 0.05. Left: left hemisphere, five subjects. Right: right hemisphere, 10 subjects. B) Mean increase of rCBF in percent during internal programming of the motor-sequence test, values corrected for diffuse increase of the blood flow. Left: left hemisphere, three subjects; right hemisphere, five subjects, rCBF = regional cerebral blood flow, (Roland *et al.*, 1980).

section of Fig. 8B at Lam. IV. Nomarski optics (Fig. 9) reveals in a vertical section the creation of a bundle by converging apical dendrites and its ascent to Lam. I.

Peters and Kara (1987) regard the large Lam. V pyramidal cells as being central to a bundle or cluster, to which there is accretion by the medium dendrites of Lam. V, making an average composition of about 20 in the tangential sections of Lam. IV (Figs. 6B, 7, 8B). As the bundle ascends through Lam. III and II, there is a large accretion of the apical dendrites of Lam. III and II pyramidal cells with the result that the large

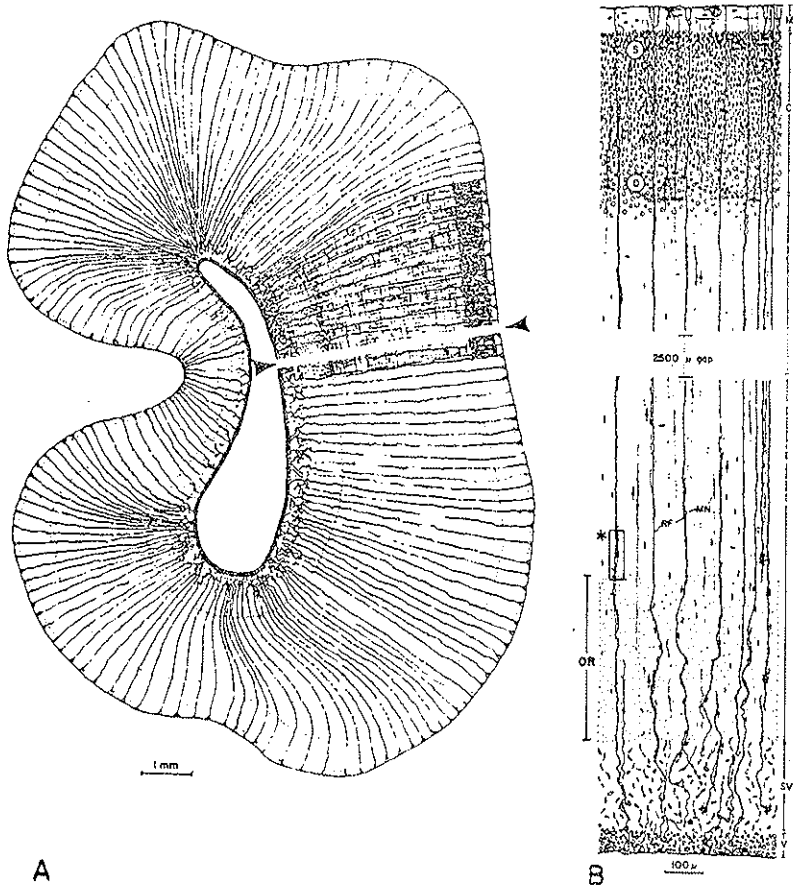

FIG. 5. A) Camera lucida drawing of a Golgi-impregnated coronal section at the parieto-occipital level of the brain of a 97-day monkey foetus. The radial fibers are inscribed in slightly thicker lines than in the actual specimen in order to illustrate their arrangement at such a low magnification (scale equals 1 mm). The area delineated by the white strip between the arrowheads is drawn in B at higher magnification. B) Composite camera lucida drawing of the cerebral wall in the area indicated by the white strip in A. The middle 2500 μ of the intermediate zone, similar in structure to the sectors drawn, is omitted. Abbreviations: C, cortical plate; D, deep cortical cells; I, intermediate zone; M, marginal layer; MN, migrating cell; OR, optic radiation; RF, radial fibre; S, superficial cortical cells; SV, subventricular layer; V, ventricular zone (Rakic, 1972).

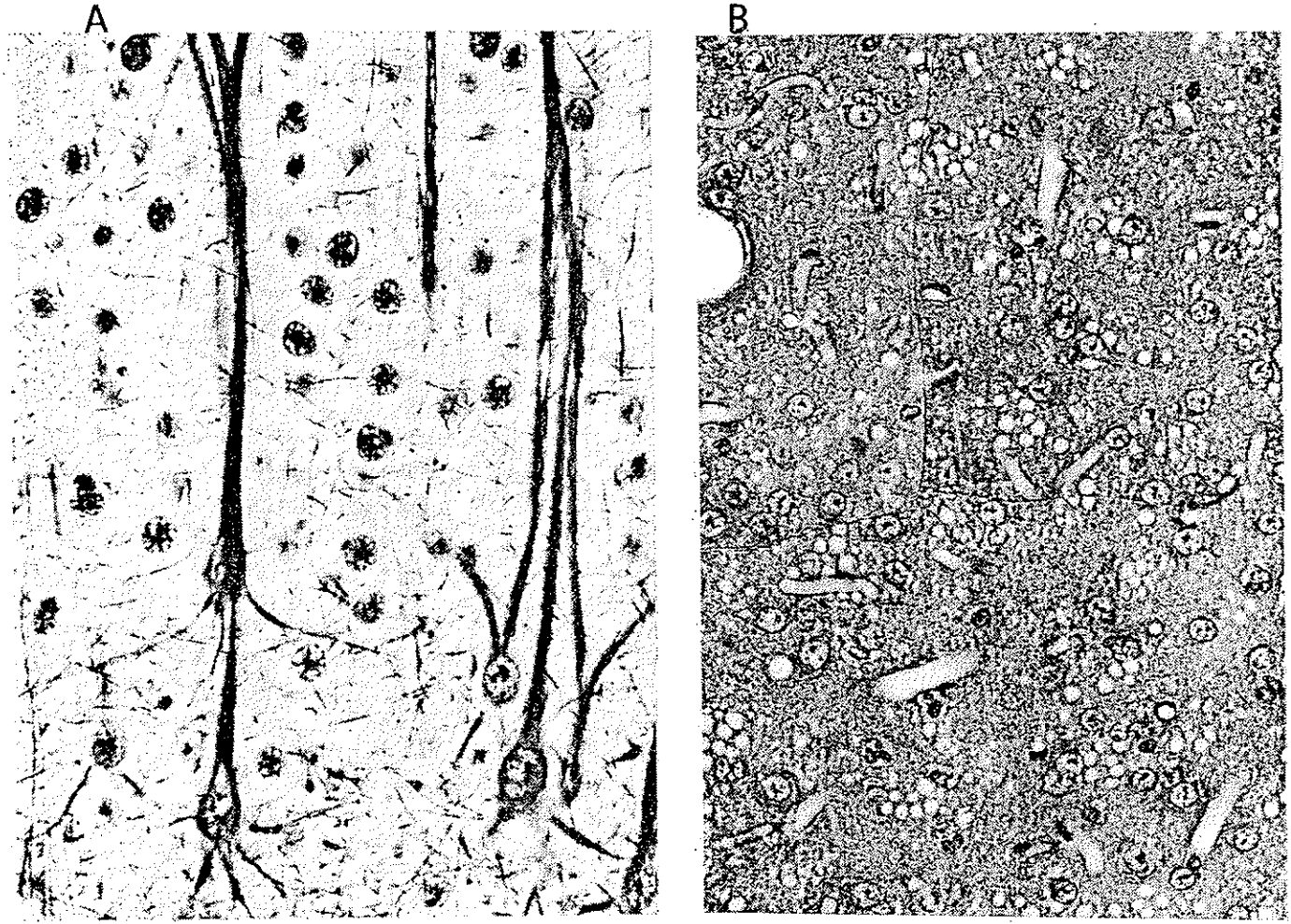

FIG. 6. A) Frontal section through the gyrus lateralis of the cat. Bundles of apical dendrites being formed in the upper part of layer V and extending through layer IV. Bodian x 350. B) Tangential section through parietal cortex of the rabbit's brain. In layer IV, many of the cross sections through large apical dendrites are organized in distinct groups, each indicating a vertical bundle of dendrites. Klüver PAS haematoxylin. (Fleischhauer *et al.*, 1972)

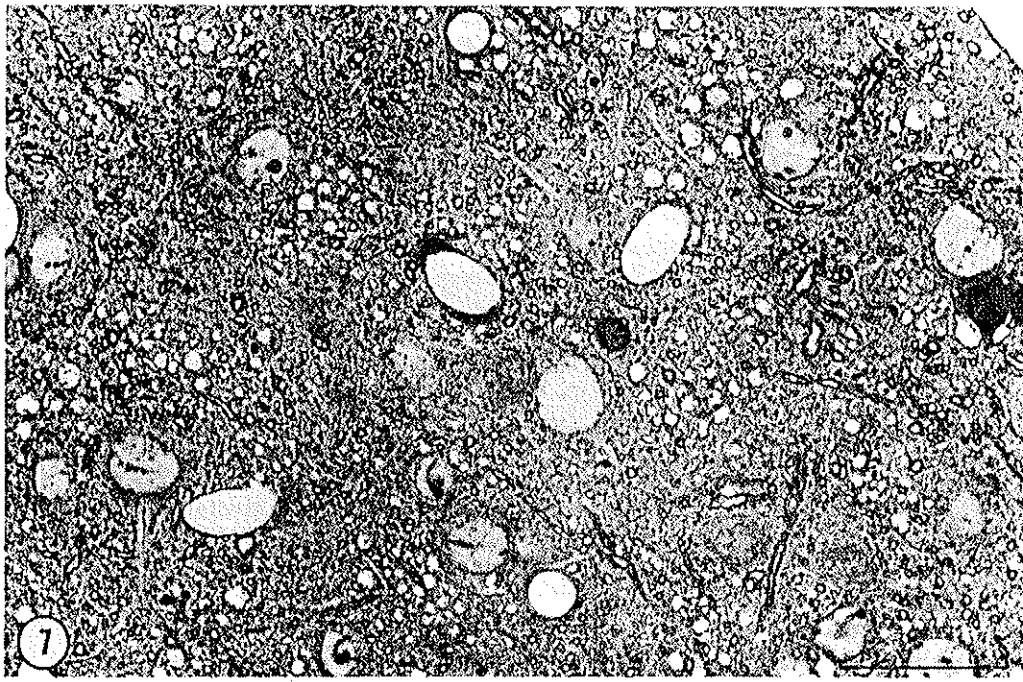

FIG. 7. Apical dendritic clusters as visualized in a tangentially oriented 2-μm plastic section at the level of layer IV of rat visual cortex. One cluster is indicated by open arrows. Calibration line, 25 μm. (Feldman, 1984).

bundles of almost 100 dendrites are no longer distinctly separated. The average spacing is given at 55 μm between centres.

Peters and Kara (1987) propose that the dendritic bundles or clusters are the smallest structural and functional units of cell assemblage in all regions of the neocortex. I will reintroduce the disused word "*dendron*" for such units. If there are 80 to 100 apical dendrites (V, III and II) in a dendron, then it can be calculated that there are about 40 million of such units in the human neocortex. I will propose that this number of dendrons is adequate for providing the unitary basis for the neocortex in all of its extreme diversity and subtlety. Naturally it is not conceived that such a unit has a precise fixed neuronal composition. As a cluster it ascends to Lam. I with enlargement by accretion of the apical dendrites of III and II pyramidal cells. The enlargement could result in partial overlap with adjacent units (Peters and Kara, 1987). Despite these

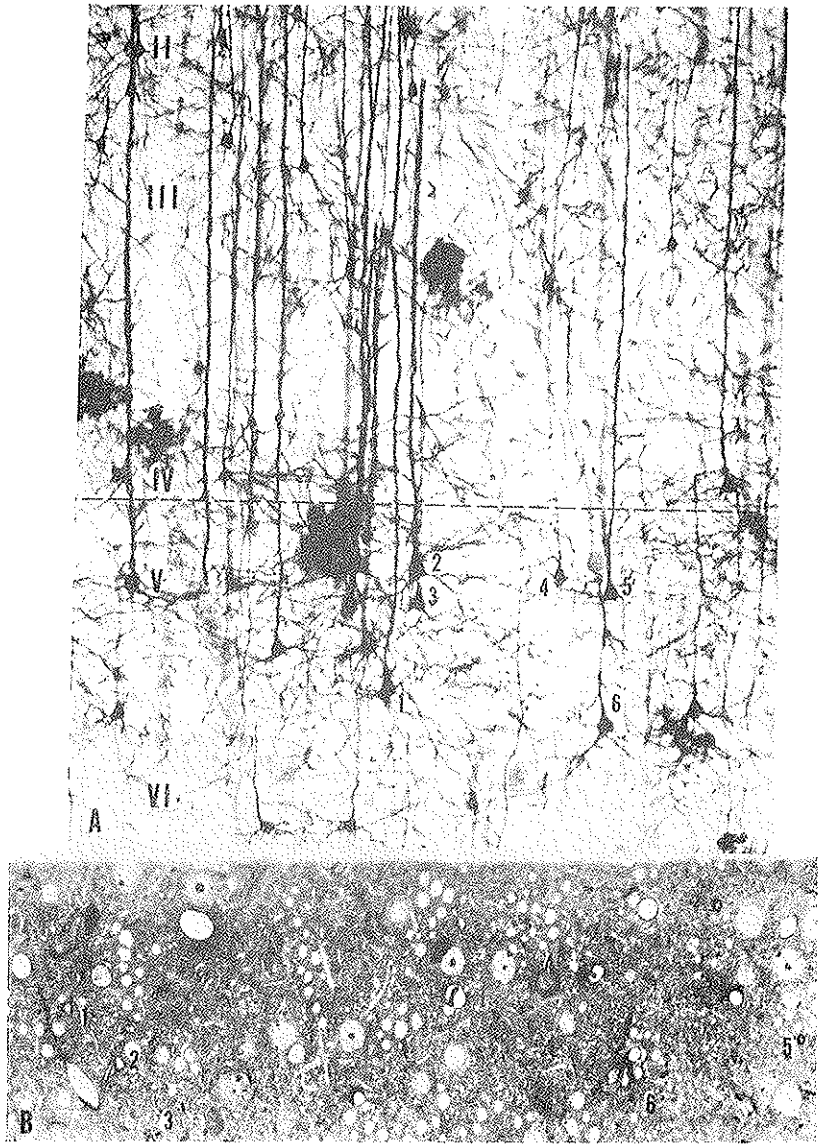

FIG. 8. A) Golgi preparation of rat visual cortex (area 17) in a vertical section through laminae II to VI to show apical dendrites of lam. V pyramidal cells projecting through lam. IV, III and II. B) Tangential section of lam. IV at the level indicated by the broken line in A. The arrangement of the apical dendrites in clusters (open circles) can be well seen. (Peters and Kara, 1987).

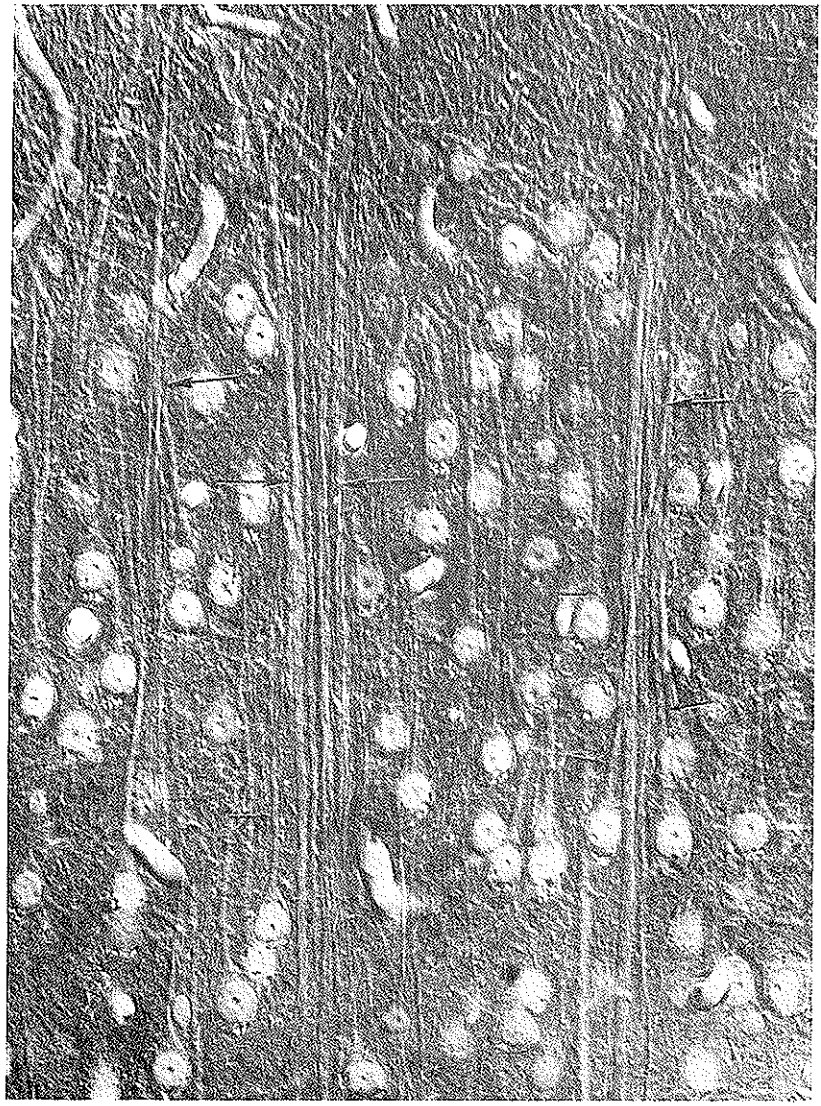

FIG. 9. Vertical section of the rat visual cortex (area 17) through laminae IV to I to show 3 clusters of dendrites as indicated by the horizontal arrows. Nomarski Optics. Note that pyramidal cells of lam. III add to the clusters (Peters and Kara, 1987).

reservations the dendron is the only possible unit for the neocortex. An important finding is that beyond about 50 μm from their origin the apical dendrites are thickly encrusted with synaptic spines (Feldman, 1984, Fig. 11).

3. *Mental Units of Conscious Experiences*

The hypothesis that the dendron is the neural unit of the neocortex leads on to the attempt to discover the mental unit which interacts with the dendron in attention and intention as shown by the reciprocal arrows across the interface in Fig. 1. At present the experimental evidence is adequate only for establishing that mental intentions and attentions can indeed excite the dendrons but the observed actions are massive (Fig. 4), hundreds of thousand of dendrons, presumably because of the operation of hundreds of thousands of mental events.

For example Fig. 10 illustrates the remarkable finding of Roland (1981) that, when the human subject was attending to a finger on which

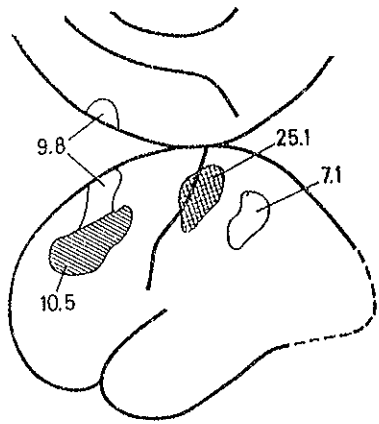

FIG. 10. Mean increase of rCBF in percent during pure selective somatosensory attention; that is, somatosensory detection without peripheral stimulation. The size and location of each focus shown is the geometrical average of the individual focus. Each individual focus has been transferred to a brain map of standard dimensions with a proportional stereotaxic system. Data from the right and left hemisphere have been pooled. The cross-hatched area has an increase of rCBF significant at the 0.0005 level (Student's test, one-side significance level). For the other areas shown the rCBF increase is significant at the 0.05 level. Eight subjects (Roland, 1981).

just-detectable touch stimuli were to be applied, there was an increase in the rCBF over the finger-touch area of the postcentral gyrus of the cerebral cortex as well as in the midprefrontal area. These increases must have resulted from the mental attention, because no touch was applied during the recording. Thus, Fig. 10 is a clear demonstration that the mental act of attention can activate appropriate regions of the cerebral cortex. A similar finding occurs with attention to the lips in expectation of a touch, but of course the activated somatosensory area is now that for the lips. A large prefrontal area was also activated during the anticipation. We have to ask if the mental attention actually had a fine grain matching the dendrons on which it was acting.

A complementary investigation was on the mental intention for carrying out a complex learnt series of movements, the motor sequence tests (Roland *et al.*, 1980). When the subject was mentally rehearsing the movement sequence without carrying out any movement, there was a large mental activation of the supplementary motor area on both sides (Fig. 4B). Again we have to ask if the mental intention had a fine grain, being a composite of mental units matching the dendrons on which it was acting.

The microsite hypothesis (Eccles, 1986) was deficient in that it did not define precisely the mental events that were assumed to be acting on the neural events. They had a rather nebulous character! However, a radical development is now necessary in the attempt to extend the microsite hypothesis to perception and to the whole range of subjective experiences in the World 2 of Fig. 1. The new hypothesis is that all mental events and experiences, in fact the entire composition of the outer and inner senses of World 2 (Fig. 1) is a composite of elemental or unitary mental events. Each of these mental units is reciprocally linked in some unitary manner to a dendron. Appropriately we can name this postulated mental unit a "*psychon*". According to the unitary hypothesis there is a unitary linkage of each dendron with its psychon.

The dendron has been a fixed anatomical structure since puberty except for the synaptic plasticity of learning, but functionally there are great variations according to the intensity of neural inputs. It is similar functionally to the linked psychon, which can be at all levels of mental intensity from zero to a maximum functional linkage with its dendron.

4. *Linkage of Psychons to Dendrons of the Neocortex. The Unitary Hypothesis*

The linkage has been crudely indicated in Fig. 1 by the reciprocal arrows across the interface, and now is more precisely drawn in Fig. 11. The pyramidal dendrites are shown for 3 dendrons in accord with the experimental evidence of Figs. 6, 7, 8, 9. There has even been shown the small proportion of apical dendrites of Lam. V that wander and do

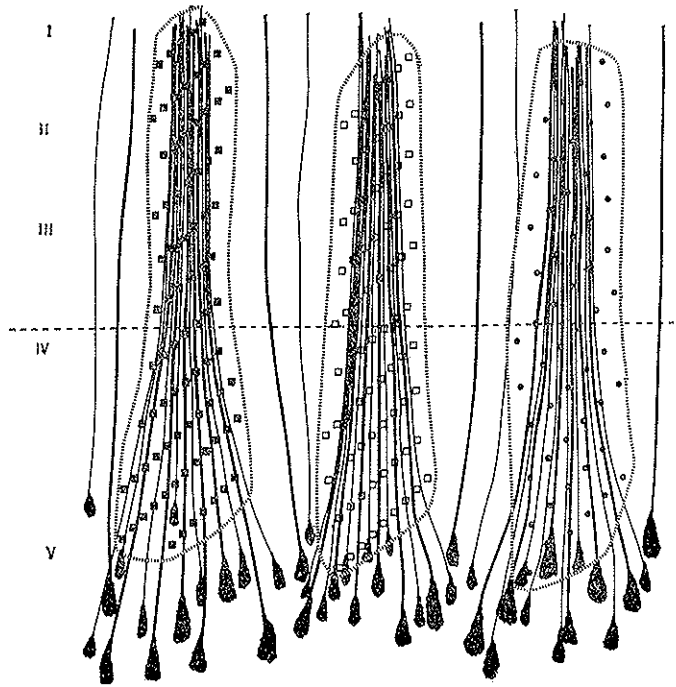

FIG. 11. Drawings of 3 minicolumns showing manner in which the apical dendrites of large and medium pyramidal cells bunch together in lam. IV and more superficially, so forming a neural unit. A small proportion of apical dendrites do not join the bunches. The apical dendrites are shown terminating in lam. I. Actually this termination is by a tuftal branching in lam. I, but that is too complicated to show in this diagram. The other principal feature of the diagram is shown by the superposition on each neural unit or dendron, of a mental unit or psychon, that has a characteristic marking (solid squares, open squares, solid circles). Some insight can be given when it is recognized that the human neocortex has about 40,000,000 dendrons each linked with a psychon that gives its own characteristic unitary experience. This figure was drawn before seeing the beautiful stereoscopic picture by C. Schmolke, « Anat. Embryol. », *176*, 203-212 (1987).

not join the bundles (Peters and Kara, 1987). Superimposed on each of these 3 dendrons are 3 psychons, each with its unique character that is indicated by squares, open squares and dots, and each covering the whole dendron. No doubt the congruity is idealized in the diagram, and of course there are multitudes of closely related psychons, that could be represented similarly by squares, open squares and dots — that are in unitary relationship with similar dendrons. The three different psychons give some feeling for the complexity of patterned relationship between dendrons and psychons. There could be thousands of types of psychons — each with its own dendron.

It may seem that, in this intimate linkage of dendrons and psychons, the new unitary hypothesis of dualist-interactionism is merely a further refinement of the materialist identity hypothesis referred to in Section 1 above. This is a mistake. Independence of existence is accorded to psychons as is indicated in Fig. 1. Fig. 1 has often been wrongly interpreted because World 2 is drawn above the World 1 of the brain. This was for diagrammatic convenience. The reciprocal arrows across the interface show that all the World 2 action is in the neocortex.

This proposed unitary linkage between mental units and neural units (Fig. 11) leads to many theoretical developments that in turn will lead to the development of experimental testing procedures. Already there is a vast literature in experimental psychology and neurology that can be assimilated to this unitary theory of mind-brain interaction. For this lecture it is of immediate interest to develop the unitary theory in attempting to explain mind-brain interaction in perception by utilizing quantum mechanics as has already been done for mental intentions activating neuronal units in the SMA (Fig. 4; Eccles, 1986).

In Fig. 3B it can be seen that to institute an exocytosis it is merely necessary to displace a small area of the double membrane that may be no more than 10 nm thick, and if it was 10 nm by 10 nm in area it would be a particle with a mass of only 10^{-18} g, which would easily bring it into the range of quantum mechanics and the uncertainty principle of Heisenberg (cf. Margenau, 1984; Eccles, 1986), particularly as the vesicles are already in position on the presynaptic vesicular grid (Fig. 3A), so that the exocytosis is not dependent on movement through a viscous medium. The postulated mental influence would do no more than *select* for exocytosis a vesicle already in apposition. In response to a triggering impulse, the probability of exocytosis is much less than unity for the ensemble of

vesicles in the presynaptic vesicular grid (Jack *et al.*, 1981; Korn and Faber, 1987).

The unitary hypothesis transforms the manner of operation of the intention. If, for example, the psychon for a mental intention is diagrammed by the pattern of squares on the left dendron of Fig. 11, it can be seen that the intention is acting on the whole dendron with its assembled pyramidal dendrites and their synapses, which could number tens of thousands. So the mental intention would have a large global operation on that dendron. On the unitary hypothesis the psychon would of course operate at each microsite of its dendron in selecting by means of the quantal probability field, a vesicle for exocytosis. However, collectively there could be tens of thousands of such microsites on one dendron. A great amplification is ensured by the unitary operation of the linked psychons and dendrons. One has to recognize that in a lifetime of learning the intention to carry out a particular movement would be channelled largely to those particular psychons that are linked to those dendrons of the neocortex (the SMA) that are appropriate for bringing about the required action (Fig. 4).

5. *How Neuronal Activity in the Sensory Systems Could Evoke Conscious Perceptions* (the outer sensing of Fig. 1)

Hitherto, for the whole range of perceptual experiences, there has been no microsite hypothesis. The additional hypothesis for all the upward arrows of Fig. 1 can be developed in stages. Perception is dependent on a *directed attention.* As seen above in Fig. 10 a mental attention to some surface of the body activates the neocortical areas specifically related to that area, and also more widely to the frontal lobe. No special hypothesis is needed beyond the microsite hypothesis already developed for the action of intention on the dendrons of the SMA (Eccles, 1986).

The response of the neocortex to attention (Fig. 10) is preparatory to the transaction whereby dendrons are activated in the perceptual process to produce the perceptual mental events. For example, it can be asked how activated dendrons of the tactual system give rise to some specific tactile perception. It is the problem of the reverse arrows from World 1 to World 2 of Fig. 1.

Let us concentrate on the attentional act whereby psychons are exciting dendrons (Fig. 10) in accord with the microsite hypothesis. On to that background there is superimposed an activation of the dendrons by

some perceptual input, for example a tactile input which could specifically excite the PVG's of the dendron linked to the psychon to the right of Fig. 11 (indicated by dots) that gives a tactual perception. So the psychon has an increase in those PVG's with vesicles available for exocytosis in accord with the quantal probability field. The hypothesis is that each such exocytosis is a "success" for the psychon giving a signal that is transmitted into the mental world, World 2 of Fig. 1.

The sequence for tactual perception would be:

1) Background activation by attention to the tactual area (Fig. 10).

2) Sensory input into the tactual nervous system.

3) Activation of dendrons in the neocortex of the tactual system.

4) Increased exocytoses from the presynaptic vesicular grid (PVG's) of the pyramidal cells giving increased opportunity for selective exocytosis by the linked psychon (cf. Fig. 11, solid circles) which is in accord with a quantum probability field.

5) The increase in vesicular selection by the psychon for touch is a "success" signal into World 2 and so to the tactual perception. All other perceptions of the outer sense in Fig. 1 could be similarly explained.

This unitary perceptual hypothesis is inadequate because it is limited to specifically linked dendrons and psychons (Fig. 11). There is no explanation of the tremendous enigma of our perceptual experiences. For example, from some dynamic activity pattern of millions of psychons, we perceive a visual picture with all its qualities and movements. It could be that an explanation may emerge from the mental integration of the diverse activities of dendrons in stage after stage of the visual processing system.

It would have to be assumed that at each stage the psychons are dependent on the dendrons. Presumably a diagram such as that of Fig. 11 is applicable even to the highest levels of the neocortex with its gnostic functions.

When considering the further program in our understanding of the neocortex, it may be of value to document some important numbers.

Except for the rat's visual cortex we can adopt the average figure of 200 dendrons per mm^2 for the whole neocortex — human as well as higher mammals. Van Essen (1985) gives the area of the human striate cortex as 26 cm^2 in each hemisphere, but with all prestriate areas it becomes 150 to 250 cm^2. Adopting a mean of 200 cm^2 there will be 4 million dendrons. This is for the early stage of visual processing. In the route test for visual

remembrance Roland and Friberg (1985) found an enormous activation of the frontal lobes, which could involve millions of dendrons. As stated above, there are about 40 million dendrons in the human neocortex.

6. *Conclusions*

An extension of the microsite hypothesis of mind-brain interaction has led to some extraordinary developments which are as yet very tentative. The original microsite hypothesis used quantum physics in explaining how a non-material mental event, an intention to move, can cause microsite activity across the interface between mind and brain — largely in the SMA (Eccles, 1986). The attempt to develop this hypothesis for the brain-mind problem in perception has necessitated a radically new hypothesis.

This hypothesis is built on recent discoveries that the neocortex is composed of dendrons. The hypothesis is further that mental events are also composed of units, called psychons, each unit being intimately linked to its dendron, as is drawn in Fig. 11. Brain-mind transactions take place between these units at the numerous microsites (tens of thousands) on the synapses of the pyramidal dendrites of a dendron.

In the original microsite hypothesis (Eccles, 1986) the mental intention acted in accord with quantum physics (Margenau, 1984) to select for exocytosis a vesicle of the activated presynaptic vesicular grid, PVG (Fig. 3). It was a unitary action at a microsite and had to be enormously amplified by assuming that there were thousands of microsites on that dendrite and on many adjacent pyramidal cells.

In this present unitary hypothesis the linked dendrons and psychons are central to the act. Thus the mental intention acting through a psychon (cf. Fig. 11) has automatically available tens of thousands of activated PVG's with their vesicles awaiting selection.

In the reverse transaction, brain to mind, it is necessary to have an extension of the hypothesis, namely, that every time a psychon successfully selects a vesicle for exocytosis (in accord with the quantal probability field) the "micro-success" is registered in the psychon for transmission through the mental world (World 2 of Fig. 1). There would of course be great amplification when the psychon successfully selected at about that same time large numbers of vesicles from the tens of thousands of PVG's of its dendron. The « success » signal of the psychon would of course carry into World 2 the special experiential character of that psychon.

The generally accepted units of the neocortex have been the modules (cf. Fig. 1) recognized by their unitary projection to other units of the neocortex, ipsilateral or contralateral (Goldman and Nauta, 1977; Szentágothai, 1978). These modular units would be about 20 times larger than the dendrons, which can be regarded as the primary units, particularly in their relation to the psychons (Fig. 11). By contrast the larger modular units are the units for transmission within the neocortex.

A tentative explanation can be offered for the observation that an input into the sensory nervous system can give rise to a sensory experience. For example, it explains how a visual input gives rise to a visual experience. An activity of an appropriate dendron of area V 4 can be exemplified by the dendron in the centre of Fig. 11. This can result in success responses of a psychon indicated by the pattern open squares and so to the experience of a red colour.

This lecture has been restricted to the mind-brain interaction in both directions across the interface of Fig. 1, that is between World 1 and World 2. The transmission through World 2 is beyond our present comprehension, but it leads to the unity of our perceptions and of our inner world that we continually experience from moment to moment — that is for all of the World 2 experiences illustrated in Fig. 1 above the interface.

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DISCUSSION

POECK

I question your statement that mental units match neural units for life. I don't quite see how this relates to Mountcastle's statement that the microstructure of the brain is modulated by experience.

ECCLES

Thank you for this good question concerning the basic connectivity of the neocortex. However, this connectivity can be larger or smaller. It doesn't mean that you have to put in another mental unit there. This proposed neural-mental unitary interaction is not an all or nothing operation. The neural unit can be at various intensities. The mental unit can be at various levels of intensity. When you are in a learning situation you could conceivably have the intensity of the mental unit being more affected than its neural unit. In learning you don't change the connectivity pattern but only the intensities. This concept is very provisional, but somebody has to dare to go on, and you can think about it.

JONES

I can't help but express a degree of concern about the dendrite bundling concept. The first thing that one should say is that dendritic bundling does occur in the neocortex. It's a very real thing. There is no question about that. It has been known for a long time even by Ramón y Cajal. But where I have problems is in the idea that they represent some kind of modular system. There are two problems I basically have. One is that there is no regularity about them. They are not evenly distributed through an area of the cortex. I think the places you see them best in the primate cortex were actually in the frontal cortex, but they can vary greatly in size. In some places there were large stretches of cortex where you don't see significant bundling at all. What is perhaps more important in terms of the objections I would raise, is that I think it's very clear that by focusing on the apical dendrites, you are really focusing on only a very small part of the pyramidal cell, and thus you get a false impression of this narrow modularity because a) pyramidal cells have enormous

basal dendrites. So in the drawing that you put up, the basal dendrites of all of those groups of cells that you showed would overlap extensively. Thus the modules would be blurred. Secondly, the apical dendrites of many of these deep pyramids can contribute, as Ramón y Cajal showed, to different bundles, so that places a single pyramidal cell in multiple modules. Finally, to me, the real business part of a pyramidal cell is in the basal dendrites and the side branches, the oblique side branches of the apical dendrites. It is not in the very peripheral branches where you may argue nothing much is going to affect the cell body, but in those oblique branches where most of the thalamic afferents in particular terminate and probably also, the cortico-cortical afferents, rather than on the stem, the apical dendrite itself. These extend over territories from one mini column to another, and this blurs the whole picture. So I am very reluctant to accept this as the ultimate in modularity in the cortex.

ECCLES

Of course I recognize all those criticisms. I base my story on the recent study by Peters and Kara (J. Comp. Neurol. 260, 573-590, 1987), that has apparently not been seen. In that definitive paper they deal extensively with the statistics of the dendritic clusters (as they call them) of the apical dendrites. There are also values for the numbers of lam. V and lam. III apical dendrites in clusters, with their spatial distribution. The average centre to centre is 55 micrometers. They have also electronmicroscope pictures showing that the apical dendrites are not closely adhering, but are well separated. This is also known by Fleischhauer and associates. I now come to the spine synapses which are the excitatory synapses on pyramidal cells. Feldmann states that they begin about 50 micrometers from the soma. They thickly encrust the apical dendrites and their branches and the terminal tuft, there being in all several thousands on each pyramidal cell. I recognize that the spine synapses distal from the soma will be less effective than those proximal, because of the electrotonic decrement of the excitatory postsynaptic potentials. However, there has been shown to be some compensation for remote locations. I agree that the synapses on the basal dendrites and soma are not involved in the dendritic bundling, but they are mostly inhibitory. I think that the bundles or clusters are important units in the reception of synaptic excitation. The modules that Patricia discovered and John Szentágothai diagrammed are about 20 times larger. They are the units for communication within the neocortex by impulses along the axons of the pyramidal cells. These impulses result from the integration within each cell of the synaptic excitations and inhibitions to which it is

subjected from moment to moment. So the minicolumns (dendrons) would have two functions in my hypothesis. Firstly, they would be the units for integration of the synaptic inputs. Secondly, they would be the units for integration of the mental inputs. It is here that mind-brain interaction would take place as proposed in the diagram. The so-called mini-columns can be recognized in the neocortices of quite primitive mammals, so it can be proposed that they evolved for mind-brain interaction, because it is generally believed that even the most primitive mammals have consciousness.

SZENTÁGOTHAI

The bundling comes out from the development in the ventricular zone. Actually the development is a little more complicated, because the third layer of pyramids is also associated. So you have a central bundle of fifth layer pyramidal cell apical dendrites and then surrounding it, apical dendrites of third layer pyramidal cells. It's very beautiful. I have somewhere a diagram of that. I took it from Peters some time ago, and also of course from Fleischhauer.

ANDERSEN

Well, Sir John, I thought it was very interesting to hear your talk because it reminded me of the wonderful days in Canberra where you flooded the rest of us with your ideas and in this context you said that mental events select vesicles from the presynaptic terminals. Have you thought about any machinery for that? I mean, first, how could a mental event do so? And second, how do you preserve the specificity you need?

ECCLES

Well, in the first place Per Roland has produced the evidence that mental events do this. A mental event such as thinking is in World 2, having no matter or energy. What it can do, in my theory, is to select synaptic vesicles that are ready for exocytosis. In the mini-column there are up to 100 apical dendrites and their branches (laminae V, III and II pyramidal cells) with up to 100,000 spine synapses. So the mental unit has available in its mini-column an enormous number of vesicles awaiting selection. That's all a mental event can do. It is postulated that this selection is done by a process analogous to a quantum mechanical field because of the extremely small size of the particle to be displaced in the exocytosis, about 10^{-18} g, which is well within the limits of the Heisenberg Uncertainty Principle. The conservation laws of physics are not

violated in the selection. Moreover, each mental unit has in its mini-column tens of thousands of presynaptic vesicular grids, each with its array of vesicles awaiting exocytosis and selection by the mental event. There is thus an enormous amplification.

KIELY

Sir John, I go back to your initial idea of two worlds with two different ontologies. I wonder if it would not be a safer statement to say (following Professor Libet) that we have two epistemological lines of access to this strange and wonderful thing inside our heads, one line being the neurosciences and the other coming from subjective experience? Intuitively, we seem to be dealing with a unity; the interactions are very close, so much so that even 'interaction' may be a dangerous word. On the one hand, a highly abstract idea, like that discovered by Archimedes, may activate all the systems of the body; while at the same time simple chemicals like alcohol can produce very marked psychic changes.

ECCLES

Of course, but you are now fully in the materialist world. It has nothing to do with my theory. My theory relates to the mental world in its operations onto the material world.

KIELY

But I think it leads into a particular and purely philosophical difficulty, because dualism seems to imply an idealistic epistemology: one 'makes contact' with the truth, as in the interaction between these mental and neural units. That in turn leads to the classic difficulty faced by idealistic philosophies: how does one explain error?

ECCLES

I don't think this is the time to get involved in philosophy. We can do that on Tuesday, when we have the Round Table Conference. I will be presenting religious philosophers with, I think, a gift, a very great gift, which is the reality of the mental world in its operation on the brain and in its receiving from the brain. I am trying to give an explanation of how you can do that without breaking the conservation laws of physics.

CONCLUDING COMMENTS

O. CREUTZFELDT

Ladies and Gentlemen, the theme of our study week was on "Principles of design and operation of the brain". With some important excursions into the cerebellum we concentrated on the cerebral cortex. In these contributions we discussed various aspects of its design and functional organization. I was asked to introduce our general discussion and will try to do it by remembering various aspects disputed, and may add some personal comments.

The evolutionary significance of language has been discussed in extenso. Language is a symbolic representation of our outer and inner world and of our intentions. These symbols become a reality in themselves, with which our brain has to deal, and they are thus part of our internal representation of the world. Through his capacity for representing the world in symbols of our experience, Homo sapiens was able to develop beyond biological evolution. Words and symbols are a creation of the brain, but they are not immediately controlled by reality like a movement. If you hit against a stone while walking, your movements are immediately corrected through reflex loops. Words and symbols can be used in a freer manner, we can construct with them higher order connections between the different levels of reality, and thus make descriptions and models of this world without immediate control. Therefore, as Goethe put it, "Mit Worten lässt sich trefflich streiten, mit Worten ein System bereiten" ("With words you can superbly fight, with words you can concoct a scheme alright"). These models must be consistent with reality and with our experience of it, and the question of consistency of our models with reality is the very essence of scientific discussions. There is a level of mental reality on the one hand and the reality of the brain, on the other. They

are related to each other, but what this relation is, was the very issue of our discussions.

Our questioning started with the *evolution of the brain.* From the data of comparative anatomy and anthropology summarized in *P. Tobias'* contribution, it is clear that the acquisition of the neuronal machinery for language is an essential step in the emergence of Homo sapiens, but it was questioned to what extent language is the only condition of human consciousness. When discussing the evolutionary steps which led to this capacity, opinions were divided as to where the primary evolutionary changes took place: in the differentiation of the peripheral apparatus which subsequently demanded more brain, and especially more cortical space, or whether the increase of brain volume and cortical space for language functions was first. In any case, it is clear that specialization of the functional anatomy of the body and the provision of cerebral and cortical volume to control such body specializations go hand in hand.

In discussing the evolution of the cortex in mammals, main emphasis is usually put on its size and that of specific areas. This should not be over-emphasized, however. What appears to be a more dramatic change from lower to higher mammals is the increasing corticalization of function. With that I mean that all aspects of behavior become more and more dependent on the cortex. While in humans restricted lesions have a disastrous effect on functions related to the respective area, so that such a function may be completely eliminated, one can take out a lot of cortex in lower mammals without interfering that much with function. Thus, for example, in young and to some extent even in adult cats one can take out the primary visual cortex, but they still show elaborate visual behavior. Of course, we don't know to what extent the internal representation of the world has changed in these animals after such a lesion. This applies to other functions and areas as well. In the motor cortex it is also evident that its lesion does not interfere much with motor performance in lower mammals. Even in primates, area 4 is necessary essentially only for controlling the distal parts of the limbs. There exists as yet no good explanation for this increasing corticalization of function, and it would be interesting if somebody could come up with a good suggestion.

We have learned much about the *general design or Bauplan* of the cerebral cortex and its genetic and epigenetic formation in the presentations of *P. Rakic, E. Jones* and *J. Szentágothai,* and *W. Singer* offered cellular and molecular mechanisms for the post-natal moulding and adaptation of the cortex to the reality of its world. We agreed that there is a

general and somewhat uniform design of the neocortex all over with considerable local variations, however. The homogeneity of cortical structure reflects the common origin and development of its elements. There are indications that some of these local variations of this basic structure may, at least to some extent, be genetically determined, but the majority of these variations appears to be epigenetically shaped by the afferent and efferent connectivity of a given region of the cortex. There was agreement on some principles of modular organization of the cerebral cortex, and it became apparent again that modules should be defined carefully and that "the" module or "the" column may be too vague a concept. The terms module or column are being used for a variety of structural and functional entities, and thus cover a wide range. One can define modules of thalamo-cortical, of cortico-cortical and various types of intrinsic cortical connectivity, or one may put emphasis on functional aspects such as response specificity, range of excitatory or inhibitory interaction of certain cell types or pools of neurons, etc. To speak of a columnar organization without defining what one actually means is a generalization which tends to obscure rather than to elucidate the principles of neocortical organization, in my view. And I may add that I do find it therefore neither justified nor meaningful to attempt to give numbers of columns or modules for the whole cortex.

The "columnar" or modular organization of the brain is usually seen as the functional-anatomical correlate of segregation of function, but one can also defend the view that it is a general construction principle for joining inputs of various origin in small regions of the cerebral cortex — such as the somato-sensory input from superficial and deep receptors in the somato-sensory cortex, from the two eyes or from the magno- and parvocellular division of the lateral geniculate body in the visual cortex or from the contra- and ipsilateral hemispheres in the prefrontal cortex, or of thalamic and cortico-cortical input all over the cortex. This joining of inputs gives a particular cortical point or volume its characteristic signature which determines its output to other parts of the brain and to the behavior controlling systems. The special role any part of the cortex plays for function obviously does not depend so much on variable specifications of the internal structure but on the combination of afferents into and the efferents from every point.

Our discussions on cortical input and output here have concentrated mainly on *connections between cortical areas*, and important principles and details on intercortical connectivity in the frontal and visual cortex

have been presented in the contributions of *P. Goldman-Rakic* and *S. Zeki*. The significance of the topographically organized thalamic input to each part of the neocortex received, in my view, too little attention. The neocortex may be defined as that part of the cortex which gets thalamic input. We know much about how this determines the functional properties of neurons in the primary sensory areas, but the thalamo-cortical input is hardly considered in association and only a little in motor areas. There were some hints during the discussions at this conference that also in association areas the thalamic input may determine response properties, and more could be added. Yet, the fact that it was so little considered attests that we know only little about the functional organization and contribution of the thalamic association nuclei projecting to the majority of the neocortical areas.

The *distributed representation* of various extracts from sensory inputs was exemplified and discussed by *G. Baumgartner* and *S. Zeki*. Here and later it became apparent that due to the organization of sensory inputs and the internal wiring, features are being extracted from our physical environment which may not be directly apparent from straightforward physical measurements. These higher order filter processes allow us to segment the physical reality into elementary categories as essential elements for the internal synthesis into semantic categories and Gestalten. The parallel representation of these detailed and global properties in distinct groups of neurons and in different areas was emphasized. It must be realized, however, that not only the higher order synthesis of these categories but also the primary detailed features and their spatial or temporal relationship to each other enter conscious perception.

Our perception is not constructed like a pattern-recognizing serial computer which tells you in one word what it has "seen" or "heard" with its sensors, but we also perceive all the evidence for such a cognitive decision, i.e. the details of the stimulus. Thus, each additional representation of the stimulus in another cortical area adds another functional significance. In strictly adhering to hierarchical models, one may easily be trapped into the categorical mistake of naively projecting our mental concepts of perceptual analysis and logical thinking, which essentially leads to a serial model, directly onto the cortical map. I think that the algorithm that our brain uses in cognition is not the same as that which we intuitively deduce from introspection. We are faced with this difficulty especially when it comes to higher mental functions and their disturbances by

circumscribed cortical lesions, as was pointed out by *K. Poeck* when discussing *language* disturbances after cortical lesions.

Various aspects of the *detection and neuronal representation of higher order features* and, to some extent even meaning were also emphasized in other presentations, including those of *J. Desmedt, J. Levy* and to some extent in my own contribution, in various sensory systems and tasks. Wired-in properties of neuronal filters are capable of extracting properties which may reach into the level of cognitive representation that has hitherto been considered the realm of conscious mental search processes. Impressive examples of such higher order neural filter processes in the *parietal cortex* have been given by *V. Mountcastle.*

There was some discussion about using the term "construction" of features by neurons and, in fact, of mental reality in perception. I don't want to get lost in semantics here, but would prefer not to use the term construction for features and properties which are the consequence of hard wired neural connections, and which we recognize immediately or preattentively, as B. Julesz might put it, even if such properties may not be directly evident from a physical analysis of an object. As I mentioned, and I gave some examples from the auditory cortex in man, such features may indeed reach into very high levels of cognitive categorization, but many of them are already extracted by very peripheral mechanisms in the respective sensory organs themselves or at early stages of processing before the signals even reach the cortex. I personally would like to reserve the term "construction" for what we may call active perception, i.e., when the subject actually collects in successive steps the information needed to identify an object, such as discussed in connection with *V. Mountcastle*'s presentation. In fact, every attentive cognitive process is an active process of construction in that the subject actively explores the environment or an object such as touching it with his fingers or by exploring it with his gaze.

This of course involves *attention*, a subject specifically addressed by *J. Levy.* Here we are faced with the problem of focal attention and its regulation as well as with that of integration of the temporally and spatially dispersed cerebral representations into a coherent cognitive entity. The composition of temporally successive feature representations into a single idea is, of course, an obvious but major problem in language. It is clear that it involves a short term memory, a sort of sample-hold device. To my knowledge, no observation has yet come up which might provide for such a mechanism, or even indicate where such sample-hold information might be

stored. To what extent prefrontal activities such as those observed during delayed match to sample tasks or in attention (for which *P. Goldman-Rakic* gave impressive examples) might be involved here, came up during the meeting repeatedly, but it seems that such prefrontal mechanisms are not sufficient for integration of sensory messages over time. *Long term potentiation* to which *P. Andersen* introduced us might be involved, but also here one may doubt to what extent this might be a sufficient mechanism.

The question arose again and again how these multiple representations of the world not only in the sensory areas, *sensu strictu*, but also — depending on the behavioral context — across widespread regions in the visual, parietal, temporal, frontal and limbic association areas, are constituting a unified conscious experience, unified in space and time. Just imagine what happens in your brain when you look at an object or a visual scene: every 200-400 ms, with each saccade, neurons are being turned on and off in different parts of your area 17 and the different regions of your prestriate cortex, here and there in your parietal, premotor, prefrontal cortex, and so on. We do agree that there is no pontifical or highest order area or map where all this is being integrated, reconstructed so to say into an image of the world as it appears "in our mind". We are left here with a basic riddle and must confess our ignorance.

On the other hand, resynthesis of these distributed activities into an adequate and unified behavioral motor response may be understandable, in principle. Here, the model of visuo-*motor control* offered by *M. Ito*, the emphasis on contingent conditions such as activities from the limbic and the motor systems as brought up by *V. Brooks* and the demonstration of the synthesis of distributed neural events to a purposive action as demonstrated by *M. Jeannerod* may be taken as examples. But also here the question of hierarchic as opposed to parallel representation of motor command signals from the different motor areas was to some extent controversially discussed. The involvement of the SMA in motor actions, especially during continuous motor sequences was impressively demonstrated by *M. Wiesendanger* and *L. Deecke*. After these discussions I find the old metaphor of Otfried Foerster, that all motor areas collaborate in a (parallel) "working cooperative", an Arbeitsgemeinschaft, still very useful. We may remind ourselves, though, that the definition of motor areas of O. Foerster was a very broad one indeed, including large parts of the whole neocortex.

In fact, we now know that all cortical areas including the so-called primary sensory projection areas have a direct output to subcortical and

cortical motor control systems. I may come back here for a moment to cortical modules. Just as each point of the neocortex receives an input from the thalamus, each point sends out, through pyramidal cells of layer V, messages into motor control systems in a more or less direct manner. This may be obvious for the motor cortex and all its various subareas, but also for the somato-sensory areas (to the spinal cord and brain stem motor nuclei), the prefrontal (to the caudate and pretectum), the parietal (to the pontine and reticular nuclei) and temporal association areas (to the tectum and pretectum). Even the primary visual cortex as well as all prestriate areas send messages through their fifth layer cells into motor control systems of the tectum for eye movement control and, through the pontine nuclei into more widespread motor control systems of the cerebellum. Thus, the integration of the distributed activities from all modules or columns or what you like, takes place at the output level for control of adequate behavioral responses. Of course, the control of these various output levels and which output line should have priority, changes continuously, and is again subject to a higher order integrated supervision, which calls up different strategies for motor performance.

Here, the variable involvement of different *motor areas* during motor learning has been emphasized by *H. Freund.* Such variable involvements of brain areas in behaviour are not only invoked during overt performance and motor responses, but also by internal mentation, as was so impressively demonstrated by the shifts of brain work into various parts of the neocortex during mental imagination, in the contributions of *D. Ingvar* and *P. Roland.* Here, we are faced with the question, what mechanisms shift these activities from one place to another in the brain, from one region into another, or from one function or program to another. This question is directly related to the question of changing the focus of attention, and again we ask for the unifying principle, the agent.

This touches, of course, the central question of free will and of voluntary shifts of activities from one place in the brain to another which haunts the search and thinking of *Sir John Eccles.* I'm afraid we cannot give a coherent answer to this yet. Some of us have difficulties in accepting the interaction model elaborated and presented to us. I personally accept the riddle of integration of the distributed inputs to a unified consciousness and the command of our cerebral activity by a unified agent, by free will, as a mystery. In my opinion, it will remain a mystery or — in scientific terms — an unexplainable property of the brain. This should not bewilder us. There are more such unexplained properties: why, for

example, does the activity of neurons in certain places of our neocortex indicate something in our perceptual domain of vision, of other neurons in the domain of audition, taste, etc. The activity of neurons in the motor areas does not at all enter consciousness, but only has output command functions. Which neuronal activity actually enters consciousness — only the activity of some cortico-fugal pyramidal cells, of all pyramidal cells or also those of interneurons? I could name many more such unexplainable mysteries of the working of the brain, but would like to leave it at this.

Here, I'd like to end my short summary of our conference and my comments. I'm afraid I have not done justice to the rich information given to us by each participant. But I tried to lead a way through some aspects of cortical function up to the problems which face the neurosciences when trying to relate our experience of this world and of our actions within this world with the brain mechanisms which are the conditions of our mind. We are faced here with the problem of relating two domains, two levels of experience to each other — that of our immediate experience and that of what we see and record in the brain. In many domains we may find simple and straightforward isomorphic relationships, and the future will present us with more of them, but we should also be prepared to accept that these two levels of experience are not identical or even isomorphic. There is something which transcends our scientific understanding. Here, I think, we should not become impatient by trying to cross this gulf by declaring metaphors of this relationship, be they dualistic or monistic, as scientific theories.

FINAL DISCUSSION

ECCLES

Otto Creutzfeldt, at the end of his talk, spoke about isomorphic relationships. I was putting up a theory yesterday which was strictly isomorphic in the sense that each neural unit was locked permanently to its mental unit and interacted without breaking the conservation laws. That's like what the identity theorists have been proposing all along. However there is the important difference in that I give the mind autonomy over the relationship, so that mental events can *effectively* operate upon neural events, as in voluntary movement and free will.

There's the problem of how the isolated mental events, say in the visual system, can give us the visual picture we eventually have. We are not in the world of the brain any more. We are in the world of the mind and the mental events have to be integrated into the whole mental world that we live in from moment to moment. This is an immense problem, but I don't think that we have to say it is beyond our understanding. We can move into it once we've recognized the autonomy of the mental units, and can develop hypotheses.

ZEKI

I think that there are various things which do come out that you have alluded to, and I'd like to take them up one by one, with your permission Mr. Chairman. You see, if you look at the cortex, whichever cortical area you want to look at, there is a huge difference. There is a difference in the cytoarchitecture, there is a difference in microcircuitry, in size, in inputs, in outputs, in cell size, in cell density, in lamination, in functional properties, and differences in modularity, to name but a few. But there are also similarities which are obeyed everywhere. For example, there is no single cortical area which projects to only one other area. Each one has got more than two projections. Now that is a very important fact about the cortex, in my opinion. There are very few connections which are not patchy. I think most systems

that you look at have got patchy connections. There are perhaps only two or three areas in the somatosensory cortex which are not reciprocally connected. There is no single demonstrated case in the whole of the cortical literature where there is a total convergence of input on the same cells. There might be a secondary convergence within an area, but the inputs are segregated.

Now if you take all these, it gives you some clues from the anatomy, some general statements, which you can make about the cortex. The segregation of outputs, the patchy connections and the associated modularity, the conjunction of features which I spoke about the other day, I think are almost certainly telling us about the repetitive and almost unified strategy that the cortex is using to do whatever it's doing. In other words, whether you go from the analytical mode to the mental mode, these are segregated out either into mini-columns or some sort of patches, and this is also expressed anatomically in the connectivities which are always patchy.

In the rare places where you get a single patch, projection from one area into another, which I define as an operational connection, this area undertakes a certain activity, or a certain part of this area undertakes a certain activity and reports the result of that activity to the other area which alone need communicate with this area. You don't have this in any of the prestriate areas, but you find it in the frontal cortex, and also in the somato-sensory cortex there are areas with one-way connections.

There is no master area to which all areas project. This is a fact which we've got to accept, from which follows the fact that whatever integration is going to take place has got to be taking place by these reciprocal connections which, as I said, occur in all stages. Now I think this can be reduced to about five rules of cortical connectivity to which you may add perhaps others. But these are so impressive because they are so invariant. They occur all the time, and I think any theory which seeks to understand how you are going to reunify the mental image, or the visual image, would have to take into account these basically simple rules which are now extremely well documented.

I've got two other points to cover. One is about the problem of construction, and I do really think that this is not a semantic problem. I think we run the risk of shoving it under the carpet by calling it that. Otto Creutzfeldt has now redefined construction to say that it represents features that are extracted from the input. I don't think that's what I mean by that. What I mean by it is not the features that are extracted, but features that are actually created in the cortex by a process of comparison which is a property of the brain, not a property of the world outside. I think a very good example is that of the so-called illusory figures. That information — the illusory contour —

is a construction. You can't measure it, you can't do anything with it, because it is not there. So I think we have to agree, perhaps, to differ. I get the impression that Professor Mountcastle and I are in agreement that the brain is actually coming up with a category which is not in the world outside.

DEECKE

Dr. Creutzfeldt, when you presented this global view of consciousness, it came to my mind that of course you have a great unified consciousness which includes all the senses, but you must also have a modality specific subgroup of consciousness. For instance, I think you could conceive that a dog may have an olfactory consciousness, and even an olfactory world, and we may have a visual consciousness.

The other point is: why did nature invent consciousness? You could conceive that even such complex beings as we could come along without consciousness, but consciousness is there, and I think it was a necessity for data reduction. Without consciousness we would just be submerged in this abundance of sensory input. Consciousness is what helps in data reduction. Richard Jung compared consciousness to a searchlight on a stage, a focus of one's interest which makes selections from the whole environment.

KIELY

The great merit of the dualist interactionist hypothesis is that it does take seriously the data that we find in our own conscious activity. Yet, at the same time I feel that the hazard with dualism is that it claims too much — even though it has a most distinguished ancestry, going right back at the least to Plato — that it tends to claim too much, and therefore to convince, perhaps, too little. The Catholic mainstream is not really dualistic. It's a much more subtle and nuanced position which I have attempted to suggest here (*). I don't know enough about neurons to do it full justice, but I think

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Bartholomew Kiely, S.J., psychologist and professor at the Pontifical Gregorian University in Rome, attended the Study Week as an observer, and made available to the participants a brief paper entitled « The Problem of Conscious Activities », which is reproduced here in abridged form.

(*) We have two *epistemological lines of access* to what goes on in the brain; one given in the methods of neuroanatomy, neurophysiology, and neuropsychology, and one given in our direct experience of ourselves in action.

The scientific line allows us to reach a gradually expanding set of conclusions about

that the most important thing in this whole question is to be epistemologically careful, to respect all the sources of evidence and to recognize the gaps in our knowledge. If a theory claims too much, one tends perhaps to achieve less than one has hoped for.

ECCLES

Philosophy in the latter years has been built up without understanding at all the neural basis of everything that matters. We have to get into reality, and reality is that we have brains and we also have minds. William James,

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the structures and functions of the brain and reveals a very complex set of levels of operation, with a high degree of flexibility and adaptability, especially on the higher levels.

The line in which we reflect on what we know directly that we do reveals that we perform certain activities *consciously*.

The idea of consciousness is probably best represented by an *adverb*: we do certain things conscious*ly*: (1) we perceive empirically, (2) understand (i.e., generate ideas that might be true), (3) judge of their truth or falsity, absolute or probable, on the basis of sufficiency of evidence, and (4) also deliberate and decide with a sense of responsibility.

Various points suggest that the two aspects uncovered by these two lines of approach are two aspects of a *unity*. Obvious influence is exerted in *both* directions.

While we apparently have to do with two convergent approaches to the understanding of this unity, yet we still face a large gap in our understanding of this unity; the two lines are still far from converging to a point where they meet in a coherent and unified understanding.

While a dualistic-interactionist approach has the undoubted merit of taking seriously the data of our direct experience, and going well beyond any kind of closed materialism, yet it seems to bring with it certain burdens traditionally associated with dualism, including the difficulty of any idealistic epistemology in explaining the problems of (1) error and disagreement and (2) learning by a gradual and self-correcting process. If truth is « seen » or « contacted » in a way for which visual perception is an adequate metaphor, then all error becomes as hard to explain as perceptual error (hallucinations are not easy to explain), and learning by trial and error becomes as hard to explain as peceptual correction of a kind that would at the end yield very different perceptions from before.

On the other hand, if one takes knowledge as rooted in sensory experience (in turn linked to neural processes), and maintains a systematic distinction between intelligence and judgment (intelligence generating hypotheses which *might* possibly be true, and judgment pronouncing upon actual truth, falsehood, or probability, as sketched above), then the facts of error and of gradual learning (familiar to the working scientist) are much easier to handle.

In summary, the most we can hope for at present is to state the question about the mysterious but real activities (that we know we perform consciously) in a way that, as far as possible, will not compromise further reflection. It also seems to me that it is in the Thomistic tradition (as updated by authors such as Lonergan) that we can find clues to an approach which is congenial both to the working neuro-scientist and to religious traditions, including the Christian, which cannot make sense unless claims to objective knowledge and responsible freedom are allowed.

at the end of the last century, said that consciousness came when the brain was getting too complicated to control itself. It came in as a kind of super-control on top of neural control. That's my theory. I gave it yesterday, and it applies to all mammals.

WIESENDANGER

We have talked mostly about the sensory side in perception, and since Otto Creutzfeldt pointed to some similarities in the problems on the motor side, I would like to make a brief comment on that. It's clear that a percept is a unity, and Otto used the phrase: you have to resynthesize the distributed representations to a unitary percept. Most people would agree now that there is no master instance, or master map, where this resynthesis is represented. This is probably not the way it operates. Now, for motor control we can also say there is a unity in the plan if we perform a movement. This is a unitary plan, but there is also no master area for this plan. It's all distributed, a combination of cooperative action of many areas, which leads to that. And, in fact, as Otto mentioned, many areas of the cortex, even outside the motor cortex, are involved in converting the percept into an action.

FREUND

The question I ask is how far the modular concept of the cortex helps to understand brain function.

MOUNTCASTLE

I believe that there is a basic plan of the cortex upon which is built its diversity which Creutzfeldt spoke of, and which depends largely upon a variety of connections, both thalamic and cortical. I think that a major problem in understanding cortical function has to do with the mechanisms of operation about which we know a great deal. Given a common plan, I believe that there probably is also a basic operation of the cortex. If we could define such a basic operation of the cortex and build on that in describing those different operations which are determined by different connectivities, we would greatly advance our knowledge of the function of the cortex.

I think that science is a process which progresses stepwise, small steps with re-entrant correction, and that as experimentalists we must, in the present state of knowledge, aim our arrows at somewhat less global problems than

those we have discussed this morning. I think that we must aim our experimental approach at intermediate-level problems, and the one that I think is most susceptible of solution in the next decade has to do with perception. I think we will never understand consciousness without first understanding the mechanisms of perception, and that we should aim our experimental programs at that level. On the opposite side, I think we will be able to study intentionality directly. For what goes on between perception and intentionality of output, the middle level, I think we have little opportunity of direct solution in the next decades.

For the experimentalists, I'd like to think that a process of brain function that I call "minding" goes on. We operationally mind things. To think of there being a separate entity called mind I think is not useful for the experimentalist at the moment. However, there are aspects of brain function which include the complexities of what you and Eccles would call mind. So I think that with the present techniques available, there is a tremendous advantage first of all in aiming at intermediate level problems. In relation to the cortex itself, I think there is a fundamental problem to be solved, namely: what is the operation of the cortex as contrasted to the physiological mechanisms, of which we know a great deal.

Finally, I wanted to bring up a point that has not been mentioned, the extraordinary power of the central core control systems. Especially if one moves away from primary sensory and motor areas of the cortex, one sees that the excitability, the activity of the cortex is subject to control systems other than direct sensory input. You know that these systems engage the cortex in a totally non-columnar fashion, entering in a transverse way. There is some laminar dissociation, laminar differences, at least in the primate, in different regions. This, I think, should be a major experimental objective in cortical physiology, to define the role of the central core systems. — I mean all of those systems that engage the reticular and intralaminar nuclei of the thalamus, and thence to the cerebral cortex.

JEANNEROD

I would like to say something on movement organization which I think can have a lot of implications for how we understand mental functioning. The point is that actions appear to be sequentially organized, like speech for instance. In fact, they are not. If we look carefully at the intrinsic structure of movement, for instance, including language, we see that there is a lot of simultaneous processing and a lot of parallel activities going on. If we look

at the very simple behaviour of orienting the hand towards a target in order to grasp something, the eye movement will go first to the target, then there is the head turning, which will follow the eye, and then the hand movement, reaching toward the final location and grasping the target. So it looks like a very sequentially organized action. But if you look at the neuronal discharges which are related to those different movements, you will find that they are all more or less simultaneous, yet when they interact with the force field, they generate a sequential organization. In language you also have a similar organization. So I think we should not make too much of the idea that perception is organized in a parallel way, and action is organized sequentially. I think that the channels which go from the input to the output, the visual-motor channels or the sensory-motor channels, are also parallel lines which go together.

That raises the point that Otto Creutzfeldt has mentioned, that of course we need to reconstruct the perceptual entity or the object as a single thing. We approach an object by different actions; they are convergent movements on the same object. For instance, we have reaching movements with the arm, we have shaping movements with the finger. All this goes in parallel, but there is one single object. So where is the single command? Where is the unifying plan? That I think is a very challenging problem.

BROOKS

If you want to understand what is happening during a movement, it is not the movement of any particular joint, but that of the path — in Dr. Jeannerod's case, the hand path. For a different movement it might not be the hand but some other part of a limb, for instance the elbow, if you open a door with it. The path of that part that is of the greatest importance to the brain — the subject of its intention — requires a supervisory process. I think that this supervisory process is capable of being studied, and would be a fruitful thing to follow up.

FREUND

Before I hand the microphone to Sir John for a final comment, would Otto Creutzfeldt like to make a short remark?

CREUTZFELDT

In my introduction I aimed at summing up and commenting on some principles of the functional organization of the cerebral cortex which emerged

from this week's discussions. I could not avoid a personal bias, and it was the purpose of our General Discussion that individual participants' views could be specified, and my own bias be put in perspective. I think that this came out well, and it is my hope that those who read this book and the discussions may come up with further and better answers than we could give.

I would just like to add one final word. It is my impression that my use of the word mystery was interpreted sometimes as trying to mystify the relationship between brain activities and mental processes, and thus might be misinterpreted as trying to discourage our scientific endeavour. This is certainly not what I intended. As neurobiologists we look at brains, their anatomy, development and functioning, but we also want to find out the neurophysiological conditions of perception, action and consciousness. By understanding these conditions in terms of brain mechanisms we are also able to define causal relationships, but we are not explaining perception, action and consciousness as we experience them. One needs to distinguish between these two levels of understanding and explanation in order to avoid the epistemological traps of the brain-mind discussion. A simplistic reductionistic approach of just projecting one level of experience, that of the mental experience and that of the objective observation from the outside, onto one another, and then claiming an isomorphic relationship between these two is, I think, not scientific and not good for progress in our field.

FREUND

I would like to add a small personal belief coming out from the discussion, that possibly the most specific human aspects of brain function may lie in the temporal domain, in the dynamic interaction of the structures that are different from the monkey. The temporal aspects have a fantastic capacity for being very, very special and for showing much larger differences than we can see on the structural basis.

ECCLES

At the outset of this conference I said that we are a band of adventurers dedicated to understanding the most wonderful structure in existence. Our audience will recognize that we were by no means a unified group who were saying the same things and congratulating one another. We've done it quite differently. There has been a lot of disputation, and at the same time very

good will. There are still very many unresolved problems. That's what science is. Otherwise there would be nothing to do.

We raised many problems, some of them relating to the most controversial problems, the relationship of the mind to the brain, the mental route to the brain. I think we should avoid dogmatism, and I also don't like reductionism. It impedes the further subtle understanding of the human brain. Everything that we know and value comes from the brain, but only insofar as we recognize that the brain is intimately related to the conscious self.

Now I think there is a misunderstanding. If you say that all progress comes about from doing experiments on perception or movement, with the most refined study of the neural events, you overlook many other channels of investigation. None of us is competent to be an authority and say only this will work. We have to realize that there are, and be very tolerant of, all the other modes of investigation. We as brain scientists must not provisionally reject the whole mental world. Otherwise irrational arguments will dominate the discussion on the human mind.