

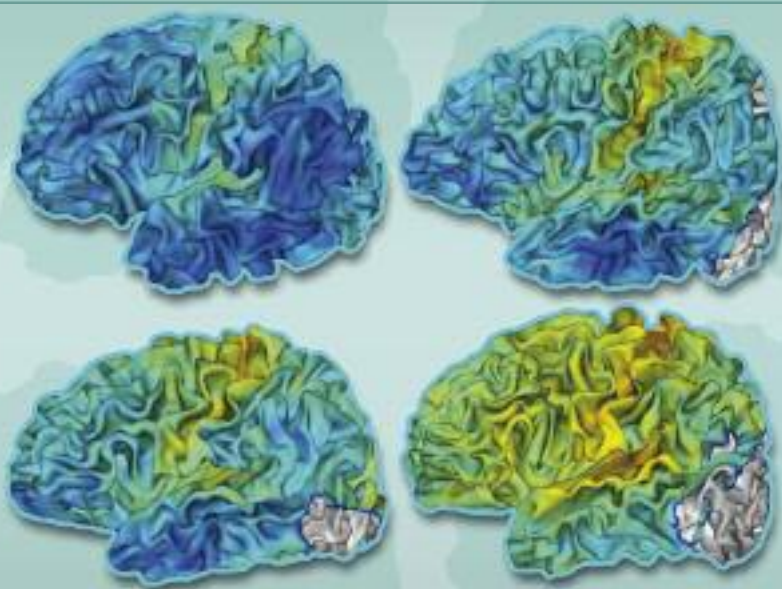


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*Edited by*  
Antonio M. Battro, Stanislas Dehaene, Wolf J. Singer

# Human Neuroplasticity and Education

*The Proceedings of the Working Group*  
*27-28 October 2010*



VATICAN CITY 2011

# Human Neuroplasticity and Education

*Pontificiae Academiae Scientiarum Scripta Varia 117*

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*The Proceedings  
of the Working Group on*

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Wolf J. Singer



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The opinions expressed with absolute freedom during the presentation of the papers of this meeting, although published by the Academy, represent only the points of view of the participants and not those of the Academy.

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Thus, Augustine's entire intellectual and spiritual development is also a valid model today in the relationship between faith and reason, a subject not only for believers but for every person who seeks the truth, a central theme for the balance and destiny of every human being. These two dimensions, faith and reason, should not be separated or placed in opposition; rather, they must always go hand in hand. As Augustine himself wrote after his conversion, faith and reason are "the two forces that lead us to knowledge" (*Contra Academicos*, III, 20, 43). In this regard, through the two rightly famous Augustinian formulas (cf. *Sermones*, 43, 9) that express this coherent synthesis of faith and reason: *crede ut intelligas* ("I believe in order to understand") – believing paves the way to crossing the threshold of the truth – but also, and inseparably, *intellige ut credas* ("I understand, the better to believe"), the believer scrutinizes the truth to be able to find God and to believe.

Benedict XVI, *General Audience*, Paul VI Audience Hall, 30 January 2008.









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# Introduction

This meeting can be considered as the continuation of the workshop on “Mind, Brain and Education” held at the Pontifical Academy of Sciences in November 2003 (Battro, A.M., Fischer, K.W & Léna, P. Editors. *The educated brain: Essays in neuroeducation*. Cambridge University Press & Pontifical Academy of Sciences, 2008). Since then the theory and practice of neuroeducation have shown a significant progress. Several advanced research institutions in America, Asia and Europe are now involved in the transdisciplinary study of the neurocognitive foundations of learning and teaching, and the topic of neuroplasticity appears as the perfect link to address some fundamental questions coming from different fields.

The human species has developed an educational system to create and transmit knowledge and values from one generation to the next. With the help of education humans have expanded their cognitive potential by many orders of magnitude, well beyond the limits imposed by biological evolution. In particular the human cerebral cortex has revealed impressive capabilities to change its functionality and even its architecture during the process of education. Several mechanisms of neuroplasticity have been detected in the laboratory, the clinic and the school, that could sustain different learning styles.

Our workshop will discuss several topics at the cutting edge of the mind, brain and education sciences. For example the theory of a neuronal recycling process provides a new framework to understand, and to improve, the way young children learn to read and calculate. A wealth of experimental results illustrates the different neurocognitive pathways in the acquisition of first and second languages and the unfolding of basic arithmetical and geometric operations. Also the development of the social aspects of cognition, essential to educational practice, is now studied with new and powerful technologies and new theoretical models. The gap between genomics and education has shown a significant reduction in recent years. Neurocognitive models of developmental dyslexia and genotype-phenotype research studies in mental retardation and learning disabilities may show that heredity is not destiny. Some unexpected outcomes for treatment of those mental handicaps will be addressed.

Perhaps one of the most relevant tendencies in the mind, brain and education sciences of today is the expansion of the neurocognitive studies beyond the laboratory into the school and the community. The possibility to monitor many aspects of the learning and teaching activities online using the powerful

tools provided by digital networks and wi-fi technology opens a new horizon of research and practice. In particular we experience the formidable impact of computer and communication devices on the new ways children learn, and even teach, in a digital environment. Brain activities can be recorded nowadays in many ways in natural conditions with portable and wearable equipment. But the great novelty is the change of scale in education that the new digital technology triggers. Millions of children around the world can now be educated in a global cognitive environment.

■ **ANTONIO M. BATTRO, STANISLAS DEHAENE AND WOLF J. SINGER**

# Programme

**WEDNESDAY, 27 OCTOBER 2010**

9:00	<i>Welcome</i> (Marcelo Sánchez Sorondo) <i>Introduction</i> (Antonio M. Battro)
SESSION I • Chair: Antonio M. Battro	
<b>LANGUAGE AND LITERACY</b>	
9:30	<i>The Massive Impact of Literacy on the Human Brain</i> <b>Stanislas Dehaene</b>
10:15	<i>The Extent and Limit of Speech and Language: Reorganization After Brain Injury in Childhood</i> <b>Faraneh Vargha-Khadem</b>
11:00	Coffee break
<b>LEARNING AND TEACHING</b>	
12:00	<i>Plasticity in Learning Pathways: Assessments That Capture and Facilitate Learning</i> <b>Kurt W. Fischer</b>
12:45	Lunch at the Casina Pio IV
14:30	<i>Natural Geometry</i> <b>Elizabeth Spelke</b>
15:15	Discussion
SESSION II • Chair: Wolf J. Singer	
<b>THE INFANT BRAIN</b>	
16:00	<i>The Architecture of the Baby Brain</i> <b>Ghislaine Dehaene-Lambert</b>
16:45	Coffee break
17:30	<i>How Infants Crack the Speech Code: Exploring the Infant Mind Using the Tools of Modern Neuroscience</i> <b>Patricia K. Kuhl</b>
<b>GENETICS AND LEARNING</b>	
18:15	<i>Experiential Genetic and Epigenetic Effects on Human Neurocognitive Development</i> <b>Helen J. Neville</b>
19:00	General Discussion (duration 45 min.)
20:00	Dinner at the Casina Pio IV

**THURSDAY, 28 OCTOBER 2010**

9:00	<i>Fulfilling the Promise of Molecular Medicine in Developmental Brain Disorders</i> <b>Mark F. Bear</b>
9:45	<i>If Learning Disabilities Have a Genetic Origin What Should Educators Know?</i> <b>Albert M. Galaburda</b>
10:30	Coffee break
11:30	<b>Papal Audience</b>
13:30	Lunch at the Casina Pio IV
SESSION III • Chair: Stanislas Dehaene	
<b>BRAIN DEVELOPMENT AND SOCIETY</b>	
15:00	<i>Synaptic and Clock Genes in Autism Spectrum Disorders</i> <b>Thomas Bourgeron</b>
15:45	<i>The Development of Social Cognition: Early Learning, Neuroplasticity and Education</i> <b>Andrew N. Meltzoff</b>
16:30	Coffee break
17:00	<i>The Second Chance</i> <b>Wolf J. Singer</b>
17:45	Conclusions
18:00	Departure from the Casina Pio IV by bus to attend the concert at Palazzo Boncompagni Ludovisi
18:30	Concert followed by dinner
21:30	Bus leaves Palazzo Boncompagni Ludovisi to take participants back to the Domus Sanctae Marthae

# List of Participants

**Prof. Antonio M. Battro**

Chief Education Officer, One Laptop Per Child (Argentina)

**Prof. Thomas Bourgeron, Ph.D.**

Geneticist and Director of the Human Genetics and Cognitive Functions Unit, Department of Neuroscience at the Institute Pasteur, Paris (France)

**Prof. Stanislas Dehaene**

Collège de France;  
Head of the INSERM-CEA Cognitive Neuroimaging Unit, NeuroSpin, Saclay (France)

**Dr. Ghislaine Dehaene-Lambertz**

Research Scientist, Cognitive Neuroimaging Unit, INSERM U562, Orsay (France)

**Dr. Kurt W. Fischer, Ph.D.**

Charles Bigelow Professor of Human Development & Psychology; Director of the Mind, Brain, and Education Program, Harvard Graduate School of Education (USA)

**Prof. Albert M. Galaburda, M.D.**

Professor of Neurology and Neuroscience, Harvard Medical School and Beth Israel Deaconess Medical Center, Boston, Massachusetts (USA)

**Prof. Patricia K. Kuhl, Ph.D.**

Co-Director, Institute for Learning and Brain Sciences; Professor of Speech & Hearing Sciences, University of Washington (USA)

**Prof. Andrew N. Meltzoff, Ph.D.**

Co-Director, UW Institute for Learning and Brain Sciences and Professor, Department of Psychology, University of Washington (USA)

**Prof. Helen J. Neville**

Brain Development Lab, University of Oregon (USA)

**H.E. Msgr. Prof. Marcelo Sánchez Sorondo** Chancellor, The Pontifical Academy of Sciences (Vatican City)

**Prof. Dr. Wolf J. Singer**

Max-Planck-Institute for Brain Research, Frankfurt am Main (Federal Republic of Germany)

**Prof. Elizabeth S. Spelke**

Cognitive Psychology, Department of Psychology, Harvard University; Director of the Laboratory for Developmental Studies (USA)

**Prof. Faraneh Vargha-Khadem**

Head of the Developmental Cognitive Neuroscience Unit and Institute of Child Health, University College London (UK)

# Scientific Papers

LANGUAGE AND LITERACY



# THE MASSIVE IMPACT OF LITERACY ON THE BRAIN AND ITS CONSEQUENCES FOR EDUCATION

■ STANISLAS DEHAENE

## Introduction

It was once claimed that the bridge from brain research to education was ‘a bridge too far’ (Bruer, 1997). In the past decade, however, important progress has been made in bridging this gap, taking advantage of the improved ability to image the human brain in adults and children, in experimental paradigms relevant to learning and education. I would like to argue that, in fact, considerable cognitive neuroscience knowledge is already highly relevant to education. Our understanding of learning algorithms, including the known importance of active prediction, prediction error, or sleep consolidation, is directly relevant to the design of efficient learning environments, at school or through educational games. Our comprehension of the role of attention and reward (and their flip sides, the negative effects of distraction and punishment), or of the switch from explicit to implicit learning, are equally important generic findings that already affect much thinking in education.

Above all, human cognitive neuroscience has made enormous strides in understanding the specific cerebral circuits underlying particular domains of education, such as mathematics, reading and second-language acquisition. The human brain can be seen as a collection of evolved devices, inherited from our evolutionary history, and that address specific problems such as navigating in space and remembering locations, representing time, acquiring a sense of number for concrete sets, recognizing objects and faces, representing sounds and particularly the speech sounds typical of our species, and so on. I have argued that, through education, we take advantage of these pre-existing representations and *recycle* them towards novel uses, particularly because we are the only species capable of attaching arbitrary *symbols* to these representations and tying them together into elaborate symbol systems (Dehaene, 1977/2011, 2005, 2009; Dehaene & Cohen, 2007). Deficient operation of these specialized subsystems, or of the ability to attach symbols to them, can explain some developmental deficits such as dyscalculia, dyslexia, or dyspraxia.

In the present chapter, I briefly recapitulate how the recycling theory plays out in the domain of reading acquisition. I focus on recent discoveries

that demonstrate how the brain is changed by learning to read, and how these results illuminate the specific hurdles that children face as they learn to read. I am convinced that empowering teachers with the appropriate knowledge of the principles of human neuroplasticity and learning will lead to better classroom practices. Indeed, it is a shame that teachers still have a better idea of how their car works than of the inner functioning of their pupils' brains! Thus, my goal here is to summarize neuroimaging results on reading in an accessible manner, and to use these results to think about their consequences for education. I am also convinced that neuro-education research should not be performed solely in brain imaging labs. Experimentation in schools is indispensable to validate and expand the hypotheses that we form about optimal education practices. Thus, another goal of this chapter is to stir communication between cognitive neuroscientists and educators, in the hope that they actively collaborate towards the development of innovative teaching devices.

### **The cerebral mechanisms of adult reading**

What is reading? It is a wonderful cultural invention that allows us to hold 'a conversation with the deceased', a way to 'listen to the dead with my eyes' (Francisco de Quevedo). By learning to read, we learn to access our knowledge of spoken language through a novel modality, one that was never anticipated by evolution: vision. Writing is a remarkably clever encryption device by which we turn spoken language into a rich visual texture of marks on stone, clay or paper. Reading corresponds to the decryption of this texture. During reading acquisition, we transform some of the visual structures of our brain in order to turn them into a specialized interface between vision and language. Because reading is an extremely recent invention in evolutionary terms, and until recently concerned a small minority of humans, the human genome cannot contain any instructions for reading-specific brain circuits. Instead, we have to recycle existing brain systems for this novel use.

Cognitive neuroimaging in literate adults has clarified how reading operates at the cortical level. A large set of regions of the left hemisphere is identically activated when we read a sentence and when we listen to it (Devauchelle, Oppenheim, Rizzi, Dehaene, & Pallier, 2009). This a-modal language network comprises temporal-lobe regions, most prominently the entire length of the superior temporal sulcus, from the temporal pole to the posterior temporal-parietal junction, as well as distinct regions of the left inferior frontal lobe. All of these regions are thus not unique to reading. Rather, these are spoken-language areas, and reading provides access to them

through vision. Indeed, their activation is already present, with a left-hemispheric lateralization, when two-month-old babies listen to sentences in their mother tongue (Dehaene-Lambertz, Dehaene, & Hertz-Pannier, 2002; Dehaene-Lambertz, *et al.*, 2006; Dehaene-Lambertz, *et al.*, 2009). They obviously reflect an ancient and probably evolved system responsible for spoken language acquisition. When a child first enters primary school, this spoken language system, with its subcomponents of lexical, morphological, prosodic, syntactic and semantic processing, is already in place. What this child has to acquire is the visual interface into the language system.

Neuro-imaging studies of single-word reading have begun to clarify the localization and organization of this visual interface system. Visual words, when presented to adult readers, systematically activate a specific region of the left-hemispheric ventral visual cortex, which my colleagues and I have termed the *visual word form area* (VWFA in short) (Cohen, *et al.*, 2000). Its response is strictly visual and pre-lexical: it responds to all sorts of strings of letters, whether they form words or pseudowords devoid of any meaning such as ‘flinter’ (Dehaene, Le Clec’H, Poline, Le Bihan, & Cohen, 2002). Its localization is remarkably reproducible across individuals and even across cultures (Bolger, Perfetti, & Schneider, 2005; Cohen, *et al.*, 2000; Dehaene, *et al.*, 2002; Jobard, Crivello, & Tzourio-Mazoyer, 2003). It is always located at the same coordinates in the left lateral occipito-temporal sulcus, within a few millimeters. Furthermore, in a literate adult, its lesion systematically causes pure alexia, a selective inability to read (Déjerine, 1891; Gaillard, *et al.*, 2006). Thus, it clearly plays an indispensable role in reading.

We now know that, with literacy, this region becomes functionally specialized for reading in a specific script. Not only does it activate more to written words than to other categories of visual knowledge, such as faces (Puce, Allison, Asgari, Gore, & McCarthy, 1996) or line drawings of objects (Szwed, *et al.*, 2011), but it also activates more to a known script (e.g. Hebrew in Hebrew readers) than to other unknown scripts (Baker, *et al.*, 2007). Indeed, it has become attuned to quite specific cultural properties of the learned script, such as the relation between upper and lower-case letters of the Western alphabet: only this region recognizes the identity between, say, the words ‘rage’ and ‘RAGE’, which requires an internalization of arbitrary reading conventions (Dehaene, *et al.*, 2004; Dehaene, *et al.*, 2001). Recently, the VWFA has even been found to be invariant for printed versus hand-written words (Qiao, *et al.*, 2010). Thus, the VWFA is the main region that allows us to recognize a word like radio, RADIO, or *radio*, regardless of its exact font, size, and location. Remarkably, these invariant processes are so automated that they are deployed non-consciously.

My colleagues and I have proposed that, in the course of reading acquisition, the VWFA region gets selected as the primary area of learning because it possesses prior properties, inherited from primate evolution, that make it especially appropriate for reading. The first property is a preference for high-resolution shapes presented in the fovea, the high-resolution center of the retina (Hasson, Levy, Behrmann, Hendler, & Malach, 2002). Such high resolution is probably indispensable in order to read small print. The second property is a sensitivity to line configurations (Szwed, *et al.*, 2011): this region is part of a chunk of bilateral cortex called the fusiform gyrus that reacts strongly whenever the image contains line junctions forming shapes like T, L, Y, F, etc. These shapes may have been selected initially for their usefulness in *object* recognition – for instance a ‘T’ contour robustly signals that one object edge lies in front of another, and piecing this information together provides view-point invariant information about 3-D shapes (Biederman, 1987). My colleagues and I hypothesize that, in our literate culture, we recycled this ancient capacity by specifically selecting letter shapes that fit with this pre-existing cortical architecture (Dehaene, 2009). There is, indeed, evidence that all writing systems of the world make use of the same elementary ‘alphabet’ of line configurations (Changizi, Zhang, Ye, & Shimojo, 2006).

Third, finally, the precise location of the visual word form area is probably determined by its proximity and tight connections to cortical areas for spoken language processing in the lateral temporal lobe. Indeed, the hemispheric lateralization of the VWFA relates to the prior lateralization of spoken language processing, which is usually but not always in the left hemisphere (Cai, Lavidor, Brysbaert, Paulignan, & Nazir, 2007; Cai, Paulignan, Brysbaert, Ibarrola, & Nazir, 2010; Pinel & Dehaene, 2009). Interestingly, in children, the region exactly symmetrical to the VWFA, in the right hemisphere, can take over when the original VWFA site is damaged in early childhood (Cohen, Lehericy, *et al.*, 2004).

Most results to date appear compatible with a model of the neural architecture of visual word recognition called the ‘local combination detector’ (LCD) model (Dehaene, Cohen, Sigman, & Vinckier, 2005). This model assumes that a hierarchy of occipito-temporal neurons become attuned to fragments of writing, from line junctions to single letters, pairs of letters (bigrams), morphemes, and small words (Dehaene, *et al.*, 2005). Indeed, fMRI has now confirmed the existence of a tuning gradient with the VWFA (Vinckier, *et al.*, 2007), with successive responses to letters (Dehaene, *et al.*, 2004), bigrams (Binder, Medler, Westbury, Liebenthal, & Buchanan, 2006), and small words (Glezer, Jiang, & Riesenhuber, 2009).

The current thinking is that, during reading of a single word, millions of hierarchically organized neurons, each tuned to a specific local property (a letter, a bigram, or a morpheme), collectively contribute to visual recognition. This massively parallel architecture explains the speed and robustness of visual word recognition. Most importantly, for educators and teachers, it creates an *illusion* of whole-word reading. Because reading is so fast and takes about the same time for short and long words, some have assumed that the overall whole-word shape is being used for recognition, and that we should therefore teach whole-word reading rather than by letter-to-sound decoding. This inference is wrong, however. All the evidence to date suggests that visual words are being analyzed into their elementary components (strokes, letters, bigrams, morphemes) before the whole word can be put back together and recognized. However, this decomposition is so fast, parallel, and efficient as to seem almost instantaneous (it actually takes about one fifth of a second). Educational evidence concurs in showing that teaching of grapheme-phoneme correspondences is the fastest, most efficient way of making children efficient readers, both for pronunciation and for comprehension purposes (Ehri, Nunes, Stahl, & Willows, 2001).

### **How literacy changes the brain**

We directly tested the VWFA's role in literacy by comparing brain organization in illiterate versus literate adults (Dehaene, Pegado, *et al.*, 2010). There were several purposes to this study. First, we wanted to make a whole-brain image of the changes induced by reading acquisition – not only in the visual word form area, but also within the temporal-lobe language system and also early in the occipital visual cortex. Second, this was a unique opportunity to test the recycling hypothesis by examining what stimuli activate the VWFA site in people who have not learned to read, and whether we gain but also lose some functionality at this site as we learn to read. Third, we wondered whether these brain changes needed to occur at an early age, in the school years, or whether the adult brain was plastic enough for them to occur later on in life, during adulthood. To this aim, we tested pure illiterates (10 Brazilian adults who did not have the possibility to attend school in childhood and could barely recognize individual letters), ex-illiterates (21 unschooled Brazilian and Portuguese adults who attended adult literacy courses and reached variable levels of reading ability), and literates (32 Brazilian and Portuguese adults of various socio-economic communities, some tightly matched to the other groups).

Our results first confirmed that the VWFA is a major correlate of literacy. Activation at the precise coordinates of the VWFA, in response either to

written sentences or to individual pseudowords, was the main correlate of reading performance (see Figures 1 and 2, pp. 237–238). A massive enhancement of the response to letter strings was seen in this region, predictive of about half of the variance in reading speed across participants. We could now ask, what activates this region prior to reading, in illiterate participants? We saw a strong response to faces, objects and checkerboard patterns, indicating that this area specializes for visual object and face recognition before committing to visual word recognition. In excellent agreement with the recycling hypothesis, we observed a small but significant decrease in responses to these non-reading categories, particularly faces, with increasing literacy. As reading performance increased, activation to faces was increasingly displaced to the right-hemispheric fusiform gyrus. Similarly, Cantlon *et al.* (Cantlon, Pinel, Dehaene, & Pelphrey, 2011), in an fMRI study of four-year-olds, found that performance in identifying digits or letters was correlated with a decrease in the responses to faces in the left lateral fusiform gyrus. Both observations suggest that there is a competition for cortical space, and that reading acquisition must compete with pre-existing categories in the visual cortex. We literally ‘make room’ for reading on the surface of the cortex, by shifting the boundaries of other nearby regions.

In fact, we found that the visual changes due to literacy extended much more broadly than expected in the visual cortex, way beyond the VWFA. The posterior occipital cortex showed a globally increased response to all contrasted black-and-white pictures in our study, suggesting that literacy refines visual coding at an early level. Indeed, even the primary visual cortex (area V1) increased its activation only in response to horizontal checkerboards, not vertical ones. We interpret this finding as showing that expertise in reading refines the precision of visual coding, precisely for those regions of the retina that are useful for reading, i.e. the horizontal part of the visual field where alphabetic words always appear in Western culture.

A third type of change was seen in the superior temporal lobe, at a site called the planum temporale. There, activation to *spoken* language changed with literacy: it nearly doubled in good readers compared to illiterates. Because that region has been associated with a phonological code (e.g. Jacquemot, Pallier, LeBihan, Dehaene, & Dupoux, 2003), we believe that it relates to the acquisition of phonemic awareness, a major correlate of literacy. Illiterate adults have long been known to be unable to consciously detect or manipulate phonemes in tasks such as dropping the first phoneme of a word (e.g. Vatican → atican) (Moraes, Cary, Alegria, & Bertelson, 1979). The ability to consciously represent the phoneme as the smallest relevant unit of speech is the result of alphabetization. The left planum temporale may be a

crucial target of reading acquisition, the point where graphemic knowledge extracted from ventral visual areas first contacts phonemic representations of spoken language, thus permitting grapheme-to-phoneme conversion. Indeed, this cortical site is sensitive to the congruity between a speech sound and a simultaneously presented visual letter (van Atteveldt, Formisano, Goebel, & Blomert, 2004), an effect which is reduced or absent in dyslexic subjects (Blau, *et al.*, 2010).

Overall, then, the comparison of literate and illiterate brains emphasizes the degree to which reading acquisition changes the brain, not just within the visual word form area, but also earlier in the visual system and later on in the phonological system. By studying the data from the ex-illiterate adults, we were able to demonstrate that these systems are highly plastic: virtually all of the above changes were visible, in partial form, in the ex-illiterate adults who learned to read during adulthood (Dehaene, Pegado, *et al.*, 2010) (see Figure 2). Thus, even a small amount of literacy training changes the brain. A longitudinal study of kindergarten children supports this conclusion (Brem, *et al.*, 2010): eight weeks of training with the GraphoGame, a computerized grapheme-phoneme training program, suffice to cause an enhanced response to letter strings relative to false fonts in the VWFA. Similarly, training adults to recognize a new script leads to massive changes in the VWFA after a few training sessions (Hashimoto & Sakai, 2004; Song, Hu, Li, Li, & Liu, 2010; Yoncheva, Blau, Maurer, & McCandliss, 2010). Interestingly, these reading-induced changes only occur with a systematic attention to the correspondences between print and speech sounds. Thus, the VWFA response is shaped not only by bottom-up statistics of the visual input, but also by top-down factors coming from the target phonological code (Goswami & Ziegler, 2006). Learning to read requires a bidirectional dialogue in the brain, between the visual areas coding for letter strings and the auditory areas coding for the phonological segments of speech. This bidirectional dialogue, with a strong top-down component, can now be directly visualized by neuroimaging techniques: even in the absence of any visual input, good readers can optionally activate their VWFA from a purely spoken language input, whenever it is useful for them to activate an orthographic code (Cohen, Jobert, Le Bihan, & Dehaene, 2004; Dehaene, Pegado, *et al.*, 2010; Desroches, *et al.*, 2010; Yoncheva, Zevin, Maurer, & McCandliss, 2010).

### Consequences for education

We should be careful about transposing these brain results directly to the education domain. Observing how the brain is changed does not lead to a direct prescription of the best education method. Nevertheless, I



strongly believe that educators will strongly benefit from a better understanding of what is going on in their pupils' brains as they learn to read. Just like a mechanic can diagnose an engine problem by visualizing the engine's operation, educators who can visualize how the child's brain works will, spontaneously, conceive better ways of teaching. With this idea in mind, instead of designing a specific brain-based 'method' for teaching reading, my colleagues and I are attempting to draft a series of cognitive principles that are at work in reading acquisition and that should be taken into consideration by any teaching method.

Brain-imaging experiments lead to a clearer view of the amount of cortical transformation which is required for reading acquisition. Reading is not a natural task, and children are not biologically prepared to it by evolution (unlike spoken language acquisition). Thus, teachers must be aware that many of the reading steps that they take for granted, because they are expert readers and have a fully automated and non-conscious reading system, are not at all obvious for young children. Massive changes are needed, at the phonological and at the visual level, before children master the skill of reading. The very notion that phonemes exist, that there is the same sound at the beginning of 'rat', in the middle of 'brat', and at the end of 'car', is not available to illiterates, and is the result of alphabetization. Likewise, the notion that written words are composed of elementary objects, letters, and that each of these letters or groups of letters (graphemes) correspond to a speech sound or phoneme, is a non-trivial idea. Grapheme-phoneme correspondences must be systematically taught, one by one: the amount of such teaching is the best predictor of reading performance, including reading comprehension, in young children (Ehri, *et al.*, 2001). In brief, all aspects of the alphabetic code must be patiently explained to children: that words are made of letters or graphemes; that graphemes map onto to phonemes; that letters should be decoded from left to right; that the spatial left-to-right organization corresponds to the temporal order in which they are uttered; and that by changing their spatial order, one can compose new syllables and words.

It should be clear that I am advocating here a strong 'phonics' approach to teaching, and against a whole-word or whole-language approach. Several converging elements support this conclusion (for a longer development, see Dehaene, 2009). First, analysis of how reading operates at the brain level provides no support for the notion that words are recognized globally by their overall shape or contour. Rather, letters and groups of letters such as bigrams and morphemes are the units of recognition. Second, experiments with adults taught to read the same novel script with a whole-word versus



grapheme-phoneme approach show dramatic differences (Yoncheva, Blau, *et al.*, 2010): only the grapheme-phoneme group generalizes to novel word and trains the left-hemispheric VWFA. Adults whose attention was drawn to the global shape of words, by whole-word training, showed brain changes in the homolog region of the right hemisphere, clearly not the normal circuit for expert reading. Third, finally, these theoretical and laboratory-based arguments converge with school-based studies that prove the inferiority of the whole-word approach in bringing about fast improvements in reading acquisition. The whole-word approach will certainly not create dyslexia, which is a biological and partially genetic anomaly, but it does lead to avoidable delays in reading acquisition.

Another important observation for education is that the speed of reading acquisition varies dramatically with the regularity of grapheme-phoneme relations, which changes across languages (Paulesu, *et al.*, 2000; Seymour, Aro, & Erskine, 2003; Ziegler & Goswami, 2006). In Italy and Germany, children acquire reading in a few months, simply because the writing is highly regular, such that knowledge of the grapheme-phoneme correspondences suffices to read essentially all words. English and French lie on the other end of the scale of alphabetic transparency: they are highly irregular systems in which exceptions abound (e.g. 'though' versus 'tough') and are disambiguated only by lexical context. Behavioral research shows that English learners have to dedicate at least two more years of training before they read at the same level as Italian children (Seymour, *et al.*, 2003). Neuroimaging experiments show that, to do so, they expand their brain activation in the VWFA and the precentral cortex relative to Italian readers (Paulesu, *et al.*, 2000). Thus, teachers should be aware of the spelling irregularities in the language that they are teaching. They should prepare a rational progression, starting with the more regular and more frequent grapheme-phoneme correspondence, and ending with the exceptions. They should also pay attention to the complexity of syllables and start with the simpler consonant-vowel structures before moving on to more complex multi-consonant clusters. Mute letters, irregular spellings, and spellings inherited from Greek and Roman etymologies (e.g. 'ph') should all be addressed across the years, with frequent repetition. A good reading course should not stop at the simplest grapheme-phoneme correspondences: morphology, the understanding of prefixes, suffixes, roots, and grammatical endings is equally important in the brain of expert readers (Devlin, Jamison, Matthews, & Gonnerman, 2004).

Recently, our growing understanding of how the brain is recycled for reading has led to a clarification of another mysterious phenomenon that occurs during childhood: mirror reading and mirror writing. Many young readers confuse mirror letters such as p and q or b and d. Furthermore, they

occasionally write in mirror form, from right to left, quite competently and without seemingly noticing their error. This peculiar behavior can be explained by considering that the function of the ventral visual cortex, prior to reading, is the invariant recognition of objects, faces and scenes. In the natural world, very few objects have a distinct identity for left and right views. In most cases, the left and right views of a natural object are mirror images of each other, and it is useful to generalize across them and treat them as the same object. Single-cell recordings in monkeys show that this principle is deeply embedded in the visual system: many neurons in the occipito-temporal visual cortex fire identically to the left and right views of the same object or face (Freiwald & Tsao, 2010; Logothetis, Pauls, & Poggio, 1995; Rollenhagen & Olson, 2000). Using neuroimaging, my colleagues and I have shown that, in the human brain, it is precisely the VWFA which is the dominant site for this mirror-image invariance (Dehaene, Nakamura, *et al.*, 2010; Pegado, Nakamura, Cohen, & Dehaene, 2011). No wonder, then, that young children confuse b and d: they are trying to learn to read with precisely the brain area that confuses left and right of images! Mirror confusion is a normal property of the visual system, which is seen in all children and illiterate subjects, and which disappears for letters and geometric symbols when literacy sets in (Cornell, 1985; Kolinsky, *et al.*, 2010). Only its prolongation in late childhood is a sign of dyslexia (Lachmann & van Leeuwen, 2007; Schneps, Rose, & Fischer, 2007). Teachers should therefore be aware of the specific difficulty posed by mirror letters, and should take the time to explain why b and d are distinct letters corresponding to distinct phonemes (it is particularly unfortunate that these phonemes are quite similar and easily confused). Interestingly, teaching the gestures of writing can improve reading, perhaps because it helps store view-specific memories of the letters and their corresponding phonemes (Fredembach, de Boisferon, & Gentaz, 2009; Gentaz, Colé, & Bara, 2003).

All of the above ideas are already applied in many schools, and did not await the advent of cognitive neuroscience. I merely hope that, by bringing to light their cerebral foundations, cognitive neuroscience studies of reading can help spread the word and eventually lead to a more systematic and rational approach to reading education. A true science of reading is emerging. In the future, new experiments, involving a tight collaboration between scientists and educators, should lead to an even clearer picture of the learning algorithms used by the brain, and how they can be harnessed to facilitate learning in the classroom.

## References

- Baker, C.I., Liu, J., Wald, L.L., Kwong, K.K., Benner, T., & Kanwisher, N. (2007). Visual word processing and experiential origins of functional selectivity in human extrastriate cortex. *Proc Natl Acad Sci U S A*, 104(21), 9087-9092.
- Biederman, I. (1987). Recognition-by-components: a theory of human image understanding. *Psychol Rev*, 94(2), 115-147.
- Binder, J.R., Medler, D.A., Westbury, C.F., Liebenthal, E., & Buchanan, L. (2006). Tuning of the human left fusiform gyrus to sublexical orthographic structure. *Neuroimage*, 33(2), 739-748.
- Blau, V., Reithler, J., van Atteveldt, N., Seitz, J., Gerretsen, P., Goebel, R., et al. (2010). Deviant processing of letters and speech sounds as proximate cause of reading failure: a functional magnetic resonance imaging study of dyslexic children. *Brain*.
- Bolger, D.J., Perfetti, C.A., & Schneider, W. (2005). Cross-cultural effect on the brain revisited: universal structures plus writing system variation. *Hum Brain Mapp*, 25(1), 92-104.
- Brem, S., Bach, S., Kucian, K., Guttorm, T.K., Martin, E., Lyytinen, H., et al. (2010). Brain sensitivity to print emerges when children learn letter-speech sound correspondences. *Proc Natl Acad Sci U S A*, 107(17), 7939-7944.
- Bruer, J.T. (1997). Education and the brain: A bridge too far. *Educational Researcher*, 26(8), 4-16.
- Cai, Q., Lavidor, M., Brysbaert, M., Paulignan, Y., & Nazir, T. (2008). Cerebral lateralization of frontal lobe language processes and lateralization of the posterior visual word processing system. *J Cog Neurosci*, 20, 672-681.
- Cai, Q., Paulignan, Y., Brysbaert, M., Ibarrola, D., & Nazir, T.A. (2010). The left ventral occipito-temporal response to words depends on language lateralization but not on visual familiarity. *Cereb Cortex*, 20(5), 1153-1163.
- Cantlon, J.F., Pinel, P., Dehaene, S., & Pelphey, K.A. (2011). Cortical representations of symbols, objects, and faces are pruned back during early childhood. *Cereb Cortex*, 21(1), 191-199.
- Changizi, M.A., Zhang, Q., Ye, H., & Shimojo, S. (2006). The Structures of Letters and Symbols throughout Human History Are Selected to Match Those Found in Objects in Natural Scenes. *Am Nat*, 167(5), E117-139.
- Cohen, L., Dehaene, S., Naccache, L., Lehericy, S., Dehaene-Lambertz, G., Hénauff, M.A., et al. (2000). The visual word form area: Spatial and temporal characterization of an initial stage of reading in normal subjects and posterior split-brain patients. *Brain*, 123, 291-307.
- Cohen, L., Jobert, A., Le Bihan, D., & Dehaene, S. (2004). Distinct unimodal and multimodal regions for word processing in the left temporal cortex. *Neuroimage*, 23(4), 1256-1270.
- Cohen, L., Lehericy, S., Henry, C., Bourgeois, M., Larroque, C., Sainte-Rose, C., et al. (2004). Learning to read without a left occipital lobe: right-hemispheric shift of visual word form area. *Ann Neurol*, 56(6), 890-894.
- Cornell (1985). Spontaneous mirror-writing in children. *Can J Exp Psychol*, 39, 174-179.
- Dehaene-Lambertz, G., Dehaene, S., & Hertz-Pannier, L. (2002). Functional neuroimaging of speech perception in infants. *Science*, 298(5600), 2013-2015.
- Dehaene-Lambertz, G., Hertz-Pannier, L., Dubois, J., Meriaux, S., Roche, A., Sigman, M., et al. (2006). Functional organization of perisylvian activation during presentation of sentences in preverbal infants. *Proc Natl Acad Sci U S A*, 103(38), 14240-14245.
- Dehaene-Lambertz, G., Montavont, A., Jobert, A., Alliol, L., Dubois, J., Hertz-Pannier, L., et al. (2009). Language or

- music, mother or Mozart? Structural and environmental influences on infants' language networks. *Brain Lang.*
- Dehaene, S. (1977/2011). *The number sense (2nd edition)*. New York: Oxford University Press.
- Dehaene, S. (2005). Evolution of human cortical circuits for reading and arithmetic: The 'neuronal recycling' hypothesis. In S. Dehaene, J.R. Duhamel, M. Hauser & G. Rizzolatti (eds.), *From monkey brain to human brain* (pp. 133-157). Cambridge, Massachusetts: MIT Press.
- Dehaene, S. (2009). *Reading in the brain*. New York: Penguin Viking.
- Dehaene, S., & Cohen, L. (2007). Cultural recycling of cortical maps. *Neuron*, 56(2), 384-398.
- Dehaene, S., Cohen, L., Sigman, M., & Vinckier, F. (2005). The neural code for written words: a proposal. *Trends Cogn Sci*, 9(7), 335-341.
- Dehaene, S., Jobert, A., Naccache, L., Ciuciu, P., Poline, J.B., Le Bihan, D., et al. (2004). Letter binding and invariant recognition of masked words: behavioral and neuroimaging evidence. *Psychol Sci*, 15(5), 307-313.
- Dehaene, S., Le Clec'H, G., Poline, J.B., Le Bihan, D., & Cohen, L. (2002). The visual word form area: a prelexical representation of visual words in the fusiform gyrus. *Neuroreport*, 13(3), 321-325.
- Dehaene, S., Naccache, L., Cohen, L., Bihan, D.L., Mangin, J.F., Poline, J.B., et al. (2001). Cerebral mechanisms of word masking and unconscious repetition priming. *Nat Neurosci*, 4(7), 752-758.
- Dehaene, S., Nakamura, K., Jobert, A., Kuroki, C., Ogawa, S., & Cohen, L. (2010). Why do children make mirror errors in reading? Neural correlates of mirror invariance in the visual word form area. *Neuroimage*, 49(2), 1837-1848.
- Dehaene, S., Pegado, F., Braga, L.W., Ventura, P., Nunes Filho, G., Jobert, A., et al. (2010). How learning to read changes the cortical networks for vision and language. *Science*, 330(6009), 1359-1364.
- Déjerine, J. (1891). Sur un cas de cécité verbale avec agraphie suivi d'autopsie. *Mémoires de la Société de Biologie*, 3, 197-201.
- Desroches, A.S., Cone, N.E., Bolger, D.J., Bitan, T., Burman, D.D., & Booth, J.R. (2010). Children with reading difficulties show differences in brain regions associated with orthographic processing during spoken language processing. *Brain Res.*
- Devauchelle, A.D., Oppenheim, C., Rizzi, L., Dehaene, S., & Pallier, C. (2009). Sentence syntax and content in the human temporal lobe: an fMRI adaptation study in auditory and visual modalities. *J Cogn Neurosci*, 21(5), 1000-1012.
- Devlin, J.T., Jamison, H.L., Matthews, P.M., & Gonnerman, L.M. (2004). Morphology and the internal structure of words. *Proc Natl Acad Sci U S A*, 101(41), 14984-14988.
- Ehri, L.C., Nunes, S.R., Stahl, S.A., & Willows, D.M.M. (2001). Systematic phonics instruction helps students learn to read: Evidence from the National Reading Panel's meta-analysis. *Review of Educational Research*, 71, 393-447.
- Fredembach, B., de Boisferon, A.H., & Gentaz, E. (2009). Learning of arbitrary association between visual and auditory novel stimuli in adults: the 'bond effect' of haptic exploration. *PLoS One*, 4(3), e4844.
- Freiwald, W.A., & Tsao, D.Y. (2010). Functional compartmentalization and viewpoint generalization within the macaque face-processing system. *Science*, 330(6005), 845-851.
- Gaillard, R., Naccache, L., Pinel, P., Clemen-ceau, S., Volle, E., Hasboun, D., et al. (2006). Direct intracranial, fMRI, and lesion evidence for the causal role of left inferotemporal cortex in reading. *Neuron*, 50(2), 191-204.

- Gentaz, E., Colé, P., & Bara, F. (2003). Evaluation d'entraînements multisensoriels de préparation à la lecture pour les enfants en grande section de maternelle : une étude sur la contribution du système haptique manuel. *L'Année Psychologique*, 104, 561-584.
- Glezer, L.S., Jiang, X., & Riesenhuber, M. (2009). Evidence for highly selective neuronal tuning to whole words in the 'visual word form area'. *Neuron*, 62(2), 199-204.
- Goswami, U., & Ziegler, J.C. (2006). A developmental perspective on the neural code for written words. *Trends Cogn Sci*, 10(4), 142-143.
- Hashimoto, R., & Sakai, K.L. (2004). Learning letters in adulthood: direct visualization of cortical plasticity for forming a new link between orthography and phonology. *Neuron*, 42(2), 311-322.
- Hasson, U., Levy, I., Behrmann, M., Hendler, T., & Malach, R. (2002). Eccentricity bias as an organizing principle for human high-order object areas. *Neuron*, 34(3), 479-490.
- Jacquemot, C., Pallier, C., LeBihan, D., Dehaene, S., & Dupoux, E. (2003). Phonological grammar shapes the auditory cortex: a functional magnetic resonance imaging study. *J Neurosci*, 23(29), 9541-9546.
- Jobard, G., Crivello, F., & Tzourio-Mazoyer, N. (2003). Evaluation of the dual route theory of reading: a metaanalysis of 35 neuroimaging studies. *Neuroimage*, 20(2), 693-712.
- Kolinsky, R., Verhaeghe, A., Fernandes, T., Mengarda, E.J., Grimm-Cabral, L., & Morais, J. (2010). Enantiomorphy through the Looking-Glass: Literacy effects on mirror-image discrimination. *JEP: General*, in 2nd revision.
- Lachmann, T., & van Leeuwen, C. (2007). Paradoxical enhancement of letter recognition in developmental dyslexia. *Dev Neuropsychol*, 31(1), 61-77.
- Logothetis, N.K., Pauls, J., & Poggio, T. (1995). Shape representation in the inferior temporal cortex of monkeys. *Curr Biol*, 5(5), 552-563.
- Morais, J., Cary, L., Alegria, J., & Bertelson, P. (1979). Does awareness of speech as a sequence of phones arise spontaneously? *Cognition*, 7, 323-331.
- Paulesu, E., McCrory, E., Fazio, F., Menoncello, L., Brunswick, N., Cappa, S.F., et al. (2000). A cultural effect on brain function. *Nat Neurosci*, 3(1), 91-96.
- Pegado, F., Nakamura, K., Cohen, L., & Dehaene, S. (2011). Breaking the symmetry: Mirror discrimination for single letters but not for pictures in the Visual Word Form Area. *Neuroimage*, 55, 742-749.
- Pinel, P., & Dehaene, S. (2009). Beyond hemispheric dominance: brain regions underlying the joint lateralization of language and arithmetic to the left hemisphere. *J Cogn Neurosci*, 22(1), 48-66.
- Puce, A., Allison, T., Asgari, M., Gore, J.C., & McCarthy, G. (1996). Differential sensitivity of human visual cortex to faces, letterstrings, and textures: a functional magnetic resonance imaging study. *Journal of Neuroscience*, 16, 5205-5215.
- Qiao, E., Vinckier, F., Szwed, M., Naccache, L., Valabregue, R., Dehaene, S., et al. (2010). Unconsciously deciphering handwriting: subliminal invariance for handwritten words in the visual word form area. *Neuroimage*, 49(2), 1786-1799.
- Rollenhagen, J.E., & Olson, C.R. (2000). Mirror-image confusion in single neurons of the macaque inferotemporal cortex. *Science*, 287(5457), 1506-1508.
- Schneeps, M.H., Rose, L.T., & Fischer, K.W. (2007). Visual learning and the brain: Implications for dyslexia. *Mind, Brain and Education*, 1(3), 128-139.
- Seymour, P.H., Aro, M., & Erskine, J.M. (2003). Foundation literacy acquisition in European orthographies. *Br J Psychol*, 94(Pt 2), 143-174.
- Song, Y., Hu, S., Li, X., Li, W., & Liu, J. (2010). The role of top-down task context in learning to perceive objects. *J Neurosci*, 30(29), 9869-9876.

- Szwed, M., Dehaene, S., Kleinschmidt, A., Eger, E., Valabregue, R., Amadon, A., *et al.* (2011). Specialization for written words over objects in the visual cortex. *Neuroimage*.
- van Atteveldt, N., Formisano, E., Goebel, R., & Blomert, L. (2004). Integration of letters and speech sounds in the human brain. *Neuron*, 43(2), 271–282.
- Vinckier, F., Dehaene, S., Jobert, A., Dubus, J.P., Sigman, M., & Cohen, L. (2007). Hierarchical coding of letter strings in the ventral stream: dissecting the inner organization of the visual word-form system. *Neuron*, 55(1), 143–156.
- Yoncheva, Y.N., Blau, V.C., Maurer, U., & McCandliss, B.D. (2010). Attentional focus during learning impacts N170 ERP responses to an artificial script. *Dev Neuropsychol*, 35(4), 423–445.
- Yoncheva, Y.N., Zevin, J.D., Maurer, U., & McCandliss, B.D. (2010). Auditory selective attention to speech modulates activity in the visual word form area. *Cereb Cortex*, 20(3), 622–632.
- Ziegler, J.C., & Goswami, U. (2006). Becoming literate in different languages: similar problems, different solutions. *Dev Sci*, 9(5), 429–436.

# BRAIN MECHANISMS UNDERLYING THE CRITICAL PERIOD FOR LANGUAGE: LINKING THEORY AND PRACTICE

■ PATRICIA K. KUHL

## Introduction

Half a century ago, humans' capacity for speech and language provoked classic debates on what it means to be human by strong proponents of nativism (Chomsky, 1959) and learning (Skinner, 1957). The debate centered on learning and development, and the remarkable transition that all children make as they acquire a language. While we are now far beyond these debates and informed by a great deal of data about infants, their innate predispositions and incredible abilities to learn once exposed to natural language (Kuhl, 2009; Saffran, Werker, and Werner, 2006), we are still just breaking ground with regard to the neural mechanisms that underlie language development and its 'critical period' (see Friederici and Wartenburger, 2010; Kuhl and Rivera-Gaxiola, 2008; Kuhl *et al.*, 2008). Developmental neuroscience is beginning to deepen our understanding of the nature of language and its 'window of opportunity' for learning.

To explore the topic of the critical period for language, and its practical implications, I will focus on the youngest learners – infants in the first year of life – and compare them to adult learners. The linguistic data will focus on the most elementary units of language – the consonants and vowels that make up words. Infants' responses to the basic building blocks of speech provide an experimentally accessible window on the roles of nature and nurture in language acquisition. Comparative studies at the phonetic level have allowed us to examine humans' unique language processing abilities at birth and as they respond to language experience. We are beginning to discover how exposure to two languages early in infancy produces a bilingual brain, and bilingualism is allowing us to test theories of the critical period. Neuroimaging of infants is advancing our understanding of the uniquely human capacity for language.

## Windows to the young brain

Rapid advances have been made in noninvasive techniques that examine language processing in young children (Figure 1, see p. 239). They include



Electroencephalography (EEG)/Event-Related Potentials (ERPs), Magnetoencephalography (MEG), functional Magnetic Resonance Imaging (fMRI), and Near-Infrared Spectroscopy (NIRS).

Event-Related Potentials (ERPs) have been widely used to study speech and language processing in infants and young children (for reviews, see Conboy, Rivera-Gaxiola, Silva-Pereyra, and Kuhl, 2008; Friederici, 2005; Kuhl, 2004). ERPs, a part of the EEG, reflect electrical activity that is time-locked to the presentation of a specific sensory stimulus (for example, syllables or words) or a cognitive process (for example, recognition of a semantic violation within a sentence or phrase). By placing sensors on a child's scalp, the activity of neural networks firing in a coordinated and synchronous fashion in open field configurations can be measured, and voltage changes occurring as a function of cortical neural activity can be detected. ERPs provide precise time resolution (milliseconds), making them well suited for studying the high-speed and temporally ordered structure of human speech. ERP experiments can also be carried out in populations who cannot provide overt responses because of age or cognitive impairment. Spatial resolution of the source of brain activation is, however, limited.

Magnetoencephalography (MEG) is another brain imaging technique that tracks activity in the brain with exquisite temporal resolution. The SQUID (superconducting quantum interference device) sensors located within the MEG helmet measure the minute magnetic fields associated with electrical currents that are produced by the brain when it is performing sensory, motor, or cognitive tasks. Going beyond EEG, MEG allows precise localization of the neural currents responsible for the sources of the magnetic fields. Cheour *et al.* (2004) and Imada *et al.* (2006) used new head-tracking methods and MEG to show phonetic discrimination in newborns and in infants in the first year of life. Sophisticated head-tracking software and hardware enables investigators to correct for infants' head movements, and allows the examination of multiple brain areas as infants listen to speech (Imada *et al.*, 2006). MEG (as well as EEG) techniques are completely safe and noiseless.

Magnetic resonance imaging (MRI) can be combined with MEG and/or EEG, providing static structural/anatomical pictures of the brain. Structural MRIs show anatomical differences in brain regions across the lifespan, and have recently been used to predict second-language phonetic learning in adults (Golestani, Molko, Dehaene, LeBihan, and Pallier, 2007). Structural MRI measures in young infants identify the size of various brain structures and these measures correlate with later language abilities (Ortiz-Mantilla, Choe, Flax, Grant, and Benasich, 2010). When structural MRI images are superimposed on the physiological activity detected by MEG or



EEG, the spatial localization of brain activities recorded by these methods can be improved.

Functional magnetic resonance imaging (fMRI) is a popular method of neuroimaging in adults because it provides high spatial-resolution maps of neural activity across the entire brain (e.g., Gernsbacher and Kaschak, 2003). Unlike EEG and MEG, fMRI does not directly detect neural activity, but rather the changes in blood-oxygenation that occur in response to neural activation. Neural events happen in milliseconds; however, the blood-oxygenation changes that they induce are spread out over several seconds, thereby severely limiting fMRI's temporal resolution. Few studies have attempted fMRI with infants because the technique requires infants to be perfectly still, and because the MRI device produces loud sounds making it necessary to shield infants' ears. fMRI studies allow precise localization of brain activity and a few pioneering studies show remarkable similarity in the structures responsive to language in infants and adults (Dehaene-Lambertz, Dehaene, and Hertz-Pannier, 2002; Dehaene-Lambertz *et al.*, 2006).

Near-Infrared Spectroscopy (NIRS) also measures cerebral hemodynamic responses in relation to neural activity, but utilizes the absorption of light, which is sensitive to the concentration of hemoglobin, to measure activation (Aslin and Mehler, 2005). NIRS measures changes in blood oxygenated and deoxy-hemoglobin concentrations in the brain as well as total blood volume changes in various regions of the cerebral cortex using near infrared light. The NIRS system can determine the activity in specific regions of the brain by continuously monitoring blood hemoglobin level. Reports have begun to appear on infants in the first two years of life, testing infant responses to phonemes as well as longer stretches of speech such as 'motherese' and forward versus reversed sentences (Bortfeld, Wruck, and Boas, 2007; Homae, Watanabe, Nakano, Asakawa, and Taga, 2006; Peña, Bonatti, Nespor, and Mehler, 2002; Taga and Asakawa, 2007). As with other hemodynamic techniques such as fMRI, NIRS typically does not provide good temporal resolution. However, event-related NIRS paradigms are being developed (Gratton and Fabiani, 2001a,b). One of the most important potential uses of the NIRS technique is possible co-registration with other testing techniques such as EEG and MEG.

## Phonetic learning

Perception of the phonetic units of speech – the vowels and consonants that make up words – is one of the most widely studied linguistic skills in infancy and adulthood. Phonetic perception and the role of experience in learning is studied in newborns, during development as infants are exposed to a

particular language, in adults from different cultures, in children with developmental disabilities, and in nonhuman animals. Phonetic perception studies provide critical tests of theories of language development and its evolution. An extensive literature on developmental speech perception exists and brain measures are adding substantially to our knowledge of phonetic development and learning (see Kuhl, 2004; Kuhl *et al.*, 2008; Werker and Curtin, 2005).

In the last decade, brain and behavioral studies indicate a very complex set of interacting brain systems in the initial acquisition of language early in infancy, many of which appear to reflect adult language processing (Dehaene-Lambertz *et al.*, 2006). In adulthood, language is highly modularized, which accounts for the very specific patterns of language deficits and brain damage in adult patients following stroke (Kuhl and Damasio, *in press*). Infants, however, must begin life with brain systems that allow them to acquire any and all languages to which they are exposed, and allow acquisition of language as either an auditory-vocal or a visual-manual code on roughly the same timetable (Petitto and Marentette, 1991). We are in a nascent stage of understanding the brain mechanisms underlying infants' early flexibility with regard to the acquisition of language – their ability to acquire language by eye or by ear, and their ability to acquire one or multiple languages – and also the reduction in this initial flexibility that occurs with age, dramatically decreasing our capacity to acquire a new language as adults (Newport, 1990). The infant brain is exquisitely poised to 'crack the speech code' in a way that the adult brain cannot. Uncovering why this is so is a very interesting puzzle.

In this review I will also explore a current working hypothesis and its implications for the critical period in language – that the critical period is not driven solely by *time* (maturation), but by *experience*. In exploring the critical period for phonetic learning we will examine the role of experience, particularly in *closing* the optimal period for learning. I will also develop the idea that systems-level top-down mechanisms, such as those controlling social cognition, play an essential role in infants' abilities to 'crack the speech code'. On this view, infants combine a powerful set of domain-general computational skills with their equally extraordinary social skills to enable learning. Thus, the underlying brain systems for social cognition and language processing mutually influence one another in controlling the opening and closing of the critical period during development. Nature's language experiments – the case of simultaneous bilinguals who learn more than one language – are revealing a great deal about how experience alters the brain, and these data are affecting arguments about the critical period as well. The data suggest revisions of theory. Of equal importance, the data show how one might facilitate language learning and literacy in young children.

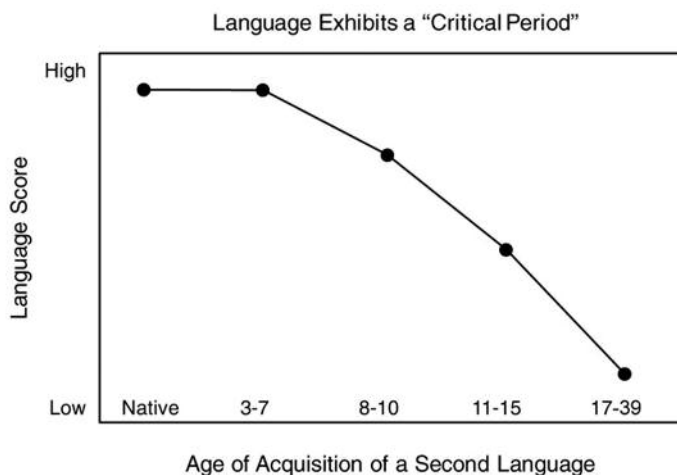
Regarding the social effects, I have suggested that the social brain – in ways we have yet to understand – ‘gates’ the computational mechanisms underlying learning in the domain of language (Kuhl, 2007; in press). The assertion that social factors gate language learning may help explain not only how typically developing children acquire language, but also why children with autism exhibit twin deficits in social cognition and language, and why nonhuman animals with impressive computational abilities do not acquire language. Moreover, this gating hypothesis may explain why social factors play a far more significant role than previously realized in human learning across domains throughout our lifetimes (Meltzoff, Kuhl, Movellan, and Sejnowski, 2009). Theories of social learning have traditionally emphasized the role of social factors in language acquisition (Bruner, 1983; Tomasello, 2003a, b; Vygotsky, 1962). However, these models emphasized the development of lexical understanding and the use of others’ communicative intentions to help understand the mapping between words and objects. The new data indicate that social interaction gates an even more basic aspect of language – learning of the elementary phonetic units – suggesting a more fundamental connection between the brain mechanisms underlying human social understanding and the origins of language than has previously been hypothesized.

Research on infants’ phonetic perception in the first year of life shows how computational, cognitive, and social skills combine to form a very powerful learning mechanism. Interestingly, this mechanism does not resemble Skinner’s operant conditioning and reinforcement model of learning, nor Chomsky’s detailed view of parameter setting. The processes that infants employ when learning from exposure to language are complex and multi-modal, but also child’s play in that they grow out of infants’ heightened attention to items and events in the natural world: the faces, actions, and voices of other people.

### **Language exhibits a ‘critical period’ for learning**

A stage-setting concept for human language learning is the graph shown in Figure 2, redrawn from a study by Johnson and Newport on English grammar in native speakers of Korean learning English as a second language (1989). The graph as rendered shows a simplified schematic of second language competence as a function of the age of second language acquisition.

Figure 2 is surprising from the standpoint of more general human learning. In the domain of language, infants and young children are superior learners when compared to adults, in spite of adults’ cognitive superiority. Language is one of the classic examples of a ‘critical’ or ‘sensitive’ period in neurobiology (Bruer, 2008; Johnson and Newport, 1989; Knudsen, 2004; Kuhl, 2004; Newport, Bavelier, and Neville, 2001).



**Figure 2.** The relationship between age of acquisition of a second language and language skill (adapted from Johnson and Newport, 1989).

Scientists are generally in agreement that this learning curve is representative of data across a wide variety of second-language learning studies (Bialystok and Hakuta, 1994; Birdsong and Molis, 2001; Flege, Yeni-Komshian, and Liu, 1999; Johnson and Newport, 1989; Kuhl, Conboy, Padden, Nelson, and Pruitt, 2005a; Kuhl *et al.*, 2008; Mayberry and Lock, 2003; Neville *et al.*, 1997; Weber-Fox and Neville, 1999; Yeni-Komshian, Flege, and Liu, 2000; though see Birdsong, 1992; White and Genesee, 1996). However, not all aspects of language exhibit the same temporally defined critical window. The developmental timing of critical periods for learning phonetic, lexical, and syntactic levels of language vary, though studies cannot yet document the precise timing at each individual level. Studies indicate, for example, that the critical period for phonetic learning occurs prior to the end of the first year, whereas syntactic learning flourishes between 18 and 36 months of age. Vocabulary development explodes at 18 months of age, but does not appear to be as restricted by age as other aspects of language learning – one can learn new vocabulary items at any age. One goal of future research will be to document the ‘opening’ and ‘closing’ of critical periods for all levels of language and understand how they overlap and why they differ.

Given widespread agreement on the fact that we do not learn equally well over the lifespan, theory is currently focused on attempts to understand how and why learning is restricted to certain periods. What accounts for adults’ inability to learn a new language with the facility of an infant?

Recent data on critical periods in the visual domain – particularly in the case of ocular dominance – are exploring from a physiological perspective the pharmacological triggers at the cellular level that open the critical period and those that close the period of optimum learning. For example, we have known since the pioneering work of Hubel and Wiesel (Hubel and Wiesel, 1963; Wiesel and Hubel, 1963; Hensch, 2005) that ocular dominance in the brain's visual cortex is determined by experience at a particular point in development – input from the two eyes determines the relative dominance of one eye over another. Closing one eye during the critical period for binocular fusion results in a permanent reduction in visual acuity. Recent research indicates that in the case of binocular vision, the brain's inhibitory circuits are responsible for both the onset and offset of plasticity (Hensch and Stryker, 1996; Hensch, 2005). This finding represents an exciting new step in understanding the underlying mechanisms of the critical period for vision.

Work on the molecular components (inhibitory GABAergic systems, etc.) that control the opening and narrowing of learning periods pose an important question from a theoretical perspective: Something has to trigger these inhibitory circuits – is it maturation that triggers the cellular mechanisms causing them to initiate learning, and eventually to slow learning, or does the trigger stem from the environment? Vision research has provided a clue: Rearing animals completely in the dark (by eye-suturing for example), and then opening the animal's eye after the typical learning period is over, extends the critical period (Cho and Bear, 2010). At least for binocular vision, the critical period is not strictly maturational. Knowing whether this is the case more generally – beyond vision – will advance theory.

### **Phonetic level contributions to 'critical period' theory**

Work in my laboratory has focused on the idea that *experience*, not simply *time or maturation*, opens and closes the critical period in the case of language (Kuhl, 2000). Our published work focuses on closing mechanisms, ones that may cause phonetic learning to decline with language experience. Work on the opening of the critical period has recently begun.

Language acquisition is often cited as an example of a critical learning period that is constrained by time, or factors such as hormones, that are outside the learning process itself. The studies on speech (as well as those on birds acquiring bird song, see Doupe and Kuhl, 1999) suggest an alternative (Kuhl, 2000). The work on speech suggests that early learning itself may constrain later learning. In earlier writings, I advanced the concept of *neural commitment*, the idea that neural circuitry and overall architecture forms early in infancy to detect the phonetic and prosodic patterns of

speech (Kuhl, 2004; Zhang, Kuhl, Imada, Kotani, and Tohkura, 2005; Zhang *et al.*, 2009). The neural architecture formed with experience is designed to maximize the efficiency of processing for the language(s) experienced by the infant. Once fully established, the neural architecture arising from exposure to French or Tagalog, for example, impedes learning of a new language that does not conform.

### **Infant phonetic learning: computation ‘gated’ by the social brain**

The world’s languages contain approximately 600 consonants and 200 vowels (Ladefoged, 2001). Each language uses a unique set of distinct elements, *phonemes*, which change the meaning of a word (e.g. from *bat* to *pat* in English). But phonemes are actually groups of non-identical sounds, *phonetic units*, which are functionally equivalent in the language. Japanese-learning infants have to group the phonetic units *r* and *l* into a single phonemic category (Japanese *r*), whereas English-learning infants must uphold the distinction to separate *rake* from *lake*. Spanish learning infants must distinguish phonetic units critical to Spanish words (*baño* and *paño*), whereas English learning infants must combine them into a single category (English *b*).

If infants were exposed only to the subset of phonetic units that will eventually be used phonemically to differentiate words in their language, the problem would be trivial. But infants are exposed to many more phonetic variants than will be used phonemically. The baby’s task in the first year of life, therefore, is to make some progress in figuring out the composition of the 40-odd phonemic categories in their language before trying to acquire words that depend on these elementary units. An important discovery in the 1970s was that infants initially hear all phonetic differences; they have a universal phonetic capacity at birth (Eimas, 1975; Eimas, Siqueland, Jusczyk, and Vigorito, 1971; Lasky, Syrdal-Lasky, and Klein, 1975; Werker and Lalonde, 1988).

Between 6 and 12 months of age nonnative discrimination declines (Best and McRoberts, 2003; Rivera-Gaxiola, Silvia-Pereyra, and Kuhl, 2005a; Tsao, Liu, and Kuhl, 2006; Werker and Tees, 1984), and native language speech perception shows a significant increase (Kuhl *et al.*, 2006; Tsao *et al.*, 2006) (see Figure 3, 240).

What happens during this 2-month window to prompt the transition? Available data now allows us to create a model of the transition in phonetic perception, and our current working model of the process (Kuhl *et al.*, 2008) shows that two factors are key to phonetic learning during the sensitive period – computational learning and social cognition.

### *The computational component*

An implicit form of learning, referred to as ‘statistical learning’ (Saffran, Aslin, and Newport, 1996), plays an important role in infants’ phonetic learning. Figure 4 (p. 240) provides a cartoon version of the process. Research shows that adult speakers of English and Japanese produce the English *r*, the English /*l*/, and the Japanese *r* sounds, so it is not the mere presence of the sound in language spoken to infants that accounts for learning (Werker *et al.*, 2007). Instead, it is the patterns of distributional frequency of the sounds across the two languages that provide the information that English-learning and Japanese-learning infants use to learn phonetically.

When infants listen to English and Japanese, they attend to the distributional properties of the phonetic units contained in the two languages, and the distributional data affect their perception (Kuhl, Williams, Lacerda, Stevens, and Lindblom, 1992; Maye, Weiss, and Aslin, 2008; Maye, Werker, and Gerken, 2002; Teinonen, Fellman, Naatanen, Alku, and Huotilainen, 2009). These distributional differences are exaggerated in ‘motherese’, the prosodically and phonetically stretched utterances that are near universal in languages spoken to children around the world, (Kuhl *et al.*, 1997; Vallabha, McClelland, Pons, Weker, and Amano, 2007; Werker *et al.*, 2007).

As illustrated in the idealized case (see Figure 4, p. 240), the distributions of English and Japanese sounds differ: English motherese contains many English *r* and *l* sounds and very few of the Japanese retroflex *r* sounds, while the reverse is true for Japanese motherese. A variety of studies show that infants pick up the distributional frequency patterns in ambient speech, whether they experience them during short-term laboratory experiments or over months in natural environments, and that this alters phonetic perception (Maye *et al.*, 2002; Maye *et al.*, 2008). Statistical learning from the distributional properties in speech thus supports infants’ transition in early development from universal perception exhibited at birth to native-language perception that is exhibited by the end of the first year of life.

The foregoing data and arguments led us to suggest that statistical learning processes could govern brain plasticity (Kuhl, 2002; Kuhl *et al.*, 2008). If infants build up statistical distributions of the sounds contained in the language they hear, at some point these distributions would become stable. At the point of stability, additional language input would not cause the overall statistical distribution of sounds to change substantially, and, according to our model, this stability would cause a decline in sensitivity to language input. In other words, the decline in plasticity is hypothesized to be driven by a statistical process in which stability reduces plasticity. Hypothetically, for instance, the infants’ representation of the vowel /*a*/ might have stabilized by the time the child hears



her one-millionth token of the vowel /a/, and this could instigate the beginning of the closure of the critical period. On this account, plasticity is independent of time, and instead dependent on the amount and the variability of input provided by experience. This reasoning lends itself to testable hypotheses. Studies of bilingual infants, reviewed later in this chapter, provide one example of an empirical test of the model.

### ***Brain rhythms index statistical learning for speech***

Statistical learning is an implicit strategy that induces phonetic learning in infancy but not in adulthood – spending months in a foreign country does not change speech perception in spite of the new statistical distributions we experience. Work in my laboratory has recently shown that brain oscillations (‘rhythms’), associated with higher cognitive functions such as attention and cognitive effort, index the shift in statistical learning in speech (Bosseler, Taulu, Imada, and Kuhl, 2011).

A brain rhythm, theta (~4–8Hz), has been shown in previous studies to index attention and cognitive effort in adults (Jensen and Tesche, 2002) as well as infants (Kahana, Sekuler, Caplan, Kirschen, and Madsen, 1999). Using native and nonnative speech sounds, presented frequently or infrequently in the classic oddball paradigm, we tested three age groups: 6–8 month-old infants, 10–12 month-old infants, and adults. Data was collected using magnetoencephalography (MEG), a whole-brain imaging technology that is completely safe and noiseless.

Bosseler *et al.* (2011) predicted that early in development, when infants are maximally sensitive to language experience, attention and cognitive effort are driven by infants’ sensitivity to the distributional frequency of events, as portrayed in Figure 4. Once learning occurs (after neural commitment is complete), attention and cognitive effort are dominated by learned categories; stimuli that fit learned phonetic categories are processed easily, and increased attention and mental effort are required for novel stimuli that do not fit learned categories. We expected 6–8 month-old infants to show theta increases for any frequent stimulus, regardless of language, and adults to show theta increases for novel stimuli, regardless of frequency. 10–12 month-old infants were expected to show an intermediate pattern resembling that of adults.

Our results confirmed these predictions (Bosseler *et al.*, 2011). 6–8-month-old infants demonstrated increased theta for frequently presented speech sounds, regardless of whether they were native or nonnative. Adults showed the opposite pattern of response, with increased theta shown to nonnative sounds regardless of frequency. The 10–12-month-old infants showed an intermediate pattern of results, approximating the adult theta pattern.



These results show that theta indexes the well-established change in speech perception that is brought about by exposure to a specific language – as infants experience a particular language, the brain’s neural circuitry focuses on registering high frequency speech events that represent the phonetic categories used in the ambient language. This implicit strategy provides infants with an ability to learn through experience with language to attend to the sounds that are critical to the ambient language used in their cultural community. Adults no longer implicitly absorb the statistical properties of phonetic units in a new language. Attention and cognitive effort is driven by learned category structure.

The question that remains is whether the implicit strategy indexed by theta brain rhythms is unique to speech. A range of studies show that the perceptual narrowing first observed for speech perception (Werker and Teas, 1984) occurs in other domains. Infants show perceptual narrowing between 8 and 12 months of age for visual discrimination of faces (Pascalis, de Haan, and Nelson, 2002) or languages (Weikum, *et al.*, 2007), for recognition of the conceptual distinctions that underpin word meanings (Hespos and Spelke, 2004), and when detecting inter-sensory correspondences (Lewkowicz and Ghazanfar, 2006). In all cases, young infants’ abilities are initially better than those shown in adults and decline during the second half of the first year. Infants begin life with the capacity to differentiate many forms, and this initial capacity narrows as a function of experience.

The perceptual narrowing phenomenon may therefore reflect a domain-general developmental shift in perceptual strategy brought about by the brain’s response to experience rather than a specific critical learning window for speech. Stimuli that reflect cultural categories that are learned socially (speech, faces, conceptual categories, musical intervals) are candidate domains for which this pattern might hold. Further empirical research will be needed to test this broader hypothesis with a variety of stimuli.

### *The social component*

Whether or not the perceptual narrowing indexed by theta and observed in speech turns out to be a domain-general phenomenon, studies on phonetic learning have gone one step further than studies in other domains in understanding the complex conditions that must be met in order for infants to learn during the period from 6–12 months. In the domain of speech, data now show that infants’ computational skills cannot solely account for the transition in phonetic perception that occurs in the second half of the first year of life. Our studies demonstrate that infant language learning in complex natural environments requires something more than raw compu-

tation. Laboratory studies testing infant phonetic and word learning from exposure to complex natural language demonstrated limits on statistical learning, and provided new information suggesting that social brain systems are integrally involved and, in fact, may be necessary to instigate natural phonetic learning (Kuhl, Tsao, and Liu, 2003; Conboy and Kuhl, 2011).

The new experiments tested infants in the following way: At 9 months of age, the age at which the initial universal pattern of infant perception has changed to one that is more language-specific, infants were exposed to a foreign language for the first time (Kuhl *et al.*, 2003). Nine-month-old American infants listened to 4 different native speakers of Mandarin during 12 sessions scheduled over 4–5 weeks. The foreign language ‘tutors’ read books and played with toys in sessions that were unscripted. A control group was also exposed for 12 sessions but heard only English from native speakers. After infants in the experimental Mandarin exposure group and the English control group completed their sessions, all were tested with a Mandarin phonetic contrast that does not occur in English. Both behavioral and ERP methods were used. The results indicated that infants showed a remarkable ability to learn from the ‘live-person’ sessions – after exposure, they performed significantly better on the Mandarin contrast when compared to the control group that heard only English. In fact, they performed equivalently to infants of the same age tested in Taiwan who had been listening to Mandarin for 10 months (Kuhl *et al.*, 2003).

The study revealed that infants can learn from first-time natural exposure to a foreign language at 9 months, and answered what was initially the experimental question: can infants learn the statistical structure of phonemes in a new language given first-time exposure at 9 months of age? If infants required a long-term history of listening to that language – as would be the case if infants needed to build up statistical distributions over the initial 9 months of life – the answer to our question would have been no. However, the data clearly showed that infants are capable of learning at 9 months when exposed to a new language. Moreover, learning was durable. Infants returned to the laboratory for their behavioral discrimination tests between 2 and 12 days after the final language exposure session, and between 8 and 33 days for their ERP measurements. No ‘forgetting’ of the Mandarin contrast occurred during the 2 to 33 day delay.

Infants exposed to Mandarin were socially very engaged in the language sessions. Would infants learn if they were exposed to the same information in the absence of a human being, say, via television or an audiotope? If statistical learning is sufficient, the television and audio-only conditions should produce learning. Infants who were exposed to the same foreign-language material at the same time and at the same rate, but via standard television

or audiotape only, showed no learning – their performance equaled that of infants in the control group who had not been exposed to Mandarin at all (see Figure 5, p. 241).

Thus, the presence of a human being interacting with the infant during language exposure, while not required for simpler statistical-learning tasks (Maye *et al.*, 2002; Saffran *et al.*, 1996), is critical for learning in complex natural language-learning situations (Kuhl *et al.*, 2003). Using the same experimental design, this work has been extended to Spanish and advanced beyond the Kuhl *et al.* (2003) study. Conboy showed that infants not only learn Spanish phonemes (Conboy and Kuhl, 2011) but also the Spanish words they were exposed to during the language-exposure sessions (Conboy and Kuhl, 2010). Moreover, Conboy and colleagues demonstrated that individual differences in infants' social behaviors during the Spanish exposure sessions is significantly correlated to the degree to which infants learn both phonemes and words, as indicated by the relationship between social behaviors during the sessions and brain measures documenting learning post-exposure (Conboy, Brooks, Meltzoff, and Kuhl, 2008).

These studies suggest that infants' computational abilities are enabled by social interaction, a situation mirrored in neurobiological studies on vocal communication learning in other species, such as birds (Doupe and Kuhl, 2008). The notion that social interaction acts as a 'gate' for infants initial language learning has important implications for children with autism that we are beginning to explore (see Kuhl, Coffey-Corina, Padden, and Dawson, 2005b; Kuhl, 2010a). The broader role of socio-cultural context on language learning is also illustrated in studies focusing on language and brain with children from families with low socio-economic status. Our work in this arena links the degree of left-hemisphere specialization for language and literacy at the age of 5 years to the extent to which a child's environment provides opportunities for learning (See Raizada, Richards, Meltzoff, and Kuhl, 2008; Neville, this volume). The growing body of work suggests that the early language environment of the child has a significant effect on the trajectory of language learning.

The model we have developed indicates that the interaction between computational skills and social cognition potentially opens the critical period for phonetic learning. Infants have computational skills from birth (Teinonen *et al.*, 2009). The fact that the effects of linguistic experience on phonetic perception are not observed until 8 months of age suggests that computation itself is not the trigger for learning. As discussed, we initially reasoned that infants might require 8 months of listening to build up reliable statistical distributions of the sounds contained in the language they expe-

rienced, but our results verified that 9-month-old infants did not require 8 months of listening to learn from experiencing a new language – they learned after less than 5 hours of exposure to a new language, as long as exposure occurred in a social context.

These data raise the possibility that infants' social skills – the ability to track eye movements, achieve joint visual attention, and begin to understand others' communicative intentions and develop at this time – serve as a trigger to instigate plasticity. Social understanding might be the 'gate' that initiates phonetic learning in human infants (Kuhl, *in press*). There is a neurobiological precedent for social interaction acting as a trigger for learning in songbirds. It is well established that a more natural social setting extends the learning period and that manipulating other social features can either shorten or extend the optimum period for learning (Knudsen, 2004; Wooley and Doupe, 2008). The possibility of a social interaction plasticity trigger in humans raises many new questions, and also has implications for developmental disabilities (see Kuhl, 2010a for discussion).

### ***Bilingual language learning***

In our model of early language development (Kuhl *et al.*, 2008), bilingual language learners are expected to follow the same principles as monolingual learners – both computational and social factors influence the period of plasticity. Nonetheless, we argue that this process might result in bilingual infants reaching the developmental transition in perception at a later point in time than infants learning either language monolingually. We have argued that infants learning two first languages simultaneously would remain open to experience for a longer period of time because they are mapping language input in two forms, each with distinct statistical distributions. Social input often links the statistical distribution for a particular language to individual social partners, and thus perhaps assists infants in separating the statistics of one language from another. If this reasoning is correct, it should take a longer period of time to begin to close the critical period in bilinguals because it takes longer for sufficient data from both languages to reach distributional stability – depending on factors such as the number of people in the infant's environment producing the two languages in speech directed toward the child, and the amount of input each speaker in the infant's environment provides. It would be highly adaptive for bilingual infants to remain perceptually open for a longer period of time.

Only a few studies have addressed the timing issue and results have been mixed, perhaps due to differences in methodology, differences in the amount of language exposure to the two languages in individual bilingual participants,

and the specific characteristics of the languages and speech contrasts studied. Bosch and Sebastián-Gallés (2003a) compared 4-, 8- and 12-month-old infants from Spanish monolingual households, Catalan monolingual households, and Spanish-Catalan bilingual households on a vowel contrast that is phonemic in Catalan but not in Spanish. Their results showed that at 4 months infants discriminated the vowel contrast but that at 8 months of age only infants exposed to Catalan succeeded. Interestingly, the same group of bilinguals regained their ability to discriminate the speech contrast at 12 months of age. The authors reported the same developmental pattern in bilingual infants in a study of consonants (Bosch and Sebastián-Gallés, 2003b) and in a later study of vowels (Sebastián-Gallés and Bosch, 2009). The authors interpreted their results as evidence that different processes may underlie bilingual and monolingual phoneme category formation.

In contrast, other investigations have found that bilingual infants discriminate phonetic contrasts in their native languages on the same timetable as monolingual infants. For example, Burns, Yoshida, Hill, and Werker (2007) tested consonant discrimination using English-relevant as well as French-relevant values at 6–8, 10–12, and 14–20 months in English monolingual and English–French bilingual infants. 6–8 month old English monolingual infants discriminated both contrasts while 10–12 and 14–20 month old English monolingual infants discriminated only the English contrast. In bilingual infants, all age groups were able to discriminate both contrasts. Similarly, Sundara, Polka, and Molnar (2008) found that 10–12-month-old French–English bilingual infants were able to discriminate a French /d/ from an English /d/ while age-matched French monolingual infants were unable to do so. These studies support the view that monolingual and bilingual infants develop phonetic representations at the same pace (see also Sundara and Scutellaro, *in press*).

We conducted a longitudinal study of English–Spanish bilingual infants using a brain measure of discrimination for phonetic contrasts in both languages (Event Related Potentials, or ERPs) and assessments of language input in the home at two early points in development, followed by examination of word production in both languages months later (Garcia-Sierra *et al.*, *in press*). It is the first ERP study of speech perception in bilingual infants that combined concurrent and longitudinal methods to assess early phonetic perception, early language exposure, and later word production. The study addressed three questions: Do bilingual infants show the ERP components indicative of neural discrimination for the phonetic units of both languages on the same timetable as monolingual infants? Is there a relationship between brain measures of phonetic discrimination and the amount of exposure to the two lan-

guages? Is later word production in the infants' two languages predicted by early ERP responses to speech sounds in both languages and/or the amount of early language exposure to each language?

As predicted by our model of speech perception development, bilingual infants displayed a pattern of neural commitment that is different from that of monolingual infants previously tested using the same stimuli and methods (Rivera-Gaxiola *et al.*, 2005a; Rivera-Gaxiola, Klarman, Garcia-Sierra, and Kuhl, 2005b). Rivera-Gaxiola *et al.* (2005a, b) collected data from English monolingual infants at 7 and 11 months of age. Monolingual infants at 7 months showed neural discrimination (in the form of a Mismatch negativity, or MMN) of both the native phonetic contrast (English) and the non-native contrast (Spanish); at 11 months monolingual infants showed an MMN for the native phonetic contrast (English) only, indicating that they had learned native sounds and were no longer in the initial universal stage of perception. Bilingual infants did not show an MMN for Spanish and English contrasts at 6–8 months, but showed a non-significant positivity, a more immature response. By 10–12 months of age, the MMN was observed for both contrasts. In studies of 11- and 14-month-old monolingual and bilingual infants, this pattern is replicated; bilingual infants show the MMN to sounds from their (two) native languages at a later point in time when compared to monolingual infants. We believe this represents an extended period of openness to experience in bilingual children (see Figure 6, p. 242).

Thus, our brain measures of bilingual phonetic development provide some support for the idea that bilingual infants instigate phonetic learning at the same time as monolingual infants, but that they may remain open to experience for a longer period of time. This pattern represents bilingual infants' highly adaptive response to their more variable language environments.

We also hypothesized that bilingual infants' discrimination of the sounds of English and Spanish would be related to language exposure in the home, and that the pattern of the relationship would be influenced by age. The results showed an interesting relationship between the pattern of brain activity as a function of high vs. low exposure to the language. Specifically, only infants who had high exposure to English (or Spanish), and consequently lower exposure to the second language, showed an age effect in their brain responses to speech. Work is underway to further investigate this relationship, but the findings of Garcia-Sierra *et al.* (in press) suggest that bilingual infants exposed to high levels of one language have neural responses to that language that resemble those of monolingual infants. Given the variability in language experience in bilingual infants, more research is required to determine how much language input is sufficient to close the

critical period, and, whether there is greater plasticity for language throughout life as a function of early experience with two languages.

Finally, we hypothesized a relationship between early language brain measures and later word production, as well as relationships between early language exposure and later word production. Both hypotheses were confirmed. Children who were English dominant in word production at 15 months showed relatively better neural discrimination of the English contrast, as well as stronger English exposure in the home. Similarly, children who were Spanish dominant in word production at 15 months showed relatively better neural discrimination of the Spanish contrast and stronger Spanish exposure in the home.

Taken as a whole, the results suggest that bilingual infants tested with phonetic units from both of their native languages stay perceptually open longer when compared to monolingual infants – indicating perceptual narrowing at a later point in time. We reasoned that this is highly adaptive for bilingual infants. We also show that individual differences in infants' neural responses to speech, as well as their later word production, are influenced by the amount of exposure infants have to each of their native languages at home.

### **Is adult second language learning enhanced by social experience?**

Can understanding the role of computational and social mechanisms help design interventions that improve adults' acquisition of a second language? Our studies in Japan with native speakers of Japanese attempting to learn English suggest that it may be possible. The difficulty of the /r-l/ distinction for native speakers of Japanese is well documented, even after extensive training (Flege, Takagi, and Mann, 1996; Goto, 1971; Miyawaki *et al.*, 1975; Yamada and Tohkura, 1992). We hypothesize that processing English requires the development of new distributional frequency maps unique to English, because early exposure to Japanese caused neural commitment to the distributional patterns of Japanese which would subsume English /r/ and /l/ into the Japanese /r/ category (see Fig 4, p. 240). Computational neural modeling experiments have produced findings that are consistent with this view (Vallabha and McClelland, 2007).

New training studies conducted by our laboratory group in collaboration with the MEG researchers at Nippon Telephone and Telegraph in Tokyo suggest that training which capitalizes on a natural infant-learning strategies may provide the impetus to build new perceptual maps during second language learning. We examined perception of English /ra/ vs. /la/ in ten Japanese subjects and ten American subjects (Zhang *et al.*, 2005). Behavioral measures included identification and discrimination of the speech syllables. MEG recordings were made while subjects listened to the syllables.



Listening to native language sounds resulted in brain activation that was both significantly more focalized in the brain and occurred with shorter durations – we interpreted these patterns as greater neural efficiency when listening to native language speech. We reasoned that neural efficiency reflected the expertise resulting from early learning, and that neural efficiency developed at the expense of neural plasticity.

We tested this notion in a follow-up training study, in which we used highly social speech signals to train Japanese listeners to respond to the /r/ and /l/ stimuli (Zhang *et al.*, 2009). Taking our cue from the ‘motherese’ studies, Japanese participants heard and viewed American speakers producing acoustically modified /ra/ and /la/ syllables. Stimuli had greatly exaggerated formant frequencies, reduced bandwidths, and extended durations, like those produced by mothers when speaking to their infants. In the computer-training program, listeners were allowed to choose from many different talkers, and the syllables presented varied greatly. The listeners presented the stimuli to themselves via computer during 12 sessions, and no explicit feedback was provided. The behavioral data revealed a significant improvement in identification of these English (nonnative) speech stimuli, larger by a factor of 3 over that reported by previous studies. Correspondingly, the MEG results showed greater neural efficiency in the left hemisphere – more focal brain activation over a shorter duration – when listening to the English syllables.

These results suggest that the principles underlying motherese speech may help elicit adult second-language learning. Three parameters are of greatest interest: (a) exaggeration of the acoustic dimensions critical to the phonetic contrast, (b) an unsupervised ‘social’ learning situation, and (c) wide variability in speech, mimicking natural learning. Our studies show that feedback and reinforcement are not necessary in this process; listeners simply need the right kind of listening experience exaggerated acoustic cues, multiple instances by many talkers who can be seen and heard and selected by the participants, and mass listening experience without ‘testing’ – features that motherese provides infants – may represent a natural way to learn a language. These features, especially the more social nature of the experience – seeing talkers and choosing to listen to them – may allow listeners to create new perceptual maps rather than simply subsuming the English /r/ and /l/ stimuli into existing Japanese distributions, which would obscure the English distinction (see McClelland, Thomas, McCandliss, and Fiez, 1999). We are exploring this further in current studies.

### **Phonetic learning predicts the rate of language growth**

The forgoing review suggests that early phonetic learning is a complex process: Infants, computational skills are involved, as well as social cognition,



in opening a window of increased plasticity at about 8 months of life. Between 8 and 10 months monolingual infants show an increase in native language phonetic perception, a decrease in nonnative phonetic perception, and phonetic learning from a new language can be induced by social experience with a speaker of a new language in the laboratory (though not via a standard TV).

This early initial step in language learning is strongly correlated with the growth of future language skills, and with later pre-literacy skills. In our initial work demonstrating the link between early speech perception and later language, we conducted a longitudinal study examining whether a test of phonetic discrimination for vowels at 6 months of age predicted children's language skills measured up to 18 months later. The data demonstrated that infants' phonetic discrimination ability at 6 months of age was significantly correlated with their language skills at 13, 16, and 24 months of age (Tsao, Liu, and Kuhl, 2004). However, we recognized that in this initial study the association we observed might be due to infants' cognitive skills, such as the ability to perform in the behavioral task we used to assess discrimination, or to sensory abilities that affected auditory resolution of the differences in formant frequencies that underlie phonetic distinctions.

To address these issues, we assessed both native and nonnative phonetic discrimination in 7.5-month-old infants, and used both a behavioral (Kuhl *et al.*, 2005a) and an event-related potential measure, the mismatch negativity (MMN), to assess infants' performance (Kuhl *et al.*, 2008). Using a neural measure removed potential cognitive effects on performance; the use of both native and nonnative contrasts addressed the sensory issue, since better sensory abilities would be expected to improve both native and nonnative speech discrimination.

According to our developmental model, future language growth should be associated with early performance on both native and nonnative contrasts, but in opposite directions. We predicted that better *native* language perception should result in significantly advanced language abilities at 14, 18, 24, and 30 months of age, whereas better *nonnative* phonetic perception at the same age should show poorer language abilities at the same four future points in time. The results conformed to this prediction. When both native and nonnative phonetic discrimination was measured in the same infants at 7.5 months of age, (Kuhl *et al.*, 2005a; Kuhl *et al.*, 2008), better native speech discrimination was associated with better later language outcomes, whereas better nonnative performance was associated with poorer performance. Hierarchical linear growth modeling of vocabulary between 14 and 30 months for MMN values (see Figure 7, p. 242) showed that native and nonnative discrimination pre-

dicted future language, but in opposite directions. Better native discrimination predicted advanced future language development and better nonnative discrimination predicted less advanced future language development.

These results are explained by our model: better native phonetic discrimination enhances infants' skills in detecting words and this vaults infants towards language, whereas better nonnative abilities indicated that infants remained longer at an earlier phase of development – still sensitive to all phonetic differences. Infants' ability to *learn* which phonetic units are relevant in the language(s) in their environment, while decreasing or inhibiting their attention to the phonetic units that do not distinguish words in their language, is the necessary first step on the path toward language.

Importantly, recent data from our laboratory indicate *long-term* associations between early measures of infants' phonetic perception and future language and reading skills. Our studies show that the trajectory of change in the discrimination two simple vowels between 7 and 11 months of age predicts those children's language abilities and also their phonological awareness skills, which are critical to reading, at the age of 5 years (Cardillo, 2010; Cardillo Lebedeva and Kuhl, 2009).

Infants were tested at 7 and 11 months of age, and their patterns of speech perception development were categorized in one of three ways: (1) infants who show excellent native discrimination at 7 months and maintain that ability at 11 months – the 'high-high' group, (2) infants who show poor abilities at 7 months but increased performance at 11 months – the 'low-high' group, and (3) infants who show poor abilities to discriminate at both 7 and 11 months of age – the 'low-low' group. We followed these children until the age of 5: receptive and expressive language skills were assessed at 18 months, 24 months, and 5 years of age; phonological awareness skills, the most accurate measure of eventual reading skills, were assessed at age 5. Strong relationships were observed between infants' early speech perception performance and their later language skills at all ages, and between infants' early speech perception performance and phonological awareness skills at 5 years of age. In all cases, the infants who showed excellent skill in detecting phonetic differences in native language sounds by 11 months of age (the 'high-high' and the 'low-high' groups) had significantly higher expressive and receptive language skills at the ages of 18- and 24-months, as well as at the age of 5 years. Moreover, at the age of 5 years, these same two groups scored significantly higher in pre-literacy skills involving phonological awareness; importantly, these significance patterns held after measures of socio-economic status (SES) were partialled out in the regression analysis (Cardillo, 2010; Cardillo Lebedeva and Kuhl, 2009).

## From theory to practice

While recommendations extending theory to practice should be done cautiously, it is not difficult to extend the results of early language and literacy studies reviewed here to practice. First, the data show that the initial steps that infants take toward language in the first year of life *matter* – they appear to be a pathway to children's development of later language and literacy. Infants' early language abilities, which can be tested with fairly simple measures in the first year of life, predict language skills and literacy skills up to 4.5 years later. While these data are correlational as opposed to causal in nature, our data allow us to begin to connect the dots and suggest that the richness of the early language environment of the child creates the kind of neural architecture that is necessary for robust language and literacy development. Our model and data suggest as well that environmental influences affect these early steps. The trajectory of phonetic learning between 6 and 12 months of life (which predict children's future skills) are themselves strongly correlated with the complexity and frequency of the language young children experience at home (Raizada *et al.*, 2008; in preparation). Hearing the exaggerated speech known widely as 'motherese' early in development is strongly correlated with early speech discrimination measured in the laboratory (Liu, Kuhl and Tsao, 2003). Motherese exaggerates the critical acoustic cues in speech (Kuhl *et al.*, 1997; Werker *et al.*, 2007), and infants social interest in speech is, we believe, important to the social learning process. Thus, we assert that talking to children early in life, reading to children early in life, and doing both of these things while interacting socially with children around language and literacy activities, creates the milieu in which plasticity during the critical period can be maximized for all children.

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## References

- Aslin, R.N., & Mehler, J. (2005). Near-infrared spectroscopy for functional studies of brain activity in human infants: promise, prospects, and challenges. *Journal of Biomedical Optics*, 10, 11009.
- Best, C.C., & McRoberts, G.W. (2003). Infant perception of nonnative consonant contrasts that adults assimilate in different ways. *Language and Speech*, 46, 183–216.

- Bialystok, E., & Hakuta, K. (1994). *In other words: the science and psychology of second-language acquisition*. New York, NY: Basic Books.
- Birdsong, D. (1992). Ultimate attainment in second language acquisition. *Linguistic Society of America*, 68, 706-755.
- Birdsong, D. (1992). Ultimate attainment in second language acquisition. *Language*, 68, 706-755.
- Birdsong, D., & Molis, M. (2001). On the evidence for maturational constraints in second-language acquisitions. *Journal of Memory and Language*, 44, 235-249.
- Bortfeld, H., Wruck, E., & Boas, D.A. (2007). Assessing infants' cortical response to speech using near-infrared spectroscopy. *NeuroImage*, 34, 407-415.
- Bosch, L., & Sebastián-Gallés, N. (2003a). Simultaneous bilingualism and the perception of a language-specific vowel contrast in the first year of life. *Language and Speech*, 46, 217-243.
- Bosch, L., & Sebastián-Gallés, N. (2003b). Language experience and the perception of a voicing contrast in fricatives: Infant and adult data. In D. Recasens, M.J. Solé & J. Romero (Eds.), *Proceedings of the 15th international conference of phonetic sciences*. (pp.1987-1990). Barcelona: UAB/Casual Productions.
- Bosseler, A.N., Taulu, S., Imada, T., & Kuhl, P.K. (2011). Developmental Changes in Cortical Rhythms to Native and Non-Native Phonetic Contrasts. Symposium presentation at the 2011 Biennial Meeting for the Society for Research in Child Development, Montreal, Canada, March 31 – April 2, 2011.
- Bruner, J. (1983). *Child's talk: Learning to use language*. New York: W.W. Norton.
- Bruer, J.T. (2008). Critical periods in second language learning: distinguishing phenomena from explanation. In M. Mody & E. Silliman (Eds.), *Brain, behavior and learning in language and reading disorders* (pp. 72-96). New York, NY: The Guilford Press.
- Burns, T.C., Yoshida, K.A., Hill, K., & Werker, J.F. (2007). The development of phonetic representation in bilingual and monolingual infants. *Applied Psycholinguistics*, 28, 455-474.
- Cardillo, G.C. (2010). Predicting the predictors: Individual differences in longitudinal relationships between infant phoneme perception, toddler vocabulary, and preschooler language and phonological awareness (Doctoral dissertation, University of Washington, 2010). *Dissertation Abstracts International*.
- Cardillo Lebedeva, G.C., & Kuhl, P.K. (2009). *Individual differences in infant speech perception predict language and pre-reading skills through age 5 years*. Paper presented at the Annual Meeting of the Society for Developmental & Behavioral Pediatrics. Portland, OR.
- Cheour, M., Imada, T., Taulu, S., Ahonen, A., Salonen, J., & Kuhl, P.K. (2004). Magnetoencephalography is feasible for infant assessment of auditory discrimination. *Experimental Neurology*, 190, S44-S51.
- Cho, K.K.A., & Bear, M.F. (2010). Promoting neurologic recovery of function via metaplasticity. *Future Neurology*, 5, 21-26.
- Chomsky, N. (1959). Review of Skinner's Verbal Behavior. *Language*, 35, 26-58.
- Conboy, B.T., Brooks, R., Meltzoff, A.N., & Kuhl, P.K. (submitted). Relating infants' social behaviors to brain measures of second language phonetic learning.
- Conboy, B.T., & Kuhl, P.K. (2010, November). Brain responses to words in 11-month-olds after second language exposure. Poster presented at the American Speech-Language-Hearing Association, November 18-20, Philadelphia, PA.
- Conboy, B.T., & Kuhl, P.K. (2011). Impact of second-language experience in infancy: brain measures of first- and second-language speech perception. *Developmental Science*, 14, 242-248.
- Conboy, B.T., Rivera-Gaxiola, M., Silva-Pereyra, J.F., & Kuhl, P.K. (2008). Event-

- related potential studies of early language processing at the phoneme, word, and sentence levels. In A.D. Friederici & G. Thierry (Eds.), *Early language development: bridging brain and behaviour, Trends in language acquisition research series, Volume 5* (pp. 23–64). Amsterdam/The Netherlands: John Benjamins.
- Dehaene-Lambertz, G., Dehaene, S., & Hertz-Pannier, L. (2002). Functional neuroimaging of speech perception in infants. *Science*, 298, 2013–2015.
- Dehaene-Lambertz, G., Hertz-Pannier, L., Dubois, J., Meriaux, S., and Roche, A., Sigman, M., & Dehaene, S. (2006). Functional organization of perisylvian activation during presentation of sentences in preverbal infants. *Proceedings of the National Academy of Sciences of the United States of America*, 103, 14240–14245.
- Doupe, A., & Kuhl, P.K. (1999). Birdsong and speech: Common themes and mechanisms. *Annual Review of Neuroscience*, 22, 567–631.
- Doupe, A.J., & Kuhl, P.K. (2008). Birdsong and human speech: common themes and mechanisms. In H. P. Zeigler & P. Marler (Eds.), *Neuroscience of Birdsong* (pp.5–31). Cambridge, England: Cambridge University Press.
- Eimas, P.D. (1975). Auditory and phonetic coding of the cues for speech: discrimination of the /r-l/ distinction by young infants. *Perception and Psychophysics*, 18, 341–347.
- Eimas, P.D., Siqueland, E.R., Jusczyk, P., & Vigorito, J. (1971). Speech perception in infants. *Science*, 171, 303–306.
- Flege, J., Takagi, N., & Mann, V. (1996). Lexical familiarity and English-language experience affect Japanese adults' perception of /r/ and /l/. *Journal of the Acoustical Society of America*, 99, 1161–1173.
- Flege, J.E., Yeni-Komshian, G.H., & Liu, S. (1999). Age constraints on second-language acquisition. *Journal of Memory and Language*, 41, 78–104.
- Friederici, A.D. (2005). Neurophysiological markers of early language acquisition: from syllables to sentences. *Trends in Cognitive Science*, 9, 481–488.
- Friederici, A.D., & Wartenburger, I. (2010). Language and brain. *Wiley Interdisciplinary Reviews: Cognitive Science*, 1, 150–159. Online publication: DOI: 10.1002/WCS.9
- García-Sierra, A., Rivera-Gaxiola, M., Conboy, B.T., Romo, H., Percaccio, C.R., Klarman, L., Ortiz, S., & Kuhl, P.K. (in press). Bilingual language learning: An ERP study relating early brain responses to speech, language input, and later word production. *Journal of Phonetics*.
- Gernsbacher, M.A., & Kaschak, M.P. (2003). Neuroimaging studies of language production and comprehension. *Annual Review of Psychology*, 54, 91–114.
- Golestani, N., Molko, N., Dehaene, S., Lebihan, D., & Pallier, C. (2007). Brain structure predicts the learning of foreign speech sounds. *Cerebral Cortex*, 17, 575–582.
- Goto, H. (1971). Auditory perception by normal Japanese adults of the sounds 'l' and 'r'. *Neuropsychologia*, 9, 317–323.
- Gratton, G., & Fabiani, M. (2001a). Shedding light on brain function: The event related optical signal. *Trends in Cognitive Science*, 5, 357–363.
- Gratton, G., & Fabiani, M. (2001b). The event-related optical signal: A new tool for studying brain function. *International Journal of Psychophysiology*, 42, 109–121.
- Hensch, T.K., & Stryker, M. P. (1996). Ocular dominance plasticity under metabotropic glutamate receptor blockade. *Science*. 272, 554–557.
- Hensch, T.K. (2005) Critical period plasticity in local cortical circuits. *Nature Review Neuroscience*, 6, 877–888
- Hespos, S.J., & Spelke, E.S. (2004). Conceptual precursors to language. *Science*, 430, 453–456.
- Homae, F., Watanabe, H., Nakano, T., Asakawa, K., & Taga, G. (2006). The right

- hemisphere of sleeping infant perceives sentential prosody. *Neuroscience Research*, 54, 276-280.
- Hubel, D.H., & Wiesel, T.N. (1963). Receptive fields of cells in striate cortex of very young, visually inexperienced kittens. *Journal of Neurophysiology*, 26, 994-1002.
- Imada, T., Zhang, Y., Cheour, M., Taulu, S., Ahonen, A., & Kuhl, P.K. (2006). Infant speech perception activates Broca's area: a developmental magnetoencephalography study. *Neuroreport*, 17, 957-962.
- Jensen, O., & Tesche, C.D. (2002). Frontal theta activity in humans increases with memory load in a working memory task. *European Journal of Neuroscience*, 15, 1395-1399.
- Johnson, J., & Newport, E. (1989). Critical period effects in second language learning: the influence of maturation state on the acquisition of English as a second language. *Cognitive Psychology*, 21, 60-99.
- Kahana, M.J., Sekuler, R., Caplan, J.B., Kirschen, M., & Madsen, J.R. (1999). Human theta oscillations exhibit task dependence during visual maze navigation. *Nature*, 399, 781-784.
- Knudsen, E.I. (2004). Sensitive periods in the development of the brain and behavior. *Journal of Cognitive Neuroscience*, 16, 1412-1425.
- Kuhl, P.K. (2000). A new view of language acquisition. *Proceedings of the National Academy of Science*, 97, 11850-11857.
- Kuhl, P.K. (2004). Early language acquisition: cracking the speech code. *Nature Reviews Neuroscience*, 5, 831-843.
- Kuhl, P.K. (2007). Is speech learning 'gated' by the social brain? *Developmental Science*, 10, 110-120.
- Kuhl, P.K. (2009). Early language acquisition: Neural substrates and theoretical models. In M.S. Gazzaniga (Ed.), *The Cognitive Neurosciences*, 4th Edition (pp. 837-854). Cambridge, MA: MIT Press.
- Kuhl, P.K. (2010a). Brain mechanisms in early language acquisition. *Neuron*, 67, 713-727.
- Kuhl, P.K. (2010b, October). *The linguistic genius of babies*. A TEDTalk retrieved from TED.com website: [www.ted.com/talks/lang/eng/patricia\\_kuhl\\_the\\_linguistic\\_genius\\_of\\_babies.html](http://www.ted.com/talks/lang/eng/patricia_kuhl_the_linguistic_genius_of_babies.html)
- Kuhl, P.K. (in press). Social mechanisms in early language acquisition: Understanding integrated brain systems supporting language. In J. Decety & J. Cacioppo (Eds.), *The handbook of social neuroscience*. Oxford UK: Oxford University Press.
- Kuhl, P.K., Andruski, J.E., Chistovich, I.A., Chistovich, L.A., Kozhevnikova, E.V., Ryskina, V.L., Stolyarova, E.I., Sundberg, U., & Lacerda, F. (1997). Cross-language analysis of phonetic units in language addressed to infants. *Science*, 277, 684-686.
- Kuhl, P.K., Coffey-Corina, S., Padden, D., & Dawson, G. (2005b). Links between social and linguistic processing of speech in preschool children with autism: behavioral and electrophysiological evidence. *Developmental Science*, 8, 1-12.
- Kuhl, P.K., Conboy, B.T., Coffey-Corina, S., Padden, P., Rivera-Gaxiola, M., & Nelson, T. (2008). Phonetic learning as a pathway to language: New data and native language magnet theory expanded (NLM-e). *Philosophical Transactions of the Royal Society B: Biological Sciences*, 363, 979-1000.
- Kuhl, P.K., Conboy, B.T., Padden, D., Nelson, T., & Pruitt, J. (2005a). Early speech perception and later language development: implications for the 'critical period'. *Language and Learning Development*, 1, 237-264.
- Kuhl, P.K., & Damasio, A. (in press). Language. In E. R. Kandel, J. H. Schwartz, T. M. Jessell, S. Siegelbaum, & J. Hudspeth (Eds.), *Principles of neural science: 5th Edition*. McGraw Hill: New York.
- Kuhl, P.K., & Rivera-Gaxiola, M. (2008). Neural substrates of language acquisition.



- Annual Review of Neuroscience*, 31, 511–534.
- Kuhl, P.K., Stevens, E., Hayashi, A., Deguchi, T., Kiritani, S., & Iverson, P. (2006). Infants show facilitation for native language phonetic perception between 6 and 12 months. *Developmental Science*, 9, F13–F21.
- Kuhl, P.K., Tsao, F.M., & Liu, H.M. (2003). Foreign-language experience in infancy: effects of short-term exposure and social interaction on phonetic learning. *Proceedings of the National Academy of Sciences of the United States of America*, 100, 9096–9101.
- Kuhl, P.K., Williams, K.A., Lacerda, F., Stevens, K.N., & Lindblom, B. (1992). Linguistic experience alters phonetic perception in infants by 6 months of age. *Science*, 255, 606–608.
- Ladefoged, P. (2001). *Vowels and consonants: An introduction to the sounds of language*. Oxford: Blackwell Publishers.
- Lasky, R.E., Syrdal-Lasky, A., & Klein, R.E. (1975). VOT discrimination by four to six and a half month old infants from Spanish environments. *Journal of Experimental Child Psychology*, 20, 215–225.
- Lewkowicz, D.J. & Ghazanfar, A.A. (2006). The decline of cross-species intersensory perception in human infants. *Proceedings of the National Academy of Sciences of the United States of America*, 103, 6771–6774.
- Liu, H.M., Kuhl, P.K., & Tsao, F.M. (2003). An association between mothers' speech clarity and infants' speech discrimination skills. *Developmental Science*, 6, F1–F10.
- Mayberry, R. I., & Lock, E. (2003). Age constraints on first versus second language acquisition: evidence for linguistic plasticity and epigenesis. *Brain Language*, 87, 369–384.
- Maye, J., Werker, J.F., & Gerken, L. (2002). Infant sensitivity to distributional information can affect phonetic discrimination. *Cognition*, 82, B101–B111.
- Maye, J., Weiss, D., & Aslin, R. (2008). Statistical learning in infants: Facilitation and feature generalization. *Developmental Science*, 11, 122–134.
- McClelland, J., Thomas, A., McCandliss, B., & Fiez, J. (1999). Understanding failures of learning: Hebbian learning, competition for representational space, and some preliminary experimental data. In J. Reggia, E. Ruppini & D. Glanzman (Eds.), *Progress in Brain Research. Volume 121. Disorders of Brain, Behavior and Cognition: The Neurocomputational Perspective* (pp. 75–80). Amsterdam: Elsevier.
- Meltzoff, A.N., Kuhl, P.K., Movellan, J., & Sejnowski, T. (2009). Foundations for a new science of learning. *Science*, 17, 284–288.
- Miyawaki, K., Strange, W., Verbrugge, R., Liberman, A.M., Jenkins, J.J., & Fujimura, O. (1975). An effect of linguistic experience: the discrimination of [r] and [l] by native speakers of Japanese and English. *Perception and Psychophysics*, 18, 331–340.
- Neville, H. J., Coffey, S.A., Lawson, D.S., Fischer, A., Emmorey, K., & Bellugi, U. (1997). Neural systems mediating American Sign Language: effects of sensory experience and age of acquisition. *Brain and Language*, 57, 285–308.
- Newport, E. (1990). Maturation constraints on language learning. *Cognitive Science*, 14, 11–28.
- Newport, E.L., Bavelier, D., & Neville, H.J. (2001). Critical thinking about critical periods: Perspectives on a critical period for language acquisition. In E. Dupoux (Ed.), *Language, Brain, and Cognitive Development: Essays in Honor of Jacques Mehler* (pp. 481–502). Cambridge, MA: MIT Press.
- Ortiz-Mantilla, S., Choe, M.S., Flax, J., Grant, P.E., & Benasich, A.A. (2010). Association between the size of the amygdala in infancy and language abilities during the preschool years in normally developing children. *NeuroImage*, 49, 2791–2799.
- Pascalis, O., de Haan, M., & Nelson, C.A. (2002). Is face processing species-specific

- during the first year of life? *Science*, 296, 1321-1323.
- Peña, M., Bonatti, L., Nespor, M., & Mehler, J. (2002). Signal-driven computations in speech processing. *Science*, 298: 604-607.
- Petitto, L.A., & Marentette, P. F. (1991). Babbling in the manual mode: Evidence for the ontogeny of language. *Science*, 251, 1493-1496.
- Raizada, R.D., Richards, T.L., Meltzoff, A.N., & Kuhl, P.K. (2008). Socioeconomic status predicts hemispheric specialization of the left inferior frontal gyrus in young children. *NeuroImage*, 40, 1392-1401.
- Rivera-Gaxiola, M., Silvia-Pereyra, J., & Kuhl, P.K. (2005a). Brain potentials to native and non-native speech contrasts in 7- and 11-month-old American infants. *Developmental Science*, 8, 162-172.
- Rivera-Gaxiola, M., Klarman, L., Garcia-Sierra, A., & Kuhl, P.K. (2005b). Neural patterns to speech and vocabulary growth in American infants. *NeuroReport*, 16, 495-498.
- Sebastián-Gallés, N., & Bosch, L. (2009). Developmental Shift in the Discrimination of Vowel Contrasts in Bilingual Infants: Is the distributional account all there is to it? *Developmental Science*, 12, 874-887.
- Saffran, J., Aslin, R., & Newport, E. (1996). Statistical learning by 8-month-old infants. *Science*, 274, 1926-1928.
- Saffran, J., Werker, J., & Werner, L.A. (2006). The infant's auditory world: Hearing, speech and the beginnings of language. In D. Kuhn & R.S. Siegler (Eds.), *Handbook of Child Psychology, Vol. 2, Cognition, Perception and Language* (6th edition) (pp. 58-108). New York, NY: Wiley.
- Skinner, B. F. (1957). *Verbal Behavior*. New York: Appleton-Century-Crofts.
- Sundara, M., Polka, L., & Molnar, M. (2008). Development of coronal stop perception: Bilingual infants keep pace with their monolingual peers. *Cognition*, 108, 232-242.
- Sundara, M., & Scutellaro, A. (in press). Rhythmic distance between languages affects the development of speech perception in bilingual infants. *Journal of Phonetics*.
- Taga, G., & Asakawa, K. (2007). Selectivity and localization of cortical response to auditory and visual stimulation in awake infants aged 2 to 4 months. *Neuroimage*, 36, 1246-1252.
- Teinonen, T., Fellman, V., Naatanen, R., Alku, P., & Huotilainen, M. (2009). Statistical language learning in neonates revealed by event-related brain potentials. *BMC Neuroscience*, 10, doi:10.1186/1471-2202-10-21.
- Tomasello, M. (2003a). *Constructing A Language: A Usage-Based Theory of Language Acquisition*. Cambridge, MA: Harvard University Press.
- Tomasello, M. (2003b). The key is social cognition. In D., Gentner & S. Kuczaj (Eds.), *Language and Thought* (pp. 47-51). Cambridge, MA: MIT Press.
- Tsao, F.M., Liu, H.M., & Kuhl, P.K. (2004). Speech perception in infancy predicts language development in the second year of life: a longitudinal study. *Child Development*, 75, 1067-1084.
- Tsao, F.M., Liu, H.M., & Kuhl, P.K. (2006). Perception of native and non-native affricate-fricative contrasts: cross-language tests on adults and infants. *Journal of the Acoustical Society of America*, 120, 2285-2294.
- Vallabha, G.K., McClelland, J.L., Pons, F., Werker, J.F., & Amano, S. (2007). Unsupervised learning of vowel categories from infant-directed speech. *Proceedings of the National Academy of Sciences (USA)*, 104, 13273-13278.
- Vallabha, G.K., & McClelland, J.L. (2007). Success and failure of new speech category learning in adulthood: Consequences of learned Hebbian attractors in topographic maps. *Cognitive, Affective and Behavioral Neuroscience*, 7, 53-73.



- Vygotsky, L.S. (1962). *Thought and Language*. Cambridge, MA: MIT Press.
- Weber-Fox, C.M., & Neville, H.J. (1999). Functional neural subsystems are differentially affected by delays in second language immersion: ERP and behavioral evidence in bilinguals. In D. Birdsong (Ed.), *Second Language Acquisition and the Critical Period Hypothesis* (pp. 23–38). Mahwah, NJ: Lawrence Erlbaum and Associates, Inc.
- Weikum, W.M., Vouloumanos, A., Navarra, J., Soto-Faraco, S., Sebastian-Galles, N., & Werker, J.F. (2007). Visual language discrimination in infancy. *Science*, 316, 1159.
- Wiesel, T.N., & Hubel, D.H. (1963). Single cell responses in striate cortex of kittens deprived of vision in one eye. *Journal of Neurophysiology*, 26, 1003–1017.
- Werker, J.F., & Curtin, S. (2005). PRIMIR: a developmental framework of infant speech processing. *Language Learning and Development*, 1, 197–234.
- Werker, J.F., & Lalonde, C. (1988). Cross-language speech perception: initial capabilities and developmental change. *Developmental Psychology*, 24, 672–683.
- Werker, J.F., Pons, F., Dietrich, C., Kajikawa, S., Fais, L., & Amano, S. (2007). Infant-directed speech supports phonetic category learning in English and Japanese. *Cognition*, 103, 147–162.
- Werker, J.F., & Tees, R.C. (1984). Cross-language speech perception: evidence for perceptual reorganization during the first year of life. *Infant Behavior and Development*, 7, 49–63.
- White, L., & Genesee, F. (1996). How native is near-native? The issue of ultimate attainment in adult second language acquisition. *Second Language Research*, 12, 233–265. Online publication: DOI: 10.1177/026765839601200301.
- Woolley, S.C., & Doupe, A.J. (2008). Social context-induced song variation affects female behavior and gene expression. *Public Library of Science Biology*, 6, e62.
- Yamada, R., & Tokhura, Y. (1992). The effects of experimental variables on the perception of American English /r/ and /l/ by Japanese listeners. *Perception and Psychophysics*, 52, 376–392.
- Yeni-Komshian, G.H., Flege, J.E., & Liu, S. (2000). Pronunciation proficiency in the first and second languages of Korean–English bilinguals. *Bilingualism: Language and Cognition*, 3, 131–149.
- Zhang, Y., Kuhl, P.K., Imada, T., Kotani, M., & Tohkura, Y. (2005). Effects of language experience: neural commitment to language-specific auditory patterns. *Neuroimage*, 26, 703–720.
- Zhang, Y., Kuhl, P.K., Imada, T., Iverson, P., Pruitt, J., Stevens, E.B., Kawakatsu, M., Tohkura, Y., & Nemoto, I. (2009). Neural signatures of phonetic learning in adulthood: a magnetoencephalography study. *Neuroimage*, 46, 226–240.

# EXTENT AND LIMITS OF SPEECH AND LANGUAGE ORGANIZATION AFTER EARLY LEFT HEMISPHERE INJURY

■ FARANEH VARGHA-KHADEM<sup>1</sup>

## Background

A commonly held view is that the adverse consequences of brain injury are far less severe if the damage is sustained early in life when neural plasticity and reorganizational capacity are at their peak. Whilst this principle generally holds, as demonstrated by the early studies of Margaret Kennard, a pioneer in the field of plasticity (e.g. Kennard, M.A. 1936; 1938; 1940), there are long-recognized limits and costs to reorganizational processes in the immature brain (e.g. Schneider, 1974; 1979; Isaacson, 1975) with some compensational processes leading to permanent functional deficits (Goldman-Rakic, 1980; Giza and Prins, 2006; Lidzba *et al.*, 2006).

The parade-case for plasticity in humans is the remarkable rescue of speech and language after early left hemisphere injury (e.g. Vargha-Khadem *et al.*, 1985; 1991; Ogden, 1998; Bates *et al.*, 2001; Liegeois *et al.*, 2008a). Here, the typical explanation is that the non-committed right hemisphere assumes speech and language functions after sufficiently early damage to the left hemisphere, consequently sacrificing its own later-developing specialization for nonverbal and visuospatial abilities, thus giving rise to the ‘crowding’ of two domains of cognitive function in one single hemisphere (Teuber, 1975).

## Development of hemispheric specialization for language

Reports on infants’ and children’s language networks and their lateralization patterns during different stages of development (Dehaene-Lambertz and Baillet, 1998; Dehaene-Lambertz, 2000; Dall’Oglio *et al.*, 1994;) coupled with brain imaging studies of language activation during infancy and childhood (Dehaene-Lambertz, Dehaene, and Hertz-Pannier, 2002; Gaillard *et al.*, 2000; Liegeois *et al.*, 2008b), and molecular studies of genes specifically associated with speech and language (Lai *et al.*, 2001), all point

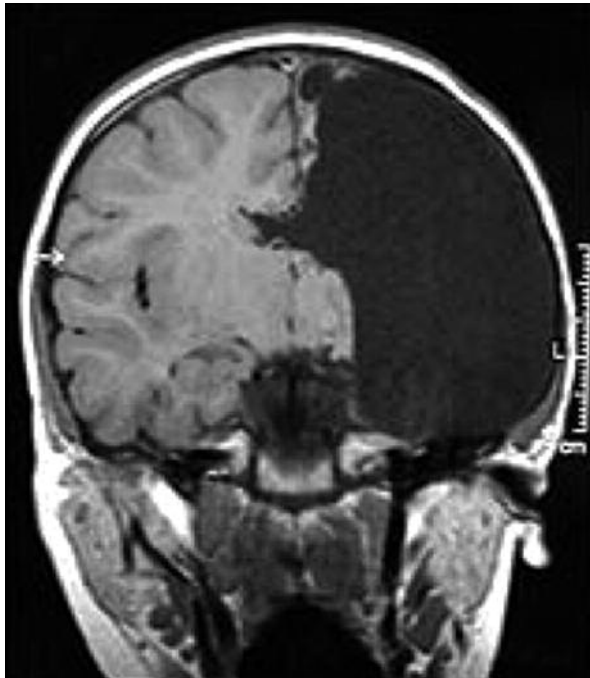
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to a genetic predisposition in the vast majority of humans to accommodate orovocal communication skills in the left hemisphere. Language ability appears to unfold as a function of age and experience during normal brain development. This predisposition is realized through interactions between neural activity which becomes progressively non-redundant, and neural plasticity which gradually declines with increasing age (Vargha-Khadem *et al.*, 1994). The former process reflects the gradual establishment of crystallized hemispheric specialization by adolescence, whilst the latter explains the selective and chronic dysphasic symptoms that appear after left hemisphere insults sustained in late childhood and adolescence (e.g. Patterson *et al.*, 1989).

Thus, early unilateral brain injury changes the balance between age- and experience-dependent neural activity and neural plasticity by counteracting the emergence of the division of labour between the two cerebral hemispheres and increasing plasticity to rescue at-risk functions in the remaining viable neural space (Vargha-Khadem *et al.*, 1994). The extent to which the normal trajectory of hemispheric specialization is thrown off its course is dependent on a number of interacting variables including: (i) age at onset of the injury, (ii) presence or absence of progressive damage (e.g. intractable epilepsy), (iii) hemispheric side of damage, (iv) extent of injury as indicated by the number of lobes involved, and whether the lesion is predominantly cortical or subcortical, (v) presence or absence of damage in the opposite hemisphere, (vi) stage of cognitive development at the time of injury, (vii) elapsed time since onset of injury to age at assessment, (viii) and age at test. To account for this number of independent variables and evaluate their effects on different aspects of speech and language requires a very large and relatively homogenous population of patients, an endeavour that is currently beyond the resources of even the largest of paediatric centres worldwide. To counter this requirement that large group studies cannot address at this time, a fruitful approach is to examine unique patients whose detailed case studies can provide answers to critical questions about the extent and limits of plasticity and reorganizational capacity of the young brain. This approach will be adopted here to examine speech and language representation in the single right hemisphere of a young adult who has undergone surgical resection of his left hemisphere in childhood to treat his intractable epilepsy. Patients who have undergone hemispherectomy during childhood provide a unique model to test the extent and limits of plasticity in the context of speech and language organization in the isolated right hemisphere (Boatman *et al.*, 1999; Devlin *et al.*, 2003; see also Battro, 2000; Immordino-Yang, 2007; Liegeois *et al.*, 2008a).

## The hemispherectomy procedures

Hemispherectomy – complete or partial removal or disconnection of one cerebral hemisphere – is one of the most common forms of pediatric neurosurgery for the relief of epilepsy (Devlin *et al.*, 2003). When children are assessed for hemispherectomy, critical questions that inform surgical decision making relate to neurological status (i.e. presence or absence, and severity of motor and/or visual field deficits), status of intellectual function, the pattern of language lateralization on fMRI, identification of risk factors for the removal of a language dominant hemisphere, and the long term consequences of surgery on speech and language development. Candidates for surgery usually present with a unilateral structural lesion and seizures, the origins of which date to neurodevelopmental pathologies of congenital or early acquired events, although some children are diagnosed with later acquired disorders such as Rasmussen's syndrome that can develop from about 1 year of age through adolescence (Freeman, 2005).



**Figure 1.** A total hemispherectomy illustrating the disconnection line from the right hemisphere, the large extra dural space created by the removal of the entire left hemisphere and the basal ganglia, and the spared thalamus on the left.

### **Is there a critical period for speech and language development in the isolated right hemisphere? The case of Alex**

A remarkable feature of normal human development is that virtually all healthy children acquire the grammar and vocabulary of their mother tongue within the first few years of life. Failure to achieve this significant milestone in the absence of hearing impairment, social deprivation, or severe intellectual disability, signals lifelong oro-vocal communication deficits leading many language theorists and linguists to hypothesize that there is a 'critical period' for the development of different aspects of speech and language (e.g. Shriberg *et al.*, 1994; Doupe and Kuhl, 1999), with this time window closing around the age of five or six (e.g. Grimshaw *et al.*, 1998).

A robust test of the 'critical period hypothesis' is provided by the case of Alex (Vargha-Khadem *et al.*, 1997), a young boy who was diagnosed at birth with Sturge-Weber syndrome, a rare congenital neurological and cutaneous disorder that is often associated with port-wine stains of the face, glaucoma, seizures, and profound intellectual restriction. Consistent with this diagnosis, within the first few months of life Alex developed infantile left hemisphere seizures, a right-sided hemiplegia, and right hemianopia. By the age of two years, he was diagnosed with severe developmental delay and hyperactivity, and a notable absence of speech, leading his physician to conclude that in his case, Sturge-Weber disease had affected the neural substrates of speech and language on both sides of the brain, thereby permanently precluding the development of this function.

This neurodevelopmental profile prevailed until the age of eight, at which time a resting Positron Emission Tomography scan revealed normal metabolism in the right hemisphere, along with virtually absent metabolic activity in the atrophic left hemisphere. Based on this evidence, the decision was taken to proceed with surgery and Alex underwent a total hemispherectomy at the age of 8:6 years.

The surgery was successful; Alex's seizures were arrested and the pre-existing neurological impairments (i.e. the hemiplegia and the right visual field defect) were not exacerbated. The anticonvulsant regime administered as prophylactic was gradually reduced and eventually discontinued 9 months after surgery, when Alex was aged 9:3 years. Approximately one month after the withdrawal of anticonvulsant medication, Alex's parents noted that he was producing syllables and single words, gradually becoming more communicative and less hyperactive. Within several months of this dramatic breakthrough, he had progressed to producing full sentences.

By the age of 11 when he was seen for a full neuropsychological investigation, Alex was speaking intelligibly in well structured, clearly enunciated

sentences and his average length of utterance had increased to 11.6 words, equivalent to the standard of a typical 6- to 7-year old. Between the ages of 9:4 and 15, Alex's linguistic and intellectual abilities were examined in detail, allowing for quantitative assessment of the development and establishment of his speech and language, and other cognitive skills (Vargha-Khadem *et al.*, 1997; Rankin and Vargha-Khadem, 2007). This report extends the follow-up investigations to about age 22 when Alex had achieved maturity as a young adult.

### *Intellectual development*

Prior to surgery at the age of 8:2, Alex's mental age in the various domains of cognitive and behavioural function was between 1:9 and 3:11 years (Griffiths Mental Development Scales, Griffiths, 1970). After the emergence of conversational language and reaching a mental age of about 6 years, however, Alex's intellectual status up to the age of about 21 years was longitudinally assessed using the Wechsler Scales of Intelligence (see Figure 2, p. 243). With increasing age and experience, Alex's verbal and nonverbal IQs on the child version of the Wechsler Scales incrementally increased up to the age of 16:10 showing a modest advantage in verbal relative to nonverbal abilities ( $\sim \frac{1}{2}$  SD). A switch to the adult Wechsler Scales at the age of 17:9 documented an impressive increase in both IQ scores (in the 70s range), but this was due to the change of scales from child to adult, as a repeat administration of the child scales at age 18:5 showed virtually the same level of performance as that obtained at age 16:10. The final assessment of intelligence on the adult scales at the age of nearly 22 years indicated IQ scores in the exceptionally low range. Overall, across a time span of almost 11 years, Alex's full scale IQ showed incremental, but nevertheless impressive gains of about 20 points, from the low 40s to the low 60s.

### *Speech and language*

At the age of 11 when Alex's speech and language abilities were assessed in detail, he was speaking fluently with an English accent and without a trace of hesitation or unintelligibility. In particular, there were no dysphasic symptoms, and no word finding difficulties. Infrequent grammatical errors were noted, however, and these are underlined in the following free recall of the Bus Story (Renfrew, 1969) that had been read to him. The immediate recall of this passage indicated an age equivalent of 7 years, an increase in verbal output of 5–6 years in a matter of approximately 18 months since the onset of speech relative to his pre-hemispherectomy state of virtual mutism. The text in *italics* refers to embellishments that Alex introduced into his account of the story (Fig. 3).

**The Bus Story**

Once upon a time there was a very naughty bus. While his driver was trying to mend him, he decided to run away. He ran along the road beside a train. They made funny faces at each other and raced each other. But the bus had to go on alone, because the train went into a tunnel. He hurried into the city where he met a policeman who blew his whistle and shouted, 'Stop, bus'.

But he paid no attention and ran on into the country. He said, 'I'm tired of going on the road'. So he jumped over a fence. He met a cow who said 'Moo, I can't believe my eyes'. The bus raced down the hill. As soon as he saw there was water at the bottom, he tried to stop. But he didn't know how to put on his brakes. So he fell in the pond with a splash and stuck in the mud. When his driver found where he was, he telephoned for a crane to pull him out and put him back on the road again.

**Immediate recall of The Bus Story**

"Once on up a time... there was a nice bus and he decided to run away. He made funny faces at each other. He went through the country knocking down the people and the policeman blew his whistle so loud. He couldn't stop and he rode through the countryside and he jumped over the fence and rushed through the fields. And the cow said 'moo' and he said 'good gracious, goodness me' and he went roaring down the hill. He fell into the water with a big splash. *The end*".

**Figure 3.** Text of the Bus Story and Alex's immediate recall of the same story (Adapted from Vargha-Khadem *et al.*, 1997, Appendix 2).

Between the ages of 14:2 and 17:9, Alex's listening comprehension and oral expression skills were evaluated on the Wechsler Objective Language Dimensions (Rust, 1996), a test of everyday language use (see Figure 4, p. 243). While his listening comprehension remained stable in the low range (i.e. standard scores in the high 70s), his oral expression skills showed impressive gains, rising from just below the standard score of 60 (i.e. exceptionally low range) to 82 (i.e. low average range).

### ***Phonological abilities***

It is well recognized that phonological awareness emerges early during development, manifesting itself as sensitivity to rhymes, sound blending, and phonological imitation, and serving as a reliable predictor of subsequent reading ability in normally developing children (Goswami and Bryant, 1990; Carroll *et al.*, 2003), as well as in cases with various neurodevelopmental or acquired disorders of language, such as developmental dyslexia (Hulme and Snowling, 2009) and *deep dyslexia* (Patterson *et al.*, 1989). Recent evidence



suggests that the left dorsolateral prefrontal cortex may play an important role in subserving phonological awareness for spoken language (Kovelman *et al.*, 2011). Thus, the integrity of this brain region in the left hemisphere may be critical for acquisition of reading skills.

To explore Alex’s phonological awareness, the Phonological Awareness Protocol devised by Muter (1994a, b) was administered between the ages of 14:11 and 16:10. This protocol comprises tests of rhyme detection, rhyme production, syllable and phoneme identification and segmentation, phoneme deletion and sound blending. Also administered was a test of non-word reading, which is particularly sensitive to detecting difficulties with phonological processing and phoneme to grapheme transcription (Non-word Reading Test, Snowling *et al.*, 1996). Results indicated that whilst Alex’s phonological awareness skills at age 14:11 were at the level of a 5- to 6-year-old (i.e. ~2 SDs below the mean) with deficits being much more pronounced on the phoneme than on the syllable subtests, there was evidence of improvement in every domain with increasing age and training experience. By the age of 16:10, the most challenging aspects of phonological processing were non-word reading (Snowling *et al.*, 1996), and sound blending (Muter, 1994b) which showed resistance to significant improvements (Table 1).

Phonological Abilities			
Test	Age		
	14:11	15:11	16:10
	%	%	%
Rhyme Detection	40	40	70
Phoneme Completion	62	75	100
Phoneme Deletion - start	12	50	100
Phoneme Deletion - end	0	25	87
Sound Blending	53	75	72
Non-word Reading	0	5	35

Table 1. Development of phonological processing skills during adolescence.



### *Acquisition and development of literacy skills*

Assessed for reading and writing skills (Wechsler Objective Reading Dimensions – WORD; Wechsler, 1993) at the age of 14:11 years, when he had completed four academic terms receiving formal literacy training, Alex had achieved an age equivalent of 6:0 years (i.e. floor level) for both single word reading and spelling. His significantly restricted sight vocabulary had precluded his scoring any points on the reading comprehension subtest of WORD.

Between the ages of 14:11 and 16:10 when Alex's phonological abilities were also being assessed, only limited improvements in literacy skills were achieved, although the acquisition of some sight vocabulary did result in a standard score for reading comprehension that was somewhat above the floor level. Thus, the improvements in certain aspects of phonological processing that took place over the span of two years (i.e. between the age of 14:11 and 16:10 years – see Table 1 above), did not appear to translate to marked changes in the level of reading.

Re-assessed on the same tests at the age of 17:9 years, Alex's scores did not reveal a significant change from when he began to acquire literacy skills at the age of 14:2 years. This, despite the fact that between the ages of 15 and 18 years, Alex was placed in an intensive cognitive and motor rehabilitation programme including literacy training for several hours per day. Yet, his literacy skills failed to improve beyond a basic sight vocabulary for reading and single word spelling (see Figure 5, p. 244).

### **Conclusions**

The remarkable emergence and subsequent development of articulate speech and everyday communication abilities during Alex's second decade of life clearly indicates that the isolated right hemisphere can develop such skills well beyond the 'critical period' of five or six years, thus raising the age for effective learning of a first language to the first decade of life, and possibly up to puberty. Whilst after the emergence of speech, language *comprehension* remained relatively stable within the upper limits of the standard Low range (i.e. 70–79), there was genuine improvement in language *expression* over the late adolescence period (see Figure 4, p. 243). Thus, Alex's standard scores increased at age 14:2 from the Exceptionally Low range (i.e. < 60) to the low average range (i.e. 80–89) at age 17:9. This is an impressive gain indeed given that during this period and beyond, Alex's intellectual abilities remained stable (see Figure 2, p. 243), within the same restricted range (i.e. < 60; Exceptionally Low range). The remarkable development of expressive language over an eight-year period from a baseline of virtual mutism suggests that everyday communication skills are of high priority and are rescued despite restricted intellectual standards.

However, the rescue of verbal communication has not been achieved without costs to other domains of function. For example, deficits have persisted in important aspects of phonological abilities and literacy skills, and in those areas previously reported, such as intelligence, particularly nonverbal intelligence, working memory, formal aspects of language processing and grammar, and visuo-perceptual skills (Vargha-Khadem *et al.*, 1997). This plethora of cognitive deficits prevailed over the period extending to early adulthood. Moreover, systematic training in certain skills, such as reading and writing, did not generalize to improve literacy standards. This pattern of a domain-specific rescue of everyday verbal communication against the background of widespread cognitive impairment raises the intriguing possibility that the right hemisphere has the same capacity as the left only for the high priority function of 'listening and speaking'. Effective development of other cognitive domains, including those involving higher order language processing, appear to require the specialized potential of the left hemisphere, with the impetus provided by intellectual capacity.

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## References

- Bates, E., Reilly, J., Wulfeck, B. *et al.* (2001). Differential effects of unilateral lesions on language production in children and adults. *Brain and Language*. 79(2), 223-265.
- Battro, A. (2000). *Half a Brain is Enough: The Story of Nico*. Cambridge, UK: Cambridge University Press.
- Boatman, D., Freeman, J., Vining, E., Pulsifer, M., Miglioretti, D., Minahan, R., Carson, B., Brandt, J. & McKhann, G. (1999). Language recovery after left hemispherectomy in children with late-onset seizures. *Annals of Neurology*. 46(4), 579-586.
- Goswami, U. and Bryant, P. (1990). *Phonological Skills and Learning to Read*. Lawrence Erlbaum Associates. London.
- Carroll, J.M., Snowling, M.J., Stevenson, J., Hulme, C. (2003). The development of phonological awareness in preschool children. *Developmental Psychology*. 39(5), 913-923.
- Dall'Oglio, A.M., Bates, E., Volterra, V., Di-Capua, M. & Pezzini, G. (1994). Early cognition, communication and language in children with focal brain injury. *Developmental Medicine and Child Neurology*. 36, 1076-98.
- Dehaene-Lambertz, G. & Baillet, S. (1998). A phonological representation in the infant brain. *Neuroreport*. 9(8), 1885-1888.
- Dehaene-Lambertz, G. (2000). Cerebral specialization for speech and non-speech

- stimuli in infants. *Journal of Cognitive Neuroscience*. 12(3), 449–460.
- Dehaene-Lambertz, G., Dehaene, S. & Hertz-Pannier, L. (2002). Functional neuroimaging of speech perception in infants. *Science*. 6, 298(5600), 2013–5.
- Dehaene-Lambertz, G., Hertz-Pannier, L. & Dubois, J. (2006). Nature and nurture in language acquisition: Anatomical and functional brain-imaging studies in infants. *Trends in Neurosciences*. 29(7), 367–73.
- Devlin, A.M., Cross, J.H., Harkness, W., Harding, B., Vargha-Khadem, F. & Neville, B. (2003). Clinical outcomes of hemispherectomy for epilepsy in childhood and adolescence. *Brain*. Vol. 126, No. 3, 556–566.
- Doupe, A.J., and Kuhl, P.K. (1999). Birdsong and human speech: Common themes and mechanisms. *Annual Review of Neuroscience*. 22:567–631.
- Freeman, J.M. (2005). Rasmussen's syndrome: progressive autoimmune multifocal encephalopathy. *Pediatric Neurology*. 32(5):295–299.
- Gaillard, W.D., Hertz-Pannier, L., Mott, S.H., Barnett, A.S., LeBihan, D. & Theodore, W.H. (2000). Functional anatomy of cognitive development: fMRI of verbal fluency in children and adults. *Neurology*. 54(1), 180–185.
- Giza, C.C., and Prins, M.L. (2006). Is being plastic fantastic? Mechanisms of altered plasticity after developmental acquired traumatic brain injury. *Developmental Neuroscience*, 28: 364–379.
- Griffiths, R. *The abilities of young children* (1970). London: Child Development Research Centre.
- Grimshaw, G.M., Adelstein, A., Bryden, M.P. & MacKinnon, G.E. (1998). First-language acquisition in adolescence: Evidence for a critical period for verbal language development. *Brain and Language*. 63, 237–255.
- Goldman-Rakic, P.S. (1980). Morphological consequences of prenatal injury to the primate brain. *Progress in Brain Research*. 53: 3–10.
- Hulme, C. and Snowling M.J. (2009) *Developmental Disorders of Language, Learning and Cognition*. Oxford: Wiley-Blackwell. pp. 37–89
- Immordino-Yang, M.H. (2007). A tale of two cases: Lessons for education from the study of two boys living with half their brains. *Mind, Brain and Education*. 1, 66–83.
- Isaacson, R.L. (1975). The myth of recovery from early brain damage. In: N.R. Ellis (Ed.). *Aberrant Development in Infancy: Human and Animal Studies*. Lawrence Erlbaum Associates, Hillsdale, NJ. 1–25.
- Kennard, M.A. (1936). Age and other factors in motor recovery from precentral lesions in monkeys. *American Journal of Physiology*. 115, 138–146.
- Kennard, M.A. (1938). Reorganization of motor function in the cerebral cortex of monkeys deprived of motor and premotor areas in infancy. *Journal of Neurophysiology*. 1, 477–496.
- Kennard, M.A. (1940). Relation of age to motor impairment in man and in subhuman primates. *Archives of Neurology and Psychiatry*. 44, 377–397.
- Kovelman, I., Norton, E.S., Christodoulou J.A., Gaab N., Lieberman, D.A., Triantafyllou, C., Wolf, M., Whitfield-Gabrieli, S., Gabrieli, J.D. (2011). Brain basis of phonological awareness for spoken language in children and its disruption in dyslexia. *Cerebral Cortex*. E-Pub ahead of publication.
- Lai, C.S.L., Fisher, S.E., Hurst, J.A., Vargha-Khadem, F. and Monaco, A.P. (2001) A novel forkhead-domain gene is mutated in a severe speech and language disorder. *Nature*. 413, 519–523.
- Lidzba, K., Staudt, M., Wilke, M., Grodd, W. & Kraggeloh-Mann, I. (2006). Visuospatial deficits in patients with early left-hemispheric lesions and functional reorganization of language: Consequence

- of lesion or reorganization? *Neuropsychologia*. 44(7), 1088-1094.
- Liegeois, F., Cross, J.H., Polkey, C., Harkness, W., & Vargha-Khadem, F. (2008a). Language after hemispherectomy in childhood: Contributions from memory and intelligence. *Neuropsychologia*. 46, 3101-3107.
- Liegeois, F., Connelly, A., Baldeweg, T. & Vargha-Khadem, F. (2008b). Speaking with a single cerebral hemisphere: fMRI language organization after hemispherectomy in childhood. *Brain and Language*. 106(3), 195-203.
- Muter, V. (1994a). *Phonology and learning to read in normal and hemiplegic children*. (Ph.D. Thesis). University of London.
- Muter, V., Snowling, M., Taylor, S. (1994b). Orthographic analogies and phonological awareness: Their role and significance in early reading development. *Journal of Child Psychology and Psychiatry*. 35(2): 293-31.
- Ogden, J.A. (1998). Language and memory functions after long recovery periods in left-hemispherectomized subjects. *Neuropsychologia*. 26(5), 645-659.
- Patterson, K., Vargha-Khadem, F., and Polkey, C.E. (1989). Reading with one hemisphere. *Brain*. 112: 39-63.
- Rankin, P. and Vargha-Khadem, F. Neuropsychological evaluation – Children. (2007). In: *Epilepsy: A Comprehensive Textbook*, Engel, J. and Pedley, T.A. (eds.). Philadelphia: Lippincott Williams & Wilkins.
- Renfrew, C.E. (1969). *The Bus Story*. Old Headington (Oxford): C.E. Renfrew.
- Rust, J. (1996). *Wechsler Objective Language Dimensions*, Psychological Corporation, London.
- Schneider, G.E. (1974). Functional recovery after lesions of the nervous system: 3 developmental processes in neural plasticity. Anomalous axonal connections implicated in sparing and alteration of function after early lesions. *Neuroscience Research Program Bulletin*. 12(2): 222-227.
- Schneider, G.E. (1979). Is it really better to have your brain lesion early? A revision of the “Kennard principle”. *Neuropsychologia*. 17(6), 557-83.
- Shriberg, L.D., Gruber, F.A., and Kwiatkowski, J. (1994). Developmental phonological disorders III: Long-term speech-sound normalization. *Journal of Speech and Hearing Research*. 37(6): 1151-1177.
- Snowling, M., Stothard, S., McLean, J. (1996). *Graded Nonword Reading Test*. Bury St Edmunds (Suffolk): Thames Valley Test Company.
- Teuber, H.L. (1975). Effects of focal brain injury on human behavior. In: Tower, D. (Editor). *The Nervous System*. Vol. 2, Raven Press, New York, pp. 182-201.
- Vargha-Khadem, F., Watters G.V., O’Gorman, A.M. (1985). Development of speech and language following bilateral frontal lesions. *Brain and Language*. 25: 167-183.
- Vargha-Khadem, F., Isaacs, E.B., Papaleoudi, H., Polkey, C.E., and Wilson, J. (1991). Development of language in six hemispherectomized patients. *Brain*. 114: 473-495.
- Vargha-Khadem, F., Isaacs, E. & Muter, V. (1994). A review of cognitive outcome after unilateral lesions sustained during childhood. *Journal of Child Neurology*. 9, supplement, 2S67-2S73.
- Vargha-Khadem, F., Carr, L.J, Isaacs, E., Brett, E., Adams, C. & Mishkin, M. (1997). Onset of speech after left hemispherectomy in a nine-year-old boy. *Brain*. 120(1), 159-182.
- Wechsler, D. (1992). *Wechsler Intelligence Scale for Children*, Edition III. UK. Sidcup, Kent. UK. The Psychological Corporation.
- Wechsler, D. (1993). *Wechsler Objective Reading Dimensions*. Sidcup, Kent, UK. The Psychological Corporation.
- Wechsler, D. (1998). *Wechsler Adult Intelligence Scale*, Edition III, UK. Sidcup, Kent, UK. The Psychological Corporation.

## ■ LEARNING AND TEACHING

# CORE SYSTEMS AND THE GROWTH OF HUMAN KNOWLEDGE: NATURAL GEOMETRY

■ ELIZABETH S. SPELKE

## Cultivating seeds of human knowledge: natural geometry

Together with the mastery of reading and the achievement of literacy (Dehaene, this volume), the mastery of elementary mathematics is the most important achievement of the early school years. A basic understanding of number and geometry is fundamental to almost all the activities of modern humans, from trade and economics to measurement and technology to science and the arts. Like reading, moreover, mathematics poses challenges for many students, who may experience difficulty learning and reasoning about numbers, maps and graphs throughout their lives. Fostering education in mathematics therefore is a central focus of efforts to improve the education of all children. Here, I focus on the foundations of an aspect of mathematical learning that has received somewhat less attention than number and arithmetic: the development of geometrical intuitions.

As a formal subject matter, Euclidean geometry typically is not introduced into mathematics education until the end of the elementary school years, because instruction in its subject matter poses challenges. Most topics in the elementary school curriculum can be connected to meaningful and engaging activities: numbers and counting can be taught in the context of board games (Siegler & Ramani, 2011), and reading in the context of stories, plays, and songs. In contrast, the objects of geometry – dimensionless points, lines of infinite extent, and ideal forms – cannot be seen nor acted upon. Perhaps as a result, formal geometry often enters the mathematics curriculum only around adolescence, where it is presented as a set of exercises in logical theorem proving.

Nevertheless, educated adults have clear geometrical intuitions, and these intuitions stand at the foundations of a body of knowledge that has long been central to human thought and action. Both the naturalness and the elusiveness of the points, lines and planes of Euclidean geometry led Socrates to argue that geometry cannot be taught or learned at all, but only recollected from ancestral memories (Plato, ca. 380 b.c.). Recent research suggests, however, that Euclidean geometry develops over the course of childhood, as a product of systems that emerge in human infancy and guide a rich array of activities that engage children long before they learn to read or count.

## Developing geometrical intuitions

Evidence for the late emergence of Euclidean geometrical intuitions comes from studies of the development of three abilities: the ability to navigate by a purely geometric map, the ability to reason about the properties of triangles on a planar or curved surface, and the ability to reflect on the fundamental properties of points and lines. These abilities have been assessed through research on adults and children living in two markedly different kinds of settings: urban, industrialized societies in North America and Europe, and scattered villages in a remote region of the Amazon. I will briefly describe the findings of these studies.

First, navigation by geometric maps has been studied both in adults and in children as young as 4 years of age (Dehaene *et al.*, 2006; Shusterman *et al.*, 2008). In these studies, participants are shown an array of three opaque containers in a specific geometric arrangement (a triangle or an unequally spaced line) and are encouraged to place or find an object in one specific container. To locate the correct container, participants are turned away from the display and shown a schematic picture of an overhead view of the array – three discs arranged in a similar triangle or line – with a star marking the target location (see Figure 1, p. 245). At all ages, children and adults used *distance* relationships on this map to locate the target in the navigable array, showing that even the 4-year-old children understood the task and were motivated to perform it. Adults in both cultures also located the target by analyzing two other fundamental properties of Euclidean geometry: *angle* (the information that distinguishes corners of a triangle that differ in size) and *sense* (the information that distinguishes a form from its mirror image; Dehaene *et al.*, 2006). Four-year-old children, in contrast, only extracted distance relations from the map (Shusterman *et al.*, 2008). Further studies revealed that children begin to use angle information at 6 years (Spelke *et al.*, in press) and sense information at adolescence (Hyde *et al.*, 2011). These studies reveal a slow, progressive development of sensitivity to Euclidean maps.

Second, geometrical reasoning has been studied by assessing the abilities of adults and children to find and reproduce the third corner of a triangle (Izard *et al.*, 2011a). For this task, participants were presented with animated images on a computer screen, depicting a large extended surface that was either flat or spherical. In an accompanying narration, the surface was described as a land with three small villages, connected by straight paths (see Figure 2a, p. 246). Two dots, each with two arrows, then appeared on the lower sides of the screen. The dots were described as villages, and the arrows were described as the beginnings of the paths that connected the villages to each other and to a third village, not shown. Participants were asked to



indicate both the location of the third village and the angle at which the two paths met at that village. When reasoning about paths on the plane, the judgments of adults and older children in both cultures accorded with the principles of Euclidean geometry: they produced an angle that, together with the two visible angles on the screen, summed to a value very close to 180 degrees, independent of the distance between the two visible points or the area of the triangle thus formed. When reasoning about paths on the sphere, these older children and adults adapted their responses in the appropriate direction, producing angles whose size increased with increases in the triangle's area (although adults and children alike tended to underestimate the degree to which this angle should increase on the sphere). In contrast, 6-year-old children showed no ability to distinguish between the planar and spherical worlds. Contrary to the basic principles of Euclidean plane geometry, the angles that they produced were independent of the angles visible on the screen and varied with the distances between the points on the screen. For the youngest children, reasoning about navigable paths in this virtual world did not accord with the basic, Euclidean properties of planar triangles.

Intuitions about points and lines were elicited from the same adults and children who participated in the virtual navigation task (Izard *et al.*, 2011a). Participants again were shown the two textured surfaces on the computer screen: the planar surface for one block of trials and the spherical surface for the other block of trials. Then the computer image approached the surface until all information for surface curvature was removed, and subjects were presented with simple displays containing a few points or short line segments, accompanied by yes/no questions (see Figure 2b, p. 246). Some of these questions probed properties of points and lines that are true of both plane and spherical geometry (for example, can a straight line be drawn between any two points? between any three points?). Other questions probed properties of points and lines that are true of one of these geometries but not the other (for example, are there pairs of lines that never cross? that cross more than once?).

As in the previous study, adults and children aged 10 and above answered these questions systematically. When questions were asked of the planar surface, their performance accorded with Euclidean geometry: participants judged with high consistency that some lines will never cross on the plane and none will cross more than once. Participants also tended to adjust the latter judgment in the case of the sphere, noting that straight lines on the sphere can cross twice (although participants in both cultures tended mistakenly to judge that some straight lines on the sphere will never cross). Once

again, the performance of 6-year-old children contrasted with that of their elders: children gave consistent judgments about some of the properties that are common to points and lines on a plane or sphere, but they did so far less systematically than did adults and older children, and they failed to differentiate between planar and spherical surfaces in their judgments.

In summary, adults and older children show knowledge of abstract, Euclidean geometry in three tasks: a map task in which they must extract information about length, angle and sense relations from a 2D picture and apply this information to a 3D navigable array, a triangle completion task in which they must reason about the properties of paths connecting villages on a flat or curved surface, and a test that elicits pure intuitions about the basic properties of dimensionless points and straight, endless lines. Before 6 years of age, however, children share only a small part of these abilities. When and how does Euclidean geometry become natural and intuitive to children, and what experiences foster this developmental change?

### **Discovering the sources of geometrical intuitions**

In the rest of this chapter, I explore an old idea: When humans learn and practice formal geometry, we take capacities of the mind and brain that evolved in our species and developed in infancy and early childhood to serve other functions, and we harness them for this new purpose. Cognitive psychologists and neuroscientists can discover those systems, and their functions, through four different strands of comparative research. One research effort compares the geometrical abilities of children of different ages, from infancy to maturity. A second research effort compares the abilities of different animal species, from humans' close primate relatives to more distant vertebrates and even invertebrates. A third research effort compares the abilities of humans living in different cultures, with differing access to education and to cultural products such as maps and rulers, and also humans who differ in their spatial abilities. A fourth research effort traces geometrical cognition across different levels of analysis, from genes to neurons to brain systems to learning and behavior.

I believe that these four strands of research converge to reveal two core systems at the foundations of human knowledge of geometry. One is a system for representing the large-scale navigable layout: a system that humans and animals use to specify their own location within such a layout. The other is a system for representing small-scale manipulable objects and forms: a system that humans and animals use to recognize and categorize objects of significant kinds. Humans discover the system of abstract, Euclidean geometry, I believe, by productively combining representations from these

two systems. Those combinations, in turn, depend on a host of uniquely human, symbolic devices.

In the rest of this chapter, I describe each of the two systems of core knowledge of geometry in turn, focusing both on its richness and on its limits. Then I turn to a third system that children and adults use to combine representations from these systems, and that therefore may foster children's construction of a more abstract geometry: the system of natural language.

### **Geometry for navigation**

'Geometry', the measurement of the earth, is aptly named. The core system of core knowledge of geometry is a system by which navigating humans and other animals compute their own positions, and those of significant objects, by measuring properties of the surrounding terrain. An experiment conducted on 18- to 24-month-old children, serves to introduce this system (Hermer & Spelke, 1996). Children were brought into a closed unfurnished rectangular room with four corner panels at which toys could be hidden (see Figure 3a, p. 247). Because the room was uniformly colored and illuminated, only the relative lengths of its walls broke its four-fold symmetry; no information distinguished any direction from its diagonal opposite. Children stood at the room's center and watched as a toy was hidden at one corner. Then they were lifted and turned slowly with eyes covered until they were disoriented. Finally they were released and encouraged to search for the toy. Children confined their search to two of the room's corners: the correct location and the opposite, geometrically congruent location. This finding provides evidence that children's navigation was guided in some way by the shape of their surroundings.

Although full disorientation is a rare event during human navigation, experiments using reorientation tasks are highly valuable, because they reveal the information about the environment that navigators encode automatically (since children don't expect to be disoriented) and later call upon to reestablish their position. As a consequence, a rich array of experiments has investigated children's reorientation at diverse ages and in diverse environments. Humans reorient by the shape of a rectangular chamber as early as 12 months of age, and they continue to do so as adults (Hermer & Spelke, 1996). By 24 months, children reorient by the shape of both large and small rectangular environments (Learmonth, Newcombe & Huttenlocher, 2001), both when the surrounding walls are homogeneous and when they are distinctive in color or are furnished by distinctive landmarks (Hermer & Spelke, 1996; Learmonth, *et al.*, 2001). Children also reorient by the distances and directions of surrounding walls when they are tested in rooms of other shapes including

isosceles triangles (Lourenco & Huttenlocher, 2006; see Figure 3b, p. 247), and squares with distinctive protrusions (Wang *et al.*, 1999; see Figure 3c, p. 247). Nevertheless, children's reorientation shows limits that provide clues to the nature of the representations that guide them, and that allow investigators to track these representations across species, across cultures, and into the brain.

One signature limit of this core geometry system concerns the kind of layout information that it accepts: children reorient by the distances and directions of extended surfaces but not by the distances and directions of freestanding objects, even large ones. A recent series of experiments illustrates this limit (Lee & Spelke, 2010; see also Lew *et al.*, 2006; Wang *et al.*, 1999). Children were disoriented in a cylindrical environment with two large, stable columns that contrasted with the walls of the cylinder in brightness and color, positioned so that they both stood on one side of the room, separated by 90 degrees (Figure 4a, p. 247). When the columns stood flush against the cylindrical wall of the room, children used them to reorient themselves and locate a hidden object, both when that object was hidden directly at one of the columns and when it was hidden elsewhere. When the columns were offset slightly from the walls, however, children failed to use their positions to locate the hidden object. This failure did not stem from a failure to attend to or remember the relation of the object to the columns: if the object was hidden directly at one of the two columns, children searched only at the columns, showing that they appreciated their relevance to the task and used each column as a 'beacon', signaling a place where an object could be hidden. Children failed, however, to confine their search to the column with the correct directional relationship to the child: if the object was hidden at the column on the *right*, children searched equally at the two columns on the right and left. Columns only specified the child's position when they were placed flush against the walls, and therefore contributed to the shape of the surrounding surface layout.

Further experiments within this series revealed a second signature limit of children's geometry-guided navigation: children reorient by the distances and directions of extended 3D surfaces but not by the distances and directions of extended 2D patterns (Lee & Spelke, 2010; see also Lee, Shusterman & Spelke, 2006; Gouteux & Spelke, 2001; Wang *et al.*, 1999). Children were tested in the same cylindrical environment, but instead of viewing two 3D columns against the wall, they were presented with two 2D patches of the same angular size as the columns, made of the same material and contrasting dramatically from the surrounding walls in brightness, texture and color (see Figure 4b, p. 247). When an object was hidden at one of these patches, children confined their search to the two patches, showing again that they

detected them and used them as beacons to directly mark an object's potential location, but they failed to distinguish between them and therefore searched equally at the correct patch (e.g., the patch on the right) and the incorrect patch (on the left). Although the patches were clearly detectable, they did not alter the shape of the cylindrical environment so as to break its symmetry. Accordingly, they were not used by the geometric navigation system to specify the position of the child and the hidden object.

The blindness of this system of core geometry to 2D patterns is very striking and has led to some surprising findings. The most dramatic of these are findings from a series of studies by Huttenlocher and Lourenco (2007; Lourenco *et al.*, 2009). In these studies, children were disoriented in a square room, such that no information from the room's shape distinguished its four corners. In different conditions, the opposite pairs of walls of this room were distinguished from one another by 2D pattern information: for example, walls were covered with crosses vs. discs (see Figure 5, p. 248). Although the distinction between a cross and a disc is purely geometric, disoriented children disregarded this information and searched the four corners equally. Children disregarded distinctive surface markings in a variety of settings, including square rooms whose walls differed in color (alternating walls were red or blue) or in the presence vs. absence of patterning (alternating walls displayed black discs on a white background or were homogeneously gray). Children's failures did not stem from a failure to detect or use the pattern information, however, because children confined their search to the two directionally consistent corners in a final condition, in which opposite walls were covered with discs that differed in size and density (large, widely spaced discs on one pair of walls and small, narrowly spaced discs on the other pair).

Why did children succeed in this last condition, given that they failed to distinguish a wall with large discs from a wall with *no* discs? Recent experiments have addressed this question and reveal the exquisite sensitivity of this core geometry system (Lee, Winkler-Rhoades & Spelke, unpublished). When perceivers view equally distant surfaces covered by forms of identical shape but different sizes and densities, they perceive the surface with larger, less dense shapes as closer to them. This depth cue of *relative size* affects depth perception in infants as young as 7 months of age (Yonas, Granrud & Pettersen, 1985). Although the room in Huttenlocher & Lourenco's studies was square, the relative size cue led children to perceive it as slightly elongated, such that the walls with large circles appeared closer to them than the walls with small circles. This conclusion comes from experiments that tested two predictions from the thesis that relative size functioned as a depth cue. First, children should reorient in uniformly colored

environments even when they are only very slightly rectangular (because the effect of the relative size depth cue is subtle). Second, the relative size cue should interact predictably with other cues to depth to enhance or diminish children's reorientation.

To test these predictions, we first tested children in two uniformly colored rooms that were almost but not quite square, with walls varying in length in a ratio of 8:9 in one condition and 23:24 in the other. Children failed to reorient by the rectangular shape in the latter condition but succeeded in the former condition, providing evidence that quite subtle departures from a square shape were sufficient to guide reorientation. Next, we created three environments with circular patterns matching those used by Huttenlocher and Lourenco (2007): a square room, a subtly rectangular room such that the larger circles appeared on the closer walls, and a subtly rectangular room in which the larger circles appeared on the more distant walls. Children searched effectively in the first two conditions but not in the third. These findings provide evidence that the patterns varying in size and density acted as a depth cue, breaking the symmetry of the square room. As in all the previous experiments, 2D geometric patterns did not serve as independent information guiding children's reorientation. These experiments provide evidence that the core geometric system for navigation is guided by extremely subtle perturbations of 3D geometric structure. Additional studies bolster this conclusion by showing that children reorient effectively in environments where the only distinctive 3D shape is provided by a tiny rectangular frame or bump on the floor (Lee & Spelke, 2011; see Figure 6, p. 249).

A final signature property of the system guiding children's reorientation concerns its imperviousness to task manipulations that influence children's state of attention. Children's ability to use a distinctively colored wall, a 2D pattern, or a freestanding object as a beacon marking the location of a hidden object is strongly modulated both by children's attention to that feature and by their understanding of its potential relevance. For example, children who are told that a colored wall will help them find a hidden object subsequently use the wall to guide their search for the object, whereas children who are simply told that the wall has a pretty color do not (Shusterman *et al.*, in press). In contrast, children's use of the geometric configuration of an arrangement of walls is unaffected by these or other manipulations of attention. As children explore an environment, they automatically encode and remember their position within the extended 3D surface layout.

In summary, research on navigating children provides evidence for a system of representation that is sensitive to the geometric configuration of the extended surfaces within the navigable layout, but not to similar configu-

rations of movable objects, or two-dimensional surface markings (unless they create an illusory 3D surface pattern). This sensitivity, moreover, is independent of the child's state of attention or awareness of the future utility of this geometric information. These signature limits allow investigators to test for the same system in other animals, in human adults in diverse cultures and circumstances, and in specific systems in the brain. I will briefly mention each of these efforts.

Studies of reorientation began with research on rats, when Cheng (1986) and Gallistel (1990) developed the reorientation task. Reorientation by the shape of the environment has now been shown in a wide range of non-human animals, from primates to birds and even to ants (Weustrach & Beugnon, 2009; see Cheng & Newcombe, 2005, for a review). Untrained animals of all these species show the same signatures of reorientation found in children. Like children, for example, ants use 2D geometric patterns as beacons but only use the shape of the 3D environment for reorientation (Wystrach & Beugnon, 2009). Moreover, newly hatched chicks, like children, use both 2D patterns and large freestanding objects as beacons but fail to reorient by them (Lee, Spelke & Vallortigara, unpublished). Chicks also reorient by the same patterns of subtle geometric information as children, and mice show the same reorientation performance as children in square rooms containing patterning information evoking the relative size depth cue (Twyman *et al.*, 2009). Finally, training regimes that alter animals' attention to environmental features and awareness of their significance markedly change animals' navigation performance in relation to surface brightness, 2D patterns, and freestanding objects (e.g., Wystrach & Beugnon, 2009; Pearce *et al.*, 2001). These manipulations, however, have little or no effect on animals' response to surface layout geometry.

Research on human adults initially appears to contrast with these patterns: adults who are disoriented in a room with distinctive landmarks will use any and all landmarks to locate hidden objects: a finding to which I will return in the last section of this chapter. Beneath adults' much more successful performance, however, is the same system of geometry-guided navigation found in children and animals. For example, adults who participate in a reorientation experiment while engaged in a continuous verbal task show the signatures of children's and animals' search performance: they use objects and 2D patterns as beacons but reorient only by 3D surface layout geometry (Hermer-Vazquez *et al.*, 1999), unless task instructions specifically alert them to the task of locating landmarks (Ratcliff & Newcombe, 2008). Even more dramatically, adults who are tested with no simultaneous interference, but who are deaf and have only limited access to a conventional sign language, reorient by the



shape of the layout as well as their hearing or linguistically more capable deaf peers, but they are less able to use a colored-surface landmark in a reorientation task (Pyers *et al.*, 2010). These findings suggest that a phylogenetically and ontogenetically ancient system of reorientation persists through human childhood and continues to function in adults, although adults use other cognitive resources, including those provided by their language, to compensate for its limitations. I return to the effects of language later in this chapter.

In research using neurophysiological methods, the same signatures have been found in the brains of navigating animals, in areas whose activity specifies the animal's location ('place cells'), heading ('head-direction cells'), or motion ('grid cells'). Place cells in the hippocampus, and head-direction and grid cells in nearby regions of the cerebral cortex, discharge in patterns that are systematically affected by the animal's distance and direction from the 3D extended surfaces within the chamber (O'Keefe & Burgess, 1996; Lever *et al.*, 2002; Solstad *et al.*, 2008). In contrast, the activity of these cells is unaffected by the positions of freestanding objects or the colors and textures of the chamber's walls (Lever *et al.*, 2002; Solstad *et al.*, 2008). Interestingly, place cell activity also changes with experience, in patterns that suggest that objects, surface textures, and other environmental features come to be encoded as animals learn their relevance (Lever *et al.*, 2002). Studies of very young rats provide evidence that this navigation system is in place very early in development. The activity of place cells and head-direction cells is detectable, in infant rats, as soon as the rats begin to locomote; the activity of grid cells develops shortly thereafter (Wills *et al.*, 2010). All these findings parallel the findings from behavioral studies of young children.

Recent research using methods of functional brain imaging provides evidence for place and grid cells in human adults as well, consistent with the behavioral research described above (Doeller *et al.*, 2008, 2010). The human hippocampus is activated when adults learn to identify locations in a virtual environment in relation to extended 3D surfaces (Doeller & Burgess, 2008; Doeller *et al.*, 2008). In contrast, when adults learn to identify locations in relation to freestanding landmark objects, a different brain region in the striatum, is associated with their task performance. Hippocampal activity associated with learning an environmental location in relation to an extended surface in the virtual layout is markedly impervious to effects of attention and interference; in contrast, activity in the striatum, associated with learning of landmarks, shows marked effects of attention. These studies reveal a remarkable convergence across humans and rodents, and across behavioral and neurophysiological methods, in the core mechanisms for encoding the shape of the surrounding surface layout.

Finally, an exciting new line of research hints that the core system of geometry may have a specific genetic basis. The research focuses on adults with Williams Syndrome, a developmental disability stemming from a genetic deletion that produces a variety of structural and cognitive abnormalities, including impairments in spatial reasoning. Lakusta, Dessalegn & Landau (2010) focused on the latter impairments and found that adults with Williams Syndrome performed a wide variety of spatial tasks at roughly the level of three-year-old children. When they tested the reorientation performance of adults with Williams Syndrome in a homogeneously colored, rectangular room, however, they discovered a novel pattern of performance: in contrast to all the findings reviewed above, adults with Williams Syndrome searched equally at the four corners of the rectangular room. Their performance did not stem from a failure to remember the location of the hidden object, because they performed well when tested in the same room after a delay of equal duration but without disorientation. Their performance also did not stem from any debilitating effects of the disorientation procedure, because they performed fairly well when tested, after disorientation, in a rectangular room with one distinctively colored wall. Tests of typical 3-year-old children revealed a striking double dissociation: whereas children successfully navigated in accord with the shape of the environment and failed to navigate in accord with the colored wall, adults with Williams Syndrome did the reverse. This developmental disability therefore seems to produce a specific deficit in the core system for navigating by layout geometry.

At the time of writing of this chapter, the genetic and epigenetic processes that sculpt this core system still are unknown, but they are now open to study. Williams Syndrome is caused by a known genetic deletion, and mouse models both of this syndrome and of reorientation now exist. Future experiments on mice therefore can probe the nature of the developmental mechanisms by which this ancient system of geometric representation emerges or goes awry.

In summary, studies of navigation across human ontogeny, across vertebrate and invertebrate phylogeny, across human cultures and languages, and across levels of analysis from cognition to neurons to genes, all provide evidence for a navigation system that relies on the geometry of the surrounding surface layout. But I end this section with a crucial question: What kinds of geometric information about the surface layout does this system represent? The last navigation research that I will describe provides evidence that children, adults and animals maintain and reestablish their sense of place by representing with two fundamental properties of Euclidean geometry – *distance* and *direction*. However, navigating children, adults and animals do not

represent the two most important geometric properties that characterize the shapes of visual forms: *length* and *angle*.

Children's insensitivity to the angles at which walls meet at corners was first shown by Hupbach & Nadel (2005), who tested children in a rhomboid environment consisting of four walls that were equal in length but met at unequal angles. In a recent replication and extension of this research, we found that such children are strikingly insensitive to angle, even in the simplest environments (Lee, Sovrano & Spelke, in review). These tests presented 2- to 3-year-old children with fragmented rhomboid arrays within a uniform cylindrical environment (see Figure 7a, p. 250). In one condition, we removed the distinctive angle information available in a complete rhombus by presenting four walls in a rhomboid arrangement, separated by gaps where the corners had been. When a toy was hidden within this array and children were disoriented, they confined their search to the two geometrically appropriate locations, providing evidence that children can reorient in fragmented as well as continuous environments and that they do not need to see corner angles directly in order to locate themselves in relation to extended surfaces. In a second condition, we removed these surfaces and presented just the four corners of the rhombus, positioned so that they were equidistant from the room's center. Although the pairs of opposite corners presented markedly different angles (obtuse angles of 120 degrees and acute angles of 60 degrees), disoriented children were not guided by this distinction and divided their search equally among the four hiding locations. Children's reorientation evidently is not guided by the angles at which surfaces meet.

Two further experiments in this series presented children with fragmented rectangular arrays and tested whether children reorient in accord with the lengths of surfaces (see Figure 7b, p. 250). First we removed the distinctive length information that is present in any complete rectangle by presenting four surfaces of equal length, positioned so as to form a rectangular array whose major and minor axes differed by a 2:1 ratio. When a toy was hidden within this array, disoriented children confined their search to the two geometrically appropriate locations, providing evidence that they do not need to see surfaces of different lengths in order to position themselves within a rectangular space. Then we presented four surfaces at two different lengths, positioned so as to form a square enclosure. Although one pair of surfaces was twice as long as the other pair, disoriented children searched the four locations at random, without regard to the length distinctions.

These new findings suggest that it is misleading to characterize the geometry-guided reorientation system as sensitive to the *shape* of the surrounding layout (as I and others have done: e.g., Hermer & Spelke, 1996).

We will see in the next section that a fundamental property of shape representations is their invariance over transformations of scale, and their dependence on the angle and length relations between the parts of an object or the contours of a form. Children, however, do not respond to these angle and length relations, and neither do the rats tested in neurophysiological experiments. When a square room is quadrupled in area, place cell activity remains anchored to the absolute distances and directions of one or more walls; place fields do not move and expand to preserve their relation to the environment's global shape (O'Keefe & Burgess, 1996).

In summary, these findings provide evidence for a core system of geometric representation guiding navigation. The system, however, has two general sorts of limits. First, it applies only to the extended surfaces in 3D navigable layouts, not to 2D patterns or freestanding objects. Second, it represents the navigator's position relative to the absolute distances and directions of those surfaces, but it does not represent the geometric relationships of angle and length that each of those surfaces bears to the other. In the next section, I describe a second core system of geometric representation that has neither of these limits.

### **Geometry for object recognition**

Although animals and young children are strikingly oblivious to surface markings and relations of length and angle in the large-scale navigable layout, they are highly sensitive to these geometric relationships when they appear in small pictures or objects. This conclusion is supported by many decades of experiments on form perception and object recognition in animals and children (see Gibson, 1969, for a classic review of the earlier literature). It also is supported by research on human infants who cannot yet locomote independently (and hence cannot be tested in the above navigation tasks). I begin with the latter findings.

Decades of experiments have investigated sensitivity to angle and length in human infants, sometimes as early as a few hours after birth (Slater, Mattock, Brown, & Bremner, 1991). In one set of studies, infants were habituated to two lines crossing at a constant angle, presented at a number of different orientations. Then they were tested with new displays presenting the same shape in a previously unseen orientation, or a shape that presented the same two lines, joined at a different angle. Infants generalized habituation to the former displays and looked longer at the latter ones, suggesting that they are sensitive to angle (Schwartz & Day, 1979; Slater *et al.*, 1991). Similar experiments showed that infants also are sensitive to length (Newcombe, Huttenlocher & Learmonth, 1999).

Further studies suggest two further differences between infants' perception of the shapes of visual forms and children's and animals' use of geometry in navigation. First, research on animals provides evidence that navigation depends on an encoding of the absolute, not relative, distances of extended surfaces: positions within a space are not encoded in a scale-invariant manner (O'Keefe & Burgess, 1996). In contrast, infants' encoding of the shapes of visual forms is largely scale-invariant. In one series of studies (Schwartz & Day, 1979), infants were habituated to a small form and then were tested with form that changed either in one dimension (altering their shape and size) or in two dimensions (preserving their shape but creating a greater change in size). In contrast to the rats in the navigation tasks described above (O'Keefe & Burgess, 1996), infants showed greater dishabituation to the change in shape, providing evidence that they perceived the distinctive lengths of the contours of a form in a relative, not absolute, manner.

Second, navigating animals and young children encode the directional relations that distinguish an array from its mirror image. In particular, children readily distinguish the corner of a rectangular room where an object is hidden from its mirror image: indeed, only this relationship distinguishes the two geometrically congruent corners of such a room from the other, incongruent corners. In contrast, studies of form perception in infancy, probing infants' detection of the directional relations that distinguish a pattern from its mirror image, have yielded mixed findings. In most studies, infants fail to distinguish between a 2D geometrical form and its mirror image (Lourenco & Huttenlocher, 2008). In the rare studies where they succeed, infants are shown a succession of events that may induce a process of 'mental rotation', and only subsets of infants succeed in engaging this process (Quinn & Liben, 2008, Moore & Johnson, 2008). These findings provide evidence that visual forms are represented in a manner that is largely blind to sense distinctions.

These properties of visual form representations are largely invariant over human development, across different human cultures, and across animal species. I will describe just one set of recent experiments probing the later development of sensitivity to length, angle and direction in humans (Izard & Spelke, 2009; Izard *et al.*, 2011b). The experiments, conducted on adults and on children ranging from 4 to 10 years of age in both the U.S. and in a remote region of the Amazon, revealed a developmentally invariant pattern of performance that agreed closely with the findings from studies of form perception in infants. At all ages, children and adults detected angle and length relationships with relative ease, but they failed to detect directional relationships until adolescence.

The experiment used a deviant detection paradigm (after Dehaene *et al.*, 2006) in which five forms in the shape of an L shared a geometric property that a sixth L-shaped form lacked. Participants were presented with the six forms in a random arrangement and at random orientations, and their task was to detect the geometrical deviant. On different trials, the deviant form differed from the other forms in line length, angle, or sense (see Figure 8, p. 251). On pure trials, all the forms were otherwise identical; on interference trials, the forms varied along a second irrelevant dimension. A comparison of the latter trials to the pure trials served to assess whether length, angle or sense was processed automatically and interfered with detection of the relevant dimension.

There were two main findings. First, participants of all ages, and in both cultures, showed highest sensitivity to angular and length relations and lowest sensitivity to the sense relation that distinguishes a form from its mirror image. Second, variations in angle and length interfered with one another and with processing of sense, but variations in sense had no effect on processing of angle or length. At all ages, therefore, sense is difficult to detect and easy to ignore.

As a large literature documents, adults' ability to distinguish a form or 3D object from its mirror image often requires the application of a mental rotation to align the objects (Cooper & Shepard, 1973). After rotation, two visual forms or objects can be compared directly by a process of template matching, with no need to represent their abstract sense relations. Mental rotation therefore appears as a strategy that is applied to compensate for the absence of abstract, orientation-independent representations of sense. In contrast, the deviant detection study showed that angle and length relations are processed reliably and rapidly in figures that vary in orientation, as well as figures that vary in sense. Processing of angle and length occurs very readily, in arrays that differ in a variety of other geometric properties including orientation and sense.

The findings of studies of 2D form perception complement those of a large body of research on 3D object recognition. Objects are recognized primarily on the basis of their shapes, beginning in early childhood (Smith *et al.*, 2002; Smith, 2009) and continuing through adulthood, although the coordinate systems within which shapes are represented is a matter of persisting dispute (see Biederman & Cooper, 2009; Riesenhuber & Poggio, 2000). Adults across cultures recognize meaningful objects by detecting basic Euclidean properties such as the presence of straight edges and parallel surfaces (Biederman, Yue & Davidoff, 2009). When objects are depicted in line drawings, junctions where distinct lines meet provide particularly important information that adults and children use to recognize them (Biederman, 1987;

Figure 9). In both behavioral and neuroimaging studies, moreover, shape-based object recognition has been found to be invariant both over a wide range of scales and over reflection (Biederman & Cooper, 2009), providing evidence for sensitivity to differences in length and angular relationships but not to the directional relationship that distinguishes a shape from its mirror image. Finally, variations in object shape elicit activation in specific regions of the occipital and temporal cortex of the brain (Grill-Spector, Golarai, & Gabrieli, 2008; Reddy & Kanwisher, 2006). These regions respond to the shapes both of three-dimensional objects and of two-dimensional forms, both in humans (e.g., Kourtzi & Kanwisher, 2001) and in non-human primates (e.g., Kriegeskorte *et al.*, 2008), further suggesting that common cognitive mechanisms underlie perception of the shapes of two-dimensional visual forms and of three-dimensional manipulable objects.

In summary, research provides evidence for a core system for representing the shapes of movable, manipulable objects. The system endures over human development (Izard & Spelke, 2009) and appears to be culturally universal (Dehaene *et al.*, 2006; Izard *et al.*, 2011b). It represents object shapes over variations in orientation, size, and sense, so as to highlight two fundamental properties of Euclidean geometry, *length* and *angle*. Yet this system falls short of full Euclidean geometry. It fails to apply to the large-scale, navigable layout, as evidenced by children's lack of response to angular relations in a rhombic room or to length relations in a rectangular room (Lee *et al.*, in review). Moreover, it captures Euclidean *distance* and *angle* but not *sense*, and therefore fails to distinguish a form from its mirror image.

The system by which children and adults analyze the shapes of objects so as to recognize them, contrasts markedly from the system by which children and adults analyze the geometric properties of the surface layout so as to maintain or recover their sense of orientation. Representations of visual shapes apply primarily to 2D visual forms and to manipulable, movable objects; representations of the shape of the navigable layout specifically exclude these 2D forms and objects. Moreover, representations of object shapes are highly sensitive to relative length and angle and generalize over changes in distance (and object size) and direction (and object sense relations). Representations of places in the layout show the reverse pattern: high sensitivity to distance and direction and little or no sensitivity to length and angle. Finally, representations of object shape depend primarily on corners and other junctions where objects meet: a drawing of an object is still recognizable when portions of its smooth lines are deleted, but it suffers with the deletions of corners and intersections (Figure 9). Representations of the navigable layout again show the reverse pattern: they are preserved over deletion





**Figure 9.** Adults and children can recognize common objects based on 2D drawings of their shapes alone (left). When contours are deleted from the centers of the lines or curves that indicate object parts with planar or smoothly curved surfaces (center), objects continue to be recognized. In contrast, recognition suffers when the same amount of contour is deleted from regions where 2 or more lines meet at a corner (right; reprinted from Biederman, 1987).

of corners and perturbed by interruption of smooth, continuous surfaces (Figure 7, p. 250). The two systems of geometry found in young children therefore differ in striking ways. The system of formal Euclidean geometry that is most intuitive to adults, in contrast, bridges these differences.

### **Beyond core knowledge**

The contrasting properties of the two core systems of geometry suggest that more powerful and abstract system of geometrical knowledge could arise if the representations from the core systems could be productively combined. If children could systematically combine the geometric properties they extract from large-scale navigable layouts and from small-scale forms, they might overcome the limits on the domains of application of these systems and increase the power of their geometrical analyses. By combining these systems, children might navigate by angle and relative length as well as by direction and absolute distance. Moreover, children might distinguish forms and objects from their mirror images by viewing those forms and objects through the lens of geometry-guided navigation, using real or mental rotation to view objects from changing perspectives.

By productively combining their systems of navigation and visual form analysis, children might also develop conceptions of truly abstract geometrical objects. Consider one such object: a line with unbounded extent and no thickness. Such lines do not exist in representations of navigable layouts, whose geometric representation consist only of extended surfaces at particular distances and directions. Such lines also do not exist in representations of 2D forms, because every visible surface marking has some thickness. Consider, however, the concepts that could emerge when children begin to use arrays of 2D forms as *pictures* or *maps* that depict a 3D surface layout. In a picture of a scene, thin markings (that we call ‘lines’, despite their visible thickness) depict the boundary between one object or surface and another. In the scene itself, however, that boundary extends only in one dimension: it has no thickness. In this sense, there are no visible ‘lines’ in the 3D scene, but only edges where a surface ends. When a child comes to view a marking on a two-dimensional surface as representing an edge in a 3D layout, however, he or she may come to grasp the more abstract geometrical object that is common to these two arrays: a line that extends only in one dimension.

To date, many questions remain concerning the development of children’s understanding of maps, pictures, and the abstract geometrical objects that they use to connect these representations with representations of 3D navigable layouts. I hypothesize that the system of abstract geometrical intuitions with which I began this paper – the system that is constructed by

children and shared by adults in diverse cultures – is constructed by processes that productively combine the two kinds of core geometrical representations found in animals and young children. Visual symbol systems like maps may provide one medium within which these two kinds of representations are productively combined. I end by discussing research that focuses on a different medium that children use to effect this productive combination. In the experiments that I will discuss, children do not use visual symbols to combine representations of places and objects, but a different representational system that is explicitly combinatorial: language.

These experiments return us to the reorientation task, and to the finding that young children reorient in accord with the distances of surfaces but not their colors. In a new series of studies, children's reorientation was tested in a rectangular chamber with three white walls and a fourth wall of a distinctive color. When this environment is large and children are disoriented, they use the large colored wall to distinguish between the two geometrically correct corners (Learmonth *et al.*, 2001), especially when the object is hidden near the colored wall (Shusterman *et al.*, in press), suggesting that the size of the wall draws children's attention to it and engages a process of beacon guidance (Lee & Spelke, 2010). When the environment is small, however, children reorient only by the geometry of the room, confining their search to the two corners with the correct distance and directional properties, (Hermer & Spelke, 1996). Although young children can use wall colors to specify beacons, and wall lengths and directions to specify their own position and heading, they do not combine these sources of information.

Children's behavior changes, however, at the time when they begin to master spatial expressions involving the terms *left* and *right*: about 6 years of age. Interestingly, the development of this ability correlates with the acquisition of spatial language in individual children (Hermer-Vazquez *et al.*, 2001) and it is accelerated by teaching children the terms *left* and *right* (Shusterman & Spelke, 2005). But what role does language play? Does language training serve only to increase children's attention to the colored landmark (as in the studies by Shusterman *et al.*, in press, already described)? Alternatively, does language serve as a more productive medium for combining information about the spatial layout with information about landmark objects?

Recent studies of adult speakers of Nicaraguan Sign Language (NSL) serve to address this question (Pyers, Shusterman, Senghas, Spelke & Emmory, 2010). NSL began to emerge in the 1970s among children attending a new school for the deaf, and it is the primary language of the school's graduates. The language developed consistent grammatical structures, however, only over successive generations of students. The first wave of students converged

on a common language that includes nouns and verbs but lacks many of the grammatical devices of fully developed signed or spoken languages. These 'first-cohort' speakers have no consistent means for expressing or interpreting spatial relationships such as *left of X*. Over the course of a single conversation, they may shift from conveying left/right relations from their own perspective or from the perspective of their conversational partner (Senghas *et al.*, 2004). Later generations of students entered the school after the development of the language was more advanced, and their language is correspondingly richer and more systematic. In particular, 'second-cohort' speakers are more consistent in their use of expressions for left-right relationships, and they communicate these relationships more effectively (Senghas *et al.*, 2004). Except for these language differences, members of different generations are similar: all the members of the first and second cohorts are now adults, and most of them live in the same city. Studies of these two cohorts therefore allow investigators to test whether differences in their language relate to any differences in their performance on non-linguistic spatial tasks.

To address this question, Pyers *et al.* (2010) presented first- and second-cohort NSL speakers with the task of reorienting in a rectangular environment with a single distinctively colored wall. After completing both this task and a second spatial task, participants were asked to describe a variety of spatial arrays, and their signed expressions were analyzed and compared across cohorts. As expected, second-cohort NSL signers showed superior language skills on a number of measures, including two measures of spatial language: they maintained a more consistent coordinate system when using expressions for *left* and *right*, and they were more consistent in their placements, within the signing space, of signs for landmark objects.

The most interesting findings come from comparisons of these adults' performance on the reorientation task. First, although signers in both cohorts confined their search for the hidden object to the two geometrically appropriate locations, those in the second cohort were better able to distinguish between those locations on the basis of the colored wall. Second, across the entire sample, use of the colored wall for reorientation correlated with one aspect of spatial language: the consistency of signing of expressions involving the relations *left* and *right*. Importantly, performance in the reorientation task did not correlate with other differences in language proficiency, and proficiency at left/right spatial language did not correlate with performance on the other spatial task. Thus, these findings do not reflect individual differences in the overall proficiency of language or spatial cognition, but a specific effect of spatial language on performance on the overtly nonverbal, reorientation task.

The NSL speakers in the studies of Pyers *et al.* (2010) all had developed some degree of spatial language. What is navigation like in a human adult with normal nonlinguistic cognitive abilities but no spatial language at all? A suggestive answer to this question comes from a recent case study of an adolescent referred to as IC (Hyde *et al.*, 2011), who communicated with his family by means of an idiosyncratic gestural system, or *homesign* (Goldin-Meadow, 2003). IC had little or no formal education or conventional language, but is he highly intelligent and skilled both at navigation and at numerical reasoning. In one series of studies, IC was asked to describe in gestures a set of images of objects under conditions designed to elicit object names (e.g., monkey in one image, a tree in another), number words (e.g., two monkeys in one image, three monkeys in another), or spatial expressions (e.g., a monkey above a tree in one image and below a tree in the other: examples of these images appear in Figure 10, p. 251). IC spontaneously and readily produced gestures designating kinds of objects and numbers, but he never produced gestures designating the spatial relationships among objects. (The only apparent exception occurred in the case of the relations *on* and *under*, where IC's gestures suggested that he distinguished these images by referring to actions or mechanical relationships rather than spatial relations). Across three testing sessions, and despite numerous hints and attempts at teaching, IC never produced any expressions that distinguished arrays of two objects by their directional (left/right) relationships.

IC was, however, a superb navigator. He traveled around his home city with ease, and was reported to have done so from a very early age. Could IC combine spatial and geometric information so as to locate an object to the left or right of a distinctively colored wall? Our first attempts to address this question used the reorientation task, and they failed decisively: IC reoriented perfectly in every environment in which he was tested, including a circular room with no geometric or non-geometric structure whatsoever! Evidently, our best efforts to create a perfectly symmetrical environment were not good enough to fool IC, who reoriented himself by detecting extremely subtle asymmetries in our testing environment.

Our next attempts therefore tested IC's memory for movable spatial arrays. Under these conditions, IC reliably used the shape of the environmental configuration to specify the location of a hidden object, and he also reliably used the distinctive color of a landmark object as a direct beacon to the hidden object's location, consistent with past research on young children. Nevertheless, IC failed to combine these sources of information reliably. These data provide suggestive evidence that spatial language fosters this combinatorial capacity.

How might spatial expressions such as *left of the blue wall* serve to combine geometric and landmark information automatically and productively?

I suggest that this effect depends on three central properties of all natural languages (Spelke, 2003). First, languages consist in part of a lexicon of words for many kinds of entities, including words for environmental features (*wall*), their properties (*far*, *blue*), and their spatial relationships to other environmental features (*left*, *behind*). Second, languages consist in part of a set of rules for combining these words to form expressions, and those rules depend only on the grammatical properties of the words that they serve to combine, not on their content domains. Although *far* refers to property that the core navigation system can represent whereas *blue* does not, both are adjectives, and so any grammatical expression that includes one could instead include the other. Third, the meanings of the expressions of a language follow from the meanings of its words and the rules for combining them: If one learns a new object term (say, *iPad*) and already knows the meaning of expressions like *the left side of the wall*, one needs no further learning to know the meaning of new expressions such as *the left side of the iPad*.

With these three properties, language could serve as a medium in which information about object properties, and information about the shape of the surrounding layout, could be productively combined. With a cognitive system for representing objects, children can learn terms like *red* and *triangle* by mapping words and expressions to object representations. And with a separate cognitive system for representing distances and directions in the navigable environment, children can learn terms like *far* and *left* by mapping words and expressions to representations of the extended surface layout. The combinatorial machinery of natural language could do the rest, specifying the meanings of expressions that combine these terms, and thereby serving as a medium in which information from distinct cognitive systems can be productively integrated.

Language might, however, improve children's navigation in a different way. Perhaps language does not allow children to combine core representations but to bypass them. When children learn an expression like *left of the blue wall*, they may gain a new means for encoding properties of the environment that frees them from their core systems of geometry. Research on adults with Williams Syndrome, described earlier in this chapter, sheds light on this possibility (Lakusta *et al.*, 2010).

As noted, WS adults appear to lack altogether the core system of geometry for navigation: they show no ability to reorient themselves by representing the distances and directions of the walls of a rectangular room. In contrast, these adults have some spatial language and also some ability to use the distinctive color of a wall to specify the location of a hidden object. If language serves to bypass geometric representations, then these two abilities should be related to one another as they are for Nicaraguan signers:

WS adults with more consistent spatial language should be more consistent in their search to the left or right of a colored wall.

Lakusta, Dessalegn and Landau (2010) tested this prediction and decisively disconfirmed it. WS adults showed no relation between the consistency of their spatial language and the consistency of their reorientation performance in a room with one colored wall (Lakusta *et al.*, 2010). These findings support the hypothesis that language serves to combine core representations. Because adults with Williams Syndrome lack a core representation of layout geometry, their spatial language cannot play this role, however well it develops. Adults with WS likely outperform young children on navigating by a colored wall, because they have learned that they must attend to landmarks in order to maintain a sense of their own location. Like children and many animals, WS adults are able to attend and navigate by local landmarks, including color. Unlike other human adults, however, WS adults lack geometric layout representations and so cannot use language to combine landmarks and productively with geometric representations of the navigable layout.

### **Toward a developmental cognitive neuroscience of education**

The research described in this chapter suggests that our simplest, abstract geometrical intuitions have a complex history. They are rooted, first and foremost, in specialized neural systems that guide navigation and object perception both in animals and in humans from infancy onward. The representations delivered by these systems then are combined by a host of representational devices, including pictures and maps. Perhaps above all, they are combined productively as children master the words and rules of their natural language. Together, all these developments may underlie the universal abilities of adults, and of children from the age of 10 years, to navigate by purely geometric maps, to deduce the unseen position and size of the third angle of a triangle, and to intuit the behavior of points so small they have no size, and of lines that are infinitely thin, perfectly straight, and never end.

Can the insights from this research serve to foster children's education in mathematics? Because formal geometry is not explicitly taught in most elementary mathematics curricula, research linking children's early developing geometrical abilities to their later learning of geometry is only beginning. Even at this early stage, however, research on the cognitive and neural foundations of geometrical reasoning suggest ways that education in geometry might be enhanced for all students, including the youngest ones.

Formal geometry tends to be introduced in contexts that are far removed from the tasks of navigation and visual form analysis in which our geometrical intuitions may originate. The displays on which it focuses are tracings



created by a ruler and compass; the processes that it engages are those of logical reasoning, especially theorem-proving. Many students fail to be engaged by these tasks or appreciate their relevance to all the activities in which geometry is naturally engaged. In contrast, navigation and visual form analysis are tasks that young children enjoy, and that are both challenging and satisfying. Instruction in geometry might be both more enjoyable and more meaningful to students if it were introduced early in the educational system, in these task contexts.

Much of Euclidean geometry could be taught in the context of real or virtual tasks of navigation and form analysis, as in the studies of Shusterman *et al.* (2006) and Izard *et al.* (2011a) with which I began this chapter. Using these tasks, a mathematics curriculum could build upon the geometrical knowledge that young children already possess. Recent research bridging education and cognitive neuroscience suggests fruitful ways to enhance children's literacy by educational programs building on their preexisting representations of language, as the chapters in this volume by Dehaene and Kuhl describe. Instruction in geometry, so necessary for the development of higher, uniquely human cognitive skills, also may be enhanced by building on the foundational systems of geometrical analysis that arise in us as infants. These systems are embodied in distinct and early developing brain systems that have been intensively studied both in humans and in animals; many of the fundamental properties of these brain systems are now understood. Research that uses their findings to craft and test new educational initiatives should be a high priority for investigators in the fields of education and developmental cognitive neuroscience.

## References

- Biederman, I. (1987). Recognition-by-components: A theory of human image understanding. *Psychological Review*, 92(2), 115–147.
- Biederman, I. & Cooper, E.E. (2009). Translational and reflectional priming invariance: A retrospective. *Perception*, 38, 809–825.
- Biederman, I., Yue, X., & Davidoff, J. (2009). Representations of shape in individuals from a culture with minimal exposure to regular, simple artifacts. *Psychological Science*, 20, 1437–1442.
- Cheng, K. (1986). A purely geometric module in the rats' spatial representation. *Cognition*, 23, 149–178.
- Cheng, K., & Newcombe, N.S. (2005). Is there a geometric module for spatial reorientation? Squaring theory and evidence. *Psychonomic Bulletin and Review*, 12, 1–23.
- Cooper, L.A., & Shepard, R.N. (1973). Chronometric studies of the rotation of mental images. In W.G. Chase (Ed.), *Visual Information Processing* (pp. 75–176). New York: Academic Press.

- Dehaene, S., Izard, V., Pica, P., & Spelke, E. (2006). Core knowledge of geometry in an Amazonian indigene group. *Science*, 311, 381-384.
- Doeller, C.F., & Burgess, N. (2008). Distinct error-correcting and incidental learning of location relative to landmarks and boundaries. *Proceedings of the National Academy of Sciences*, 105, 5909-5914.
- Doeller, C.F., King, J.A., & Burgess, N. (2008). Parallel striatal and hippocampal systems for landmarks and boundaries in spatial memory. *Proceedings of the National Academy of Sciences*, 105, 5915-5920.
- Doeller, C. F., Barry, C. & Burgess, N. (2010). Evidence for grid cells in a human memory network, *Nature*, 463, 657-661.
- Gallistel, C.R. (1990). *The Organization of Learning*. Cambridge, M.A.: MIT Press.
- Gibson, E.J. (1969). *Principles of Perceptual Learning and Development*. New York: Appleton-Century-Crofts.
- Goldin-Meadow S. (2003) *The Resilience of Language*. New York: Psychology Press.
- Gouteux, S., & Spelke, E.S. (2001). Children's use of geometry and landmarks to reorient in an open space. *Cognition*, 81, 119-148.
- Grill-Spector, K., Golarai, G., & Gabrieli, J. (2008). Developmental neuroimaging of the human ventral visual cortex. *Trends in Cognitive Science*, 12, 152-162.
- Hermer, L., & Spelke, E.S. (1996). Modularity and development: The case of spatial reorientation. *Cognition*, 61, 195-232.
- Hermer-Vazquez, L., Moffet, A., Munkholm P. (2001). Language, space, and the development of cognitive flexibility in humans: the case of two spatial memory tasks, *Cognition*, 79, 263-299.
- Hermer-Vasquez, L., Spelke, E.S., & Katsnelson, A.S. (1999). Sources of flexibility in human cognition: Dual-task studies of space and language. *Cognitive Psychology*, 39, 3-36.
- Hupbach, A. and Nadel, L. (2005) Reorientation in a rhombic environment: no evidence for an encapsulated geometric module. *Cognitive Development*, 20, 279-302.
- Huttenlocher, J., & Lourenco, S.F. (2007). Coding location in enclosed spaces: is geometry the principle? *Developmental Science*, 10, 741-746.
- Hyde, D.C., Winkler-Rhoades, N., Lee, S.A., Izard, V., Shapiro, K.A., & Spelke, E.S. (2011). Spatial and numerical abilities without a complete natural language. *Neuropsychologia*, 49(5), 924-936.
- Izard, V., Pica, P., Spelke, E.S., & Dehaene, S. (2011a). Flexible intuitions of Euclidean geometry in an Amazonian indigene group. *Proceedings of the National Academy of Sciences*.
- Izard, V., Pica, P., Dehaene, S., Hinchey, D., & Spelke, E. (2011b). Geometry as a universal mental construction. In S. Dehaene & E. M. Brannon (Eds.) *Space, time and number in the brain. Attention & Performance*, Vol. 24. (pp. 319-333). London: Academic Press.
- Izard, V., & Spelke, E. S. (2009). Development of sensitivity to geometry in visual forms. *Human Evolution*, 24, 213-248.
- Kourtzi, Z. & Kanwisher, N. (2001). Representation of perceived object shape by the human lateral occipital complex. *Science*, 293, 1506-1509.
- Kriegeskorte, N., Mur, M., Ruff, D.A., Kiani, R., Bodurka, J., Esteky, H., Tanaka, K., & Bandettini, P.A. (2008). Matching Categorical Object Representations in Inferior Temporal Cortex of Man and Monkey. *Neuron*, 60(6), 1126-1141.
- Lakusta, L., Dessalegn, B. & Landau, B. (2010). Impaired geometric reorientation caused by genetic defect. *Proceedings of the National Academy of Sciences*.
- Learmonth, A.E., Newcombe, N.S., & Huttenlocher, J. (2001). Toddlers' use of metric information and landmarks to reorient. *Journal of Experimental Child Psychology*, 80, 225-244.
- Lee, S.A., Shusterman, A., & Spelke, E.S. (2006). Reorientation and landmark-

- guided search by young children: Evidence for two systems. *Psychological Science*, 17(7), 577–582.
- Lee, S.A. & Spelke, E.S. (2010). A modular geometric mechanism for reorientation in children. *Cognitive Psychology*, 61(2), 152–176.
- Lee, S.A., & Spelke, E.S. (2011). Young children reorient by computing layout geometry, not by matching images of the environment. *Psychonomic Bulletin & Review*, 18(1), 192–198.
- Lever, C., Wills, T., Cacucci, F., Burgess, N., & O'Keefe, J. (2002). Long-term plasticity in hippocampal place-cell representation of environmental geometry. *Nature*, 416, 90–94.
- Lew, A.R., Foster, K.A., & Bremner, J.G. (2006). Disorientation inhibits landmark use in 12–18-month-old infants. *Infant Behavior & Development*, 29, 334–341.
- Lourenco, S., Addy, D., & Huttenlocher, J. (2009). Location representation in enclosed spaces: What types of information afford young children an advantage? *Journal of Experimental Child Psychology*, 104, 313–325.
- Lourenco, S.F., & Huttenlocher, J. (2006). How do young children determine location? Evidence from disorientation tasks. *Cognition*, 100, 511–529.
- Lourenco, S.F., & Huttenlocher, J. (2008). The representation of geometric cues in infancy. *Infancy*, 13, 103–127.
- Moore, D.S., & Johnson, S.P. (2008). Mental rotation in young infants: A sex difference. *Psychological Science*, 19, 1063–1066.
- Newcombe, N.S., Huttenlocher, J., & Learmonth, A.E. (1999). Infants' coding of location in continuous space. *Infant Behavior and Development*, 22, 483–510.
- O'Keefe, J. & Burgess, N. (1996) Geometric determinants of the place fields of hippocampal neurons. *Nature*, 381, 425–428.
- Pearce, J.M., Ward-Robinson, J., Good, M., Fussell, C., & Aydin, A. (2001). Influence of a beacon on spatial learning based on the shape of the test environment. *Journal of Experimental Psychology: Animal Behavior Processes*, 27, 329–344.
- Plato (ca. 380 B.C.). *Meno*: available online at classics.mit.edu
- Pyers, J.E., Shusterman, A., Senghas, A., Spelke, E.S., & Emmorey, K. (2010). Evidence from an emerging sign language reveals that language supports spatial cognition. *Proceedings of the National Academy of Sciences*, 107(27), 12116–12120.
- Quinn, P.C., & Liben, L.S. (2008). A sex difference in mental rotation in young infants. *Psychological Science*, 19, 1067–1070.
- Ratcliff, K.R., & Newcombe, N.S. (2008). Is language necessary for human spatial reorientation? Reconsidering evidence from dual task paradigms. *Cognitive Psychology*, 56, 142–163.
- Reddy, L., & Kanwisher, N. (2006). Coding of visual objects in the ventral stream. *Current Opinion in Neurobiology*, 16, 408–414.
- Riesenhuber, M. & Poggio, T. (2000). Models of object recognition. *Nature Neuroscience*, 3, 1199–1204.
- Schwartz, M., & Day, R.H. (1979). Visual shape perception in early infancy. *Monographs of the Society for Research in Child Development*, 44, 1–63.
- Senghas A, Kita S, Ozyurek A (2004) Children creating core properties of language: Evidence from an emerging sign language in Nicaragua. *Science* 305:1779–1782.
- Shusterman, A.B., Lee, S.A., & Spelke, E.S. (2008). Young children's spontaneous use of geometry in maps. *Developmental Science*. 11, F1–F7.
- Shusterman, A. & Spelke, E. (2005). Language and the development of spatial reasoning. In P. Carruthers, S. Laurence and S. Stich (Eds.), *The Structure of the Innate Mind*. Oxford University Press.
- Shusterman, A., Lee, S.A., & Spelke, E.S. (in press). Cognitive effects of language on human navigation. *Cognition*.

- Siegler, R.S. & Ramani, G.B. (2011). Improving low-income children's number sense. In S. Dehaene & E.M. Brannon (Eds.), *Space, time and number in the brain. Attention & Performance, Vol. 24*. (pp. 343-354). London: Academic Press.
- Slater, A., Mattock, A., Brown, E., & Bremner, J.G. (1991). Form perception at birth: Cohen and Younger (1984) revisited. *Journal of Experimental Child Psychology*, 51, 395-406.
- Smith, L.B. (2009). From fragments to geometric shape: Changes in visual object recognition between 18 and 24 months. *Current Directions in Psychological Science*, 18(5) 290-294.
- Smith, L.B., Jones, S.S., Landau, B., Gershkoff-Stowe, L. & Samuelson, S. (2002). Early noun learning provides on-the-job training for attention. *Psychological Science*, 13, 13-19.
- Solstad, T., Boccara, C. N., Kropff, E., Moser, M., & Moser, E.I. (2008). Representation of geometric borders in the entorhinal cortex. *Science* (322), 1865-1868.
- Spelke, E.S. (2003). Developing knowledge of space: Core systems and new combinations. In S.M. Kosslyn & A. Galaburda (Eds.), *Languages of the Brain*. Cambridge, MA: Harvard Univ. Press.
- Spelke, E.S., Gilmore, C.K., & McCarthy, S. (in press). Kindergarten children's sensitivity to geometry in maps. *Developmental Science*.
- Twyman, A.D., Newcombe, N.S., & Gould, T.J. (2009). Of mice (*mus musculus*) and toddlers (*Homo sapiens*): Evidence of species-general spatial reorientation. *Journal of Comparative Psychology*, 123, 342-345.
- Wang, R.F., Hermer-Vazquez, L., & Spelke, E.S. (1999). Mechanisms of reorientation and object localization by children: A comparison with rats. *Behavioral Neuroscience*, 113, 475-485.
- Wills, T., Cacucci, F., Burgess, N. & O'Keefe, J. (2010). Development of the hippocampal cognitive map in preweanling rats. *Science*, 328, 1573-1576.
- Wystrach, A. & Beugnon, G. (2009). Ants learn geometry and features. *Current Biology*, 19, 61-66.
- Yonas, A., Granrud, C.E., & Pettersen, L. (1985). Infants' sensitivity to relative size information for distance, *Developmental Psychology*, 21, 161-167.

# **PLASTICITY IN LEARNING PATHWAYS: ASSESSMENTS THAT CAPTURE AND FACILITATE LEARNING**

■ KURT W. FISCHER, THEO L. DAWSON, AND MATTHEW SCHNEPPS

Schools have huge transformative effects on people and societies, and simultaneously they fail to educate many children effectively. In most environments, wherever schools have been established, they have had transforming effects on the societies that they exist in. At the same time most schools fail with the large majority of children (Suárez-Orozco & Suárez-Orozco, 2010). If schools effectively educate 25% of the children in a developing country, that's a great advance over educating none of them, and it has a huge effect on the developing economy and infrastructure of that country. But it is still only 25%. In the 21<sup>st</sup> century, we are trying to educate everybody. One of the main problems with schools is easily observed in most classrooms. Simply ask most children to complete this sentence: 'School is what? [Fill in the blank]'. The most common response is, 'School is boring'. This happens even in good schools! In Massachusetts we have some of the best schools in the US, and yet most of our children still say school is boring. School does not have to be boring. Students have a natural curiosity and we owe it to them to try to make schools interesting so that they can learn effectively. A large part of the reason that schools are boring lies in the process of asking students to memorize knowledge without understanding it. A related problem is the failure to show children how what they learn is relevant for their lives. Instead of just memorizing facts, students and teachers in schools can actually think about and analyze tasks, problems, and issues. Also, the focus on standardised tests exacerbates the problems with schools. We will suggest ways around these difficulties so that schools can be more interesting and relevant.

John Dewey (1933, 1963) was a great educational philosopher, with a lot of wise things to say. Dewey said, among other things, that if you want to be a good teacher, you should not teach reading and writing, but teach students. That's a good lesson for us to take, focusing on what students are actually doing in their classrooms and their lives and how they are learning and developing as individuals. We should not treat students as if they are all the same. Students take many different pathways to learning. Most of us that teach in classrooms experience this every time we step into the class-

room. Students learn in different ways, they are interested in different things, and it is a major challenge to engage all of the students in any classroom. I like to think of the tower of Babel as a metaphor for these differences. In that Biblical story God made people speak different languages. He likewise made people importantly different from each other in goals, cultures, interests, and talents. Languages and cultures represent important differences among us, but the differences are much more pervasive than language and culture, extending to what we care about and how we learn.

All these differences pose a huge problem for educators, who are stuck with an outdated model of learning in schools. The traditional way of teaching is what I call the ‘Holy Book Approach’: Here is the sacred text, or the established curriculum, which is what everyone has to learn. There is one way to learn this curriculum well – the traditional way, usually repetition and recitation, which is memorizing the sacred text. Many students are lost to education if they are allowed to learn only according to the Holy Book Approach.

### **Universal scale for learning and at the same time different ways of learning**

People learn differently, but at the same time the processes through which they learn have many similarities. Through extensive research on cognitive development and learning we have discovered a general scale that captures the way learning occurs in any domain or skill, and we can use it to measure learning in classrooms (Fischer, 1980, Fischer & Bidell, 2006; Stein, Dawson, & Fischer, 2010). One of the strengths of this universal scale is that it provides a ruler for analyzing learning differences.

In most of cognitive science (except for psychophysics) measurement scales are treated as arbitrarily created, in the way that the scale for IQ is created by fiat rather than through empirical evidence about the natural scale behind human learning. Psychology and cognitive science have been creating arbitrary scales for a long time, launched by the intelligence testing movement early in the 20<sup>th</sup> century. Psychometricians create arbitrary scales, forcing distributions based on arbitrary assumptions about scaling. (For an alternative, see van Geert & van Dijk, 2002; van Geert & Steenbeek, 2005). Instead we should be examining the natural scale that children show in learning and development.

Fortunately, the evidence is clear-cut for the existence of this universal scale for learning and development. Children and adults move through a series of reorganizations of their abilities as they learn and develop and even as they perform on standardized tests. This scale provides a powerful rubric

for assessing learning in classrooms and other learning environments (Fischer & Bidell, 2006; Stein, Dawson, & Fischer, 2010).

At its simplest, the key criterion for marking the points on the scale is the presence of discontinuities in development and learning along with gaps in test performance. Figure 1 shows an example of one of the discontinuities. We all know about this one – the emergence of language around two years of age. This graph is for one of many children, Tomas, studied by Ruhland and van Geert (1998) in the Netherlands. Tomas showed an abrupt jump in the use of personal pronouns at two years of age. The more specific the skill examined, according to research over the years, the more likely learning will show a rapid jump in performance. Research shows a series of discontinuities or reorganisations throughout childhood and into adulthood, with some of the findings being surprising.

For example, one discovery is that people continue to develop new abilities during the decade of the 20s. One of the domains with the best evidence for new abilities during this age period is what John Dewey (1933) called *reflective judgment*, asking about the basis for knowledge, using evidence and argument to determine what is true. Karen Kitchener and Patricia King

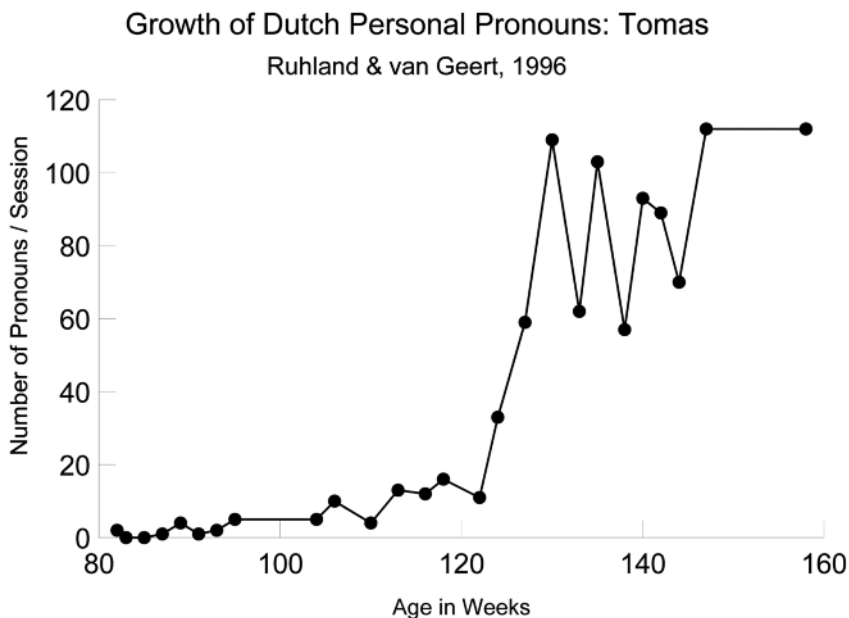


Figure 1. Spurt in vocabulary growth in a Dutch boy.



created a series of dilemmas for measuring reflective judgement based on the Dewey model, including a dilemma about chemical additives to food (Kitchener, King, Wood, & Davison, 1989; Kitchener, Lynch, Fischer, & Wood, 1993). The question is, 'Are chemical additives to food good for you or bad for you?' Chemical additives to bacon, for example, keep it from spoiling, which keeps people from getting sick. On the other hand, there is evidence that the chemical additives can in the long run cause cancer or other illnesses. The question thus becomes 'Are chemical additives to food good because they prevent illness, or are they bad because they cause cancer?' In the reflective judgment coding system the interviewee can take any position – that the additives are good because they prevent illness, that they are bad because they cause cancer, or that both positions can be true. The quality and complexity of the person's argument determine his or her level of reasoning.

In development, the levels of reflective judgment start from a conception of knowledge as absolute – either chemical additives are good for you, or they are bad for you. Then a person's skills move to a kind of relative knowledge, such as an adolescent saying, 'Well, it just depends; it's your bias'. Eventually, in the later stages people come to be able to create complex reasoning where they make specific arguments, talk about evidence, and generally do the kind of reflective judgement reasoning that Dewey was describing. The result is a seven-level learning sequence moving through a series of types of reflective judgment.

Here is an example of a level six argument: Although a person may change what s/he thinks is true, s/he can make strong and justified conclusions based on argument and evidence. Here is an elaborated answer, the gist of which is: 'It can be either way':

There is good evidence to say that some chemical additives help protect us from things like food poisoning. Evidence is open to interpretation and may change with time. Therefore, we can never know for sure. However, just like scientists, we must evaluate the evidence about a given additive. Then we must synthesize the evidence with other things we know about the world into a point of view. The conclusion is a reasonable view of the issue. Differences in point of view about this issue, which come from different ways of evaluating the evidence, can be judged as more or less reasonable.

We interviewed students from local high schools and the University of Denver between 14 and 28 years of age about reflective judgment, matched approximately for intelligence. In one condition (optimal level in Figure 2) we provided contextual support for a more complex response, showing each student a prototype of a good argument (a method called priming). In the

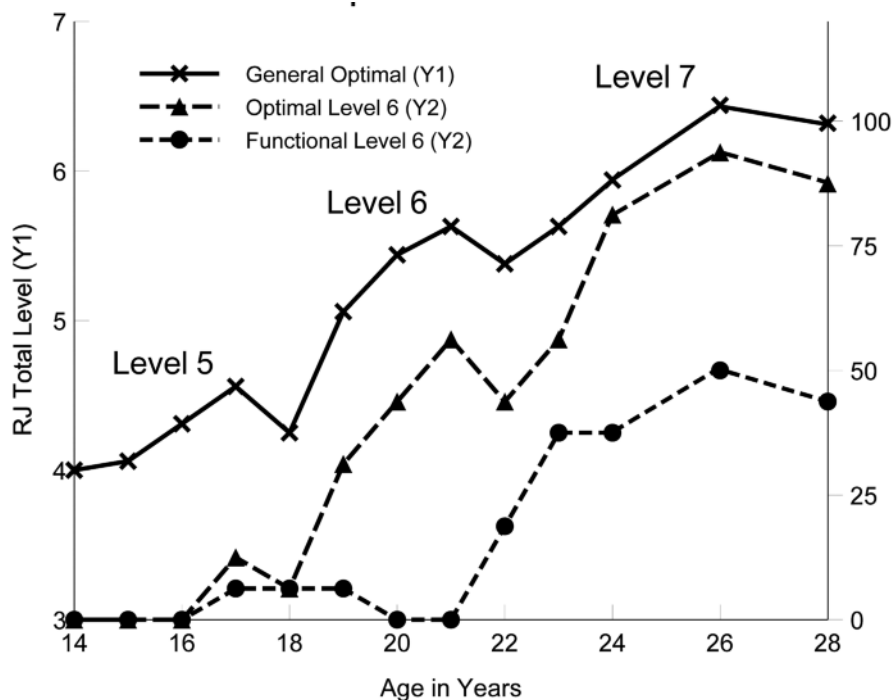


Figure 2. Development of reflective judgment: level 6 explanations.

other condition (functional level in Figure 2) we presented the dilemma without any contextual support. Prior research shows that people can often function at a higher level for several minutes when such contextual support is provided, but the higher level response falls back to baseline after several minutes (Fischer & Bidell, 2006). Thus support produces a higher level response, but the effect is transient.

This is an example from our study of what happens with no support. A student is asked about the chemicals dilemma, and s/he gives an answer and explanation. With age students show slow improvement over many years, and most of them do not understand the complex stage six argument until they are into their 20s. Even then most of them do not score above 50% at stage six, as shown in Figure 2.

When we offer support (by priming a more complex response) we see a different pattern, as shown in the higher dotted line: Students show a series of jumps in performance across the age range of the experiment, as evident

in Figure 2. Typically, assessments of supported performance show such discontinuities, such as the jump to near perfect performance for stage six at age 26. An earlier jump is also evident at age 20, but the level reached is only 50% correct. Students required about five more years after their initial creation of stage six answers to reach nearly 100%. In other words, for complex reasoning, learning takes a while. It is a slow process, requiring a long time to come together consistently. In schools we should know that learning of complex material is often slow, but we do often do not act that way.

In Figure 2 the overall score for the whole assessment shows a jump for stage five, a jump for stage six, and a jump for stage seven. Note that these performances are not fixed at a 'stage' but instead vary across 'levels'. One of the characteristics of learning and performance is that skills move around. People do not operate at one level consistently. A given person in a matter of minutes can move up and down on the developmental scale in a dynamic process. Our research is intended to articulate principles for this variation.

### **Relations of Cognitive and Brain Development**

The focus of this paper is primarily on learning environments, but also relevant is the model we have built of how brain activity patterns change systematically with cognitive development. Most of the relevant research assesses the electroencephalogram (EEG) although studies of other brain imaging tools often suggest similar cycles (Fischer & Rose, 1994; Fischer, 2006; Fischer, 2008). In the EEG one can look, among other things, at the energy in the waves. Figure 3 shows growth curves for the alpha band of the EEG for relative energy in the occipital area of the cortex (Matousek & Petersén, 1973). The similarity with the growth patterns for reflective judgment are striking, with spurts and plateaux correlating well with the ages of spurts and plateaux in cognitive developmental research. Here I've transformed the data into change scores (differences from one year to the next) to highlight the spurts.

These are the kinds of growth curves that we see repeatedly, marked by spurts and plateaux, which correlate with the emergence of new cognitive capacities. Michelle Lampl and her colleagues have shown that spurts and plateaux are the normal pattern even for physical growth (Lampl, Beldhuis, & Johnson, 1992; Lampl & Jeanty, 2003). The straight-line growth curves that paediatricians display to show children's growth do not capture the way individual growth actually occurs, but instead are normative patterns that result from averaging over many children.

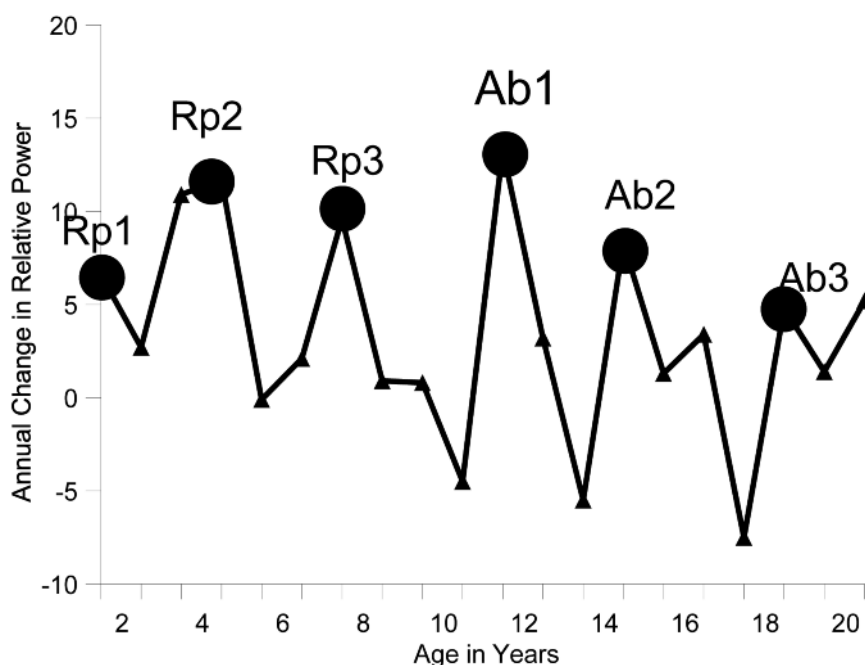


Figure 3. Growth of relative energy in the EEG.

### Combining content and complexity in developmental analysis

In cognitive development and learning, people move through different learning sequences as they master thinking about a specific content or topic. Different people learn along different pathways, based on their goals, interests, and experience. That is why schools and teachers need to deal with the large differences in how students learn. With the methods that we have devised we first analyze content and complexity separately, and then we combine them to characterize different learning sequences.

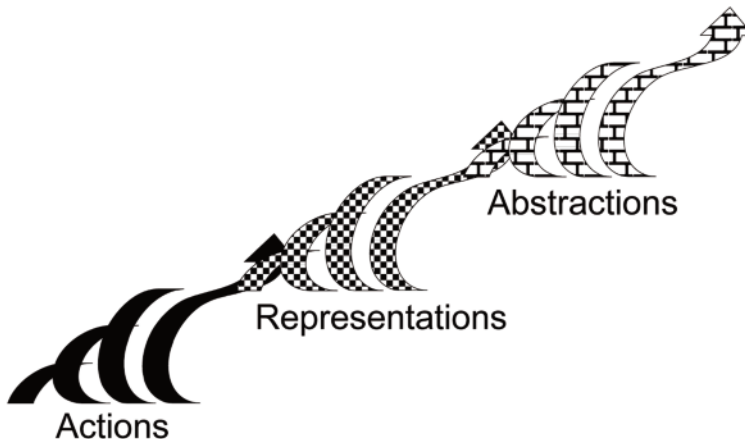
Content themes are combined with complexity to produce learning sequences. For example, categories of arguments from students' interviews include the following examples: truth is uncertain, proof is required, or people can show bias. Often these categories are connected with specific levels of complexity. Sometimes the same categories occur across multiple levels. Sometimes they are specific to one or two levels.

The complexity scale consists of ten levels of complexity, with four levels in each of a series of three cycles (actions, representations, and abstractions)

as shown in Figure 4. The scale is built strongly on prior work by Piaget (1983), James Mark Baldwin (1894), Vygotsky (1978), and Werner (1957), as well as other developmental scholars. Note that in the complexity scale,  $3 \times 4 = 10$ . The final level of each cycle – actions, for example – leads to the emergence of representations, so there is an overlap of one level from one cycle to the next.

Figure 5 (see p. 252) gives an example of how these cycles appear not only in development but also in test performance. A sample of 747 cases of moral reasoning was analyzed according to a system related to Kohlberg's analysis of moral judgment based on his standard moral dilemmas (Colby & Kohlberg, 1987). The Kohlberg system had some inaccuracies in it, especially for the levels of moral reasoning in young children (not surprising because his focus was on adolescents and adults). We have been able to correct these errors and improve the scale based on empirical evidence for moral development at early ages (Dawson & Gabrielian, 2003; Dawson-Tunik, Commons, Wilson, & Fischer, 2005).

The graph is based on Rasch (1980) analysis of the scaling of performances about moral reasoning. Note what look like jumps in performance – showing a clustering of scores at points that represent the core developmental score for each level on the Rasch scale. These findings illustrate that there is a common scale underlying learning and development, even while different children often learn in distinct ways, moving along different learning pathways.



**Figure 4.** A scale of 10 levels of skill complexity marked by reorganization of behavior & neural networks.

## Different pathways for learning to read and for dyslexics

Research on learning to read shows that young children learning English learn along three distinct pathways. They do not all develop along one common pathway! In addition, research with dyslexics (who have difficulties learning to read English) demonstrates that their visual systems have different properties from 'normal' readers, apparently indicating that the eye and the visual field for dyslexics are structured differently from the standard analysis of fovea and periphery.

The standard model of early reading development, especially for English, starts with the concept that a young reader needs to coordinate three domains: the meaning of words, the sounds of words, and the visual representation of letters. In the standard model of reading the child has to integrate these three domains. In general, developmental sequences take the form of a web, with different strands of the web marking different domains that can be integrated. Children are not at the same level in each domain but instead they show much variability, which can be captured by the model of a web of skills moving along independent strands (Fischer & Bidell, 2006).

The standard model for early reading posits full integration across domains early in the reading process, shown in Figure 6a (LaBerge & Samuels, 1974). In the model the three domains of letter identification, word defi-

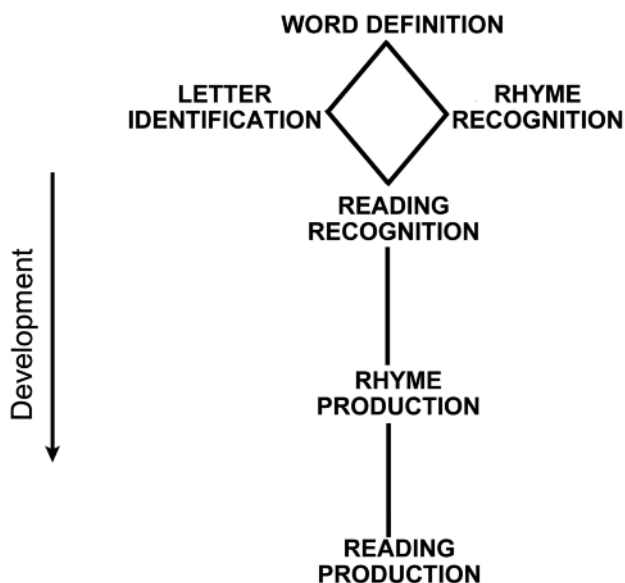


Figure 6a. Modal developmental pathway for learning to read: integration of read & rhyme.

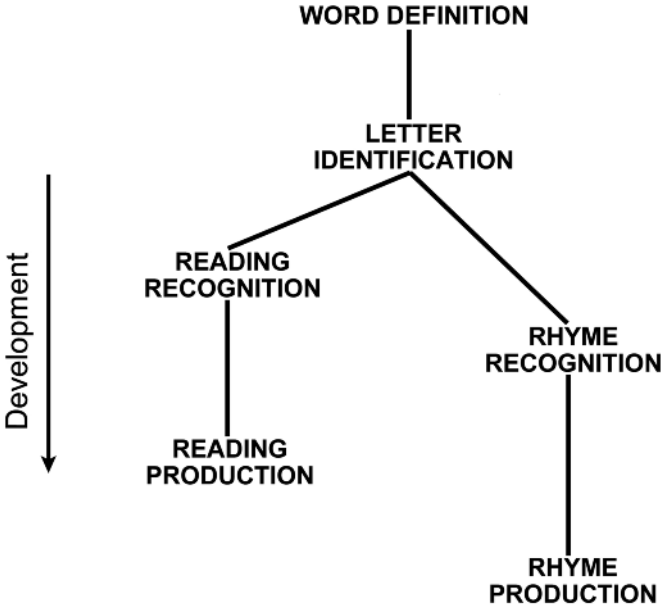


Figure 6b. Second developmental pathway: read & rhyme independent.

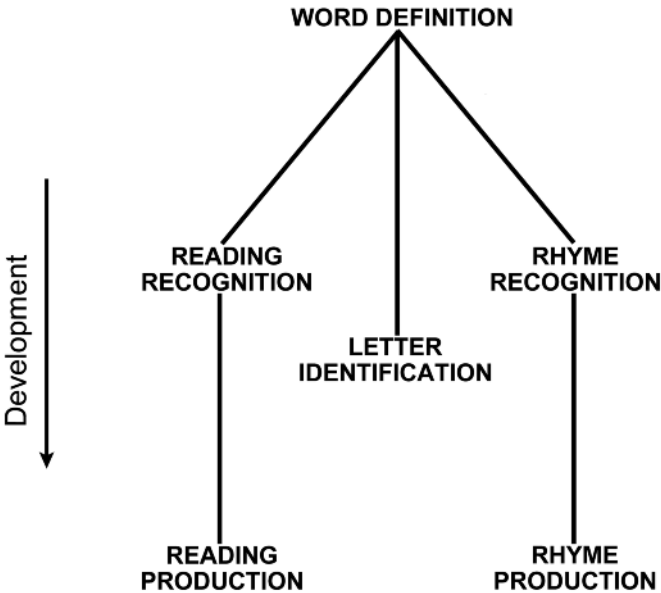


Figure 6c. Third developmental pathway: read, rhyme, and letter identification independent.



nition, and rhyme recognition are coordinated with each other in reading early words. Each item in the graph represents a test of a domain of reading skill, with a total of six tests: word definition, letter identification, rhyme recognition, reading recognition, rhyme production, and reading production. The names of the tasks capture well what each child was asked to perform. Each student needed to know what a word means, how to identify the letters, how to relate the letters to sounds, and how to match sounds with rhyme. According to the model in Figure 6a, a young reader integrates the three domains (top of sequence), which creates a simple linear sequence from reading recognition to rhyme production to reading production. Based on a statistical analysis of these six tests with 16 different words, the model was strongly confirmed.

However, we were not happy with the model or the statistical results. Of the 80 children we tested, about 20 of them did not fit the model well based on the patterns that they showed across words. We performed a pattern analysis for each of those children and found powerful support for two additional patterns of learning to read. Because we had 16 words for the six tests we could perform profile analysis for each individual child. The evidence was clear: There were two other pathways, with every child showing one of three pathways for the sixteen words.

Figure 6b shows the second pathway, in which reading and rhyming were independent of each other. Still more complex was the third pathway, where reading, rhyming, and letter identification developed independently of each other, forming separate strands in the learning web for early reading (Figure 6c). It is no surprise that these children read least skilfully.

The conclusion is that children learning to read English words develop along three different pathways. This is but one example of how different children develop in different ways, even when they are all being taught based on the standard model of learning to read. Educators need to attend to these differences. Children show many differences in the ways they learn and in the ways they are motivated to learn.

### **Different visual systems in dyslexic readers**

Dyslexia is often conceived as a simple defect in brain organization. However, research with dyslexics suggests that their brains are not defective but instead are organized differently from ‘normal’ readers – in particular, their visual systems are biased toward integrating information across wide areas of the visual field. This organization is distinct from the normative description given routinely about the nature of the eye, the retina, and the neural organization of vision.

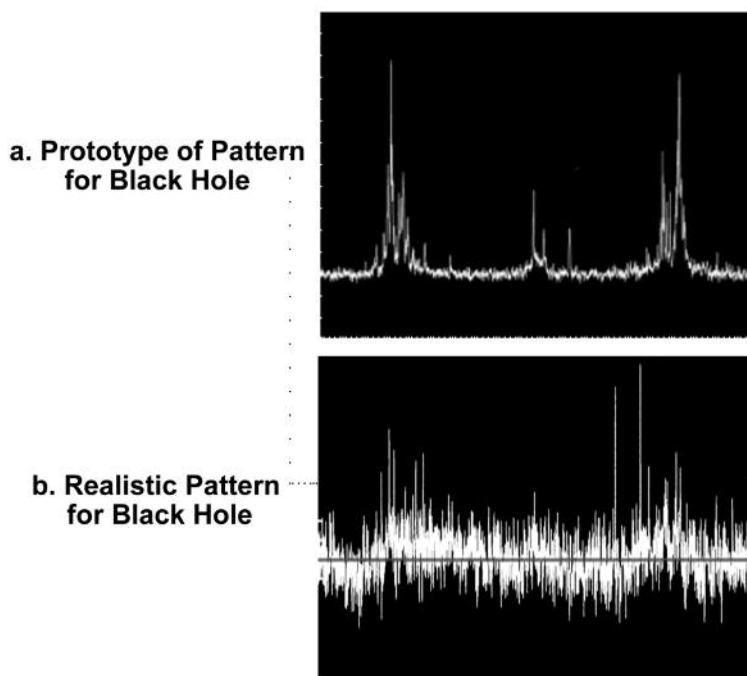
Our dyslexia research project is led by Matthew Schneps, co-director of the Harvard Smithsonian Center for Astrophysics group on Science Education. One part of the project focused on dyslexic astrophysicists. The National Science Foundation in the US has recently realized not only that learning disabilities are important but that a large number of scientists have been characterized as having disabilities such as dyslexia, attention deficit disorder, and Asperger's syndrome. More generally for science education, educators and researchers are coming to realize that children learn in different ways and that different models are needed to capture the variations in how people learn.

Our research project demonstrates a different visual system in dyslexics and establishes that many visually talented astrophysicists have dyslexia and apparently have a different visual system from the 'normal' one. For example, research has shown that dyslexics commonly have a visual talent for quickly detecting visual contradictions in graphic art, such as Escher diagrams. They detect the contradictions 50% faster than normal readers. The very beginning of this research actually started with Geiger and Lettvin (1987) and was replicated by von Károlyi, Winner, Gray, & Sherman (2003). Dyslexics are also overrepresented in art schools, which enrol twice as many dyslexics as the normal population.

An important skill in astrophysics is integrating information across wide areas of the visual field, as in star fields. We tested the astrophysicists on tasks based on real skills that are important in astrophysics. A key skill is detecting black holes by using wave patterns. Figure 7a shows a prototype for detecting a black hole, but detection with real waves is much harder because actual wave patterns are more likely to look like Figure 7b. Our testing showed that the dyslexic astrophysicists were much better at detecting black holes than the non-dyslexic ones. In fact, the best astrophysicist at detecting them has sensitivity in her periphery that is close to what we expect in the fovea for most people.

This unusual visual skill has an advantage for detecting black holes in these kinds of waveforms but it has a disadvantage for reading, because a reader needs to focus text in the fovea, mostly, and make fine discriminations (such as p versus d versus q versus b). Also when a person is highly sensitive in the periphery of the visual field, s/he is distractible – frequently distracted by events in the periphery. Peripheral events demand an obligatory eye movement toward the event. As a result, dyslexic children and dyslexic scientists are presumably much more distractible.

Our goal is to move towards an education system that honors not only people who see the trees in the forest but also people who see the forest in



**Figure 7a-b.** Prototype for black hole versus realistic pattern.

the black hole wave patterns. We need education that honors these differences instead of stigmatizing dyslexics as disabled. We need to stop talking about disabilities and instead talk about differences in patterns of abilities, including strengths as well as weaknesses.

### **Tools for assessing learning in educational settings (not with high-stakes tests)**

We now have the tools to create assessments for learning that make it possible to examine how it happens in the classroom – using, for example, dialogue among students and arguments or essays that students produce. In this way we can use actual learning activities to assess how students learn in environments such as classrooms or videogames.

Today tests are used mostly for sorting students, not improving their learning. A college or university can decide who they will accept based on standardized tests. With the new tools based on the skill scale, we can ex-

amine learning in the actual learning environments. For these assessments, we need five to seven items to produce reliable results comparable to the current high-stakes standardized tests. However, the new assessments add the feature that they examine learning as it occurs in the classroom or other learning environment – where the action is.

In this paper we will focus on computer-based assessment because it makes assessment inexpensive. We are creating a series of assessments that we call DiscoTests™, as in discourse tests. With the first versions of these tests students can enter text into a computer or speak to a computer. For example, here is a standard test item that a lot of science educators use. Figure 8 shows a balance beam with vinegar and baking soda on both sides. On one side they are separated, while on the other they are combined so that they produce a gas inside the container. The question then is, when that gas is produced, will the balance stay balanced or will one side move up or down?

Students give many answers, which we can code rigorously to analyse learning sequences. We can then use the sequences to create tools to help students move more effectively through their learning pathways. The figure



### Multiple Choice Options

What will happen to the pan with the fizzing baking soda?

- It will move up.
- It will not move.
- It will move down.
- It will first move up and then down.
- There is not enough information to answer the question.

### Student's Spontaneous Answer.

What will happen to the pan with the fizzing baking soda?

"The pan with the baking soda inside the jar will move up because when vinegar and baking soda are mixed together they make a gas that is lighter than air. So it goes up like a birthday balloon."

Figure 8. Vinegar and baking soda task.

shows both traditional multiple-choice items and a format where the student can produce his or her own answer. For example, one student said, 'The pan with the baking soda inside the jar will move up because when vinegar and baking soda are mixed together they make a gas that's lighter than air, so it goes up like a birthday balloon'. That answer is incorrect, but it shows lots of reasoning, interesting reasoning, reasoning that can be used to assess how students are thinking about the task and moving through a learning sequence.

With this kind of assessment we can address many questions. What concepts are the students working with? How do they understand the concepts? What are their lines of reasoning? How well do they explain their thinking? In addition, we can use the tests to guide the student's learning. For example, a student can answer a number of items, and then we can show them what kind of learning pattern they are showing, based on the analysis we have of learning sequences in this domain, and we can suggest to them activities that will move their learning forward.

With our methods, the first phase of research in any domain is to collect a large quantity of data from a wide range of students, first to get a description of what the common learning sequences are and then to guide students to improve their learning. For example, from the data base we can provide students with feedback into the learning process. With these kinds of assessments it is easy to provide this feedback, based on the data base in the content domain and the rubrics and learning sequences that come from those data. This is a major advantage of working with assessments based on what students actually do in the classroom.

Here is another example of a DiscoTest. We ask students questions about the energy in a bouncing ball. There are many difficulties for students in thinking about the nature of energy. For example, most physics curricula actually expect students to understand, around 9<sup>th</sup> grade, conservation of energy. From talking to physics teachers and looking at students' answers to questions about conservation of energy, it is clear that there is a mismatch. Learning sequences indicate that most 9<sup>th</sup> graders are not capable of using concepts of conservation of energy. The complex understanding requires a more sophisticated kind of thinking that they will not develop for several years.

Still we can ask questions about energy and characterize learning sequences and the effectiveness of one kind of learning support versus another. What is happening to the energy of a ball as it falls to the floor? One of the answers was: 'As it falls, some of the energy is released'. A next question is 'What is happening to the energy of a ball as it hits the floor?' A student says, 'Some of the energy is transferred to the floor and the other energy is staying

with the ball as it rebounds upwards'. Next question: 'What's happening to the energy of the ball right after it hits the floor?' Answer: 'Good question! Some of the energy remains with the ball. Does it move the ball? I don't know'. So these are the kinds of answers we can get from talking to students or from asking them to answer questions on the computer. And they are the same kinds of questions that teachers and students talk about as they are seeking to understand energy in a bouncing ball.

### **Conclusion: a new kind of assessment based on cognitive science**

In conclusion we have discovered a common scale for development and learning that makes it possible to assess students in their actual learning environments, such as classrooms. It is particularly easy and inexpensive if students can answer questions on a computer (writing or speaking). The scale was originally based on analyses of discontinuities in learning patterns with age, and eventually research showed that the same discontinuities appear as clusters and gaps in Rasch analysis of test performance.

With this set of tools based on a common scale and coding of content categories, we analyse diverse learning sequences, uncovering common sequences in school domains, such as learning to read and learning about energy concepts in physics. This toolkit can be used in any domain that students learn about. For example, we are working now with a school that teaches students about cultural history, and we are able to analyse learning sequences in understanding cultural differences and commonalities. Eventually we aim to create DiscoTests for at least a dozen common learning domains, making tools for teachers and students to create a feedback process where with computer facilitation they can receive feedback on what they are saying and understanding and how their arguments and explanations connect to their goals for their own learning. With these new assessment tools we will help students and teachers go shape their own learning.

### **References**

- Baldwin, J.M. (1894). *Mental development in the child and the race*. New York: MacMillan.
- Dawson, T.L., & Gabrielian, S. (2003). Developing conceptions of authority and contract across the lifespan: Two perspectives. *Developmental Review* 23, 162-218.
- Dawson-Tunik, T.L., Commons, M., Wilson, M., & Fischer, K.W. (2005). The shape of development. *European Journal of Developmental Psychology* 2, 163-195.
- Dewey, J. (1933). *How we think: A restatement of the relation of reflective thinking to the educative process*. Lexington, MA: Heath.
- Dewey, J. (1963). *Experience and education*. New York: Macmillan.
- Fischer, K.W. (1980). A theory of cognitive development: The control and construc-

- tion of hierarchies of skills. *Psychological Review* 87, 477-531.
- Fischer, K.W. (1987). Relations between brain and cognitive development. *Child Development* 3, 58, 623-632.
- Fischer, K.W. (2008). Dynamic cycles of cognitive and brain development: Measuring growth in mind, brain, and education. In A.M. Battro, K.W. Fischer & P. Léna (Eds.), *The educated brain* (pp. 127-150). Cambridge U.K.: Cambridge University Press.
- Fischer, K.W., & Bidell, T.R. (2006). Dynamic development of action and thought. In W. Damon & R.M. Lerner (Eds.), *Theoretical models of human development. Handbook of child psychology* (6th ed., Vol. 1, pp. 313-399). New York: Wiley.
- Fischer, K.W., & Rose, S.P. (1994). Dynamic development of coordination of components in brain and behavior: A framework for theory and research. In G. Dawson & K.W. Fischer (Eds.), *Human behavior and the developing brain* (pp. 3-66). New York: Guilford Press.
- Geiger, G., & Lettvin, J.Y. (1987). Peripheral vision in persons with dyslexia. *New England Journal of Medicine*, 316, 1238-1243.
- Kitchener, K.S., King, P.M., Wood, P.K., & Davison, M.L. (1989). Sequentiality and consistency in the development of reflective judgment: A six-year longitudinal study. *Journal of Applied Developmental Psychology* 10, 73-95.
- Kitchener, K.S., Lynch, C.L., Fischer, K.W., & Wood, P.K. (1993). Developmental range of reflective judgment: The effect of contextual support and practice on developmental stage. *Developmental Psychology* 29, 893-906.
- LaBerge, D., & Samuels, S.J. (1974). Toward a theory of automatic information processing in reading. *Cognitive Psychology* 6, 293-323.
- Matousek, M., & Petersén, I. (1973). Frequency analysis of the EEG in normal children and adolescents. In P. Kellaway & I. Petersén (Eds.), *Automation of clinical electroencephalography* (pp. 75-102). New York: Raven Press.
- OECD (2012). *Talking global: Learning to read and speak the world*. Paris: Organization of Economic Cooperation and Development.
- Piaget, J. (1983). Piaget's theory. In W. Kessen (Ed.), *History, theory, and methods* (Vol. 1, pp. 103-126). New York: Wiley.
- Rasch, G. (1980). *Probabilistic model for some intelligence and attainment tests*. Chicago: University of Chicago Press.
- Ruhland, R., & van Geert, P. (1998). Jumping into syntax: Transitions in the development of closed class words. *British Journal of Developmental Psychology* 16 (Pt 1), 65-95.
- Schnepps, M.H., Rose, L.T., & Fischer, K.W. (2007). Visual learning and the brain: Implications for dyslexia. *Mind, Brain, and Education*, 1(3), 128-139.
- Stein, Z., Dawson, T., & Fischer, K.W. (2010). Redesigning testing: Operationalizing the new science of learning. In M.S. Khine & I.M. Saleh (Eds.), *New science of learning: Cognition, computers, and collaboration in education* (pp. 207-224). New York: Springer.
- Suárez-Orozco, C., Suárez-Orozco, M., & Todorova, I. (2010). *Learning a new land: Immigrant students in American Society*. Cambridge MA: Harvard University Press.
- van Geert, P., & Steenbeek, H. (2005). Explaining after by before: Basic aspects of a dynamic systems approach to the study of development. *Developmental Review* 25, 408-442.
- van Geert, P., & van Dijk, M. (2002). Focus on variability: New tools to study intra-individual variability in developmental data. *Infant Behavior & Development*, 25(4), 340-374.
- von Károlyi, C., Winner, E., Gray, W., & Sherman, G.F. (2003). Dyslexia linked to talent: Global visual-spatial ability. *Brain & Language* 85, 427-431.



- Vygotsky, L. (1978). *Mind in society: The development of higher psychological processes* (M. Cole, V. John-Steiner, S. Scribner & E. Souberman, Trans.). Cambridge MA: Harvard University Press.
- Werner, H. (1957). The concept of development from a comparative and organismic point of view. In D.B. Harris (Ed.), *The concept of development* Minneapolis: University of Minnesota Press.

## ■ GENETICS AND LEARNING

# FRAGILE X SYNDROME: FROM NEUROPLASTICITY TO NEW HOPE

■ MARK F. BEAR

## Introduction

We have entered the era of ‘molecular medicine’ in which it is anticipated that the knowledge of the human genome will reveal causes and treatments for mental illnesses. This process begins with careful clinical identification of patients who can be distinguished by a common set of phenotypic traits, thus defining a syndrome. Molecular genetic studies are then undertaken to test the hypothesis that the syndrome has a shared genetic cause. In the event that disruption of a defined region of the genome causes the disease (a ‘highly penetrant’ mutation in the language of geneticists), then an animal model (usually a mouse) is generated that carries the same genetic disruption. Although the effects of the genetic lesion may (and often do) manifest differently at the behavioral level in animals and humans due to differences in the complexity of the brains, disruptions in elementary neuronal functions are likely to be shared. Understanding this neuronal pathophysiology can lead to identification and validation of potential therapeutic targets. Target discovery drives chemistry to develop molecules that can engage the target and satisfy the pharmacodynamic and pharmacokinetic requirements of a drug. If they can be shown to be safe, drug candidates may then advance to human clinical trials and if successful, become new medicines.

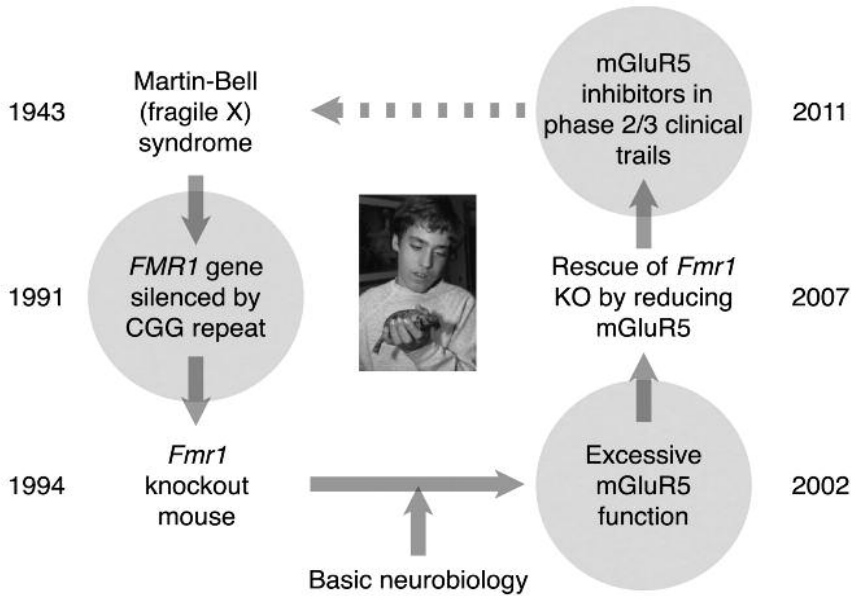
For most major psychiatric disorders, unfortunately, we are still far from fulfilling this promise of molecular medicine. Major disorders such as schizophrenia and bipolar disorder are, despite their simple labels, highly heterogeneous both in presentation and in genetic origin. Disease progression and outcome are also affected by environmental influences that are difficult to study or reproduce in animal models. This daunting phenotypic and etiologic complexity has slowed progress towards developing new therapies.

However, there is a strong sense of optimism that the possibility of substantial progress may soon be realized for autism spectrum disorder (ASD) and associated intellectual disability (ID). First, the genes have been discovered for a number of syndromic disorders that have as prominent features ASD and ID. Second, these gene mutations have been reproduced in animal models that allow detailed examination of the underlying brain

pathophysiology. Third, animal research has converged on altered synaptic function as the likely basis for impaired cognition and possibly ASD. Fourth, insights gained on how synapses function differently in the face of these mutations have suggested novel therapeutic interventions that have been validated in preclinical models and have shown promise in preliminary human clinical trials. Fifth, the fact that ASD and ID can be diagnosed in early childhood maximizes the potential benefit of therapy because it can be started at a time when the brain is most plastic. Finally, animal studies using gene reactivation or pharmacological interventions have suggested that substantial improvements can be seen even when treatments are begun in adulthood.

There have been exciting recent developments in several genetic syndromes associated with ASD and ID, including tuberous sclerosis complex (TSC), neurofibromatosis type 1 (NF1), Rett syndrome, and Down Syndrome. Here I will focus on fragile X syndrome (FXS) where we perhaps are closest to fulfilling the promise of molecular medicine in a psychiatric disorder (Figure 1). FXS was originally called Martin-Bell syndrome, named for the clinicians who recognized it (Martin and Bell, 1943). Features of the syndrome include ID, ASD, hyperactivity and attention deficit, seizures during childhood, and physical differences including a long face, protruding ears, flexible joints, and in males, enlarged testes. Subsequently the disorder was found to associate with an unusual constriction on the X chromosome (Lubs, 1969) and this led researchers to discover the affected gene in 1991 (Verkerk *et al.*, 1991). In FXS, the *FMR1* gene is silenced and the protein product, called FMRP, is not produced. FMRP is an mRNA binding protein that is highly expressed in neurons throughout the brain.

Shortly after the discovery of the gene, a mouse model of the disease was created (Dutch Belgian Fragile X Consortium *et al.*, 1994). The *Fmr1* knockout (KO) mouse has been extensively characterized by neurobiologists motivated not only by an interest in the disease, but also in role of the FMRP protein in synaptic plasticity. Indeed, it was work on synaptic plasticity that led to the discovery of a therapeutic approach that is now in human clinical trials. Here I will briefly trace the history of the neurobiological insights that contributed to these exciting developments. This story teaches the unexpected rewards of fundamental brain research, the importance of sharing data and ideas, and that disease-altering treatments for developmental brain disorders are not only feasible, they are close at hand.



**Figure 1.** Fulfilling the promise of molecular medicine in FXS. Martin and Bell described in 1943 a group of patients characterized by a common set of features that included intellectual disability and social withdrawal. The causative gene mutation was discovered in 1991. The *FMR1* gene on the X chromosome is silenced, and the protein FMRP is not produced. Shortly thereafter, the *Fmr1* knockout mouse model was generated and has been intensively studied by neurobiologists interested both in the disease and the FMRP protein. In 2002 it was discovered that a form of synaptic plasticity – mGluR-LTD – was exaggerated in the *Fmr1* KO mouse. This led to the mGluR theory of fragile X, which posits that many symptoms of the disease are due to exaggerated responses to activation of the mGluR5 receptor. The theory was validated in 2007 with the demonstration that multiple fragile X phenotypes are corrected in the *Fmr1* KO mouse by genetic reduction of mGluR5 protein production. In addition, numerous animal studies showed that pharmacological inhibition of mGluR5 ameliorates fragile X mutant phenotypes. In 2009, inhibitors of mGluR5 entered into human phase 2 trials. If these are successful, this will represent the first pharmacological treatment for a neurobehavioral disorder that was developed from the bottom-up: from gene discovery to pathophysiology in animals to novel therapeutics in humans. Abbreviations: CGG: cytosine-guanine-guanine, mGluR5: metabotropic glutamate receptor 5, KO: knock out, LTD: long-term synaptic depression. Image courtesy of FRAXA Research Foundation, with permission.

## From amblyopia to LTD

The neurobiological thread of discovery originates with the seminal studies of David Hubel and Torsten Wiesel, beginning in the early 1960s. Hubel and Wiesel were the first to systematically explore with microelectrodes the organization of the visual pathway in mammals, from retina to thalamus to visual cortex. They discovered that the primary visual cortex (area 17; striate cortex; V1) is the most peripheral station in the ascending

visual pathway where information from the two eyes is combined. That is, they found in visual cortex neurons that would respond to stimulation of both the right eye and the left eye. This convergence of input from the two eyes is the neurobiological substrate of binocular vision – why we see one world with two eyes. They recognized that the precision with which these connections were established likely required, in addition to genetic instructions, a comparison of the activity patterns arising in the two eyes. As Wolf Singer elegantly describes it, inputs that ‘fire together’ should be those that ‘wire together’ in the visual cortex.

Wiesel and Hubel (1963) tested this idea by temporarily degrading image formation in one eye, a paradigm called monocular deprivation. They found that if this procedure was performed in a young animal, before adolescence, then there was a profound consequence in visual cortex. When normal image formation was restored, the eye that had been deprived no longer was effective in driving robust visual responses in the cortex. This dramatic form of experience-dependent plasticity has fascinated a generation of neuroscientists over the past 50 years. Not only is ocular dominance plasticity a robust example of the role of sensory experience in brain development, it is responsible for a highly prevalent form of childhood visual disability called amblyopia (affecting ~1% of the human population) that results when optical defects are not corrected during infancy or early childhood.

Ocular dominance plasticity is multifaceted, but a key question has concerned the mechanisms responsible for the loss of visual responsiveness wrought by monocular deprivation. The primary modification occurs at excitatory synapses in visual cortex, particularly thalamocortical synapses. Intuition suggests that these synapses simply atrophy due to disuse. However, this is not the case. In fact, inputs from the visually deprived eye are actually protected from disconnection by injecting an anesthetic into the eye (Rittenhouse *et al.*, 1999; Frenkel and Bear, 2004). The data instead support the theoretical suggestion (Bienenstock *et al.*, 1982) that poorly correlated activity that arises in the retina in the absence of crisp image formation is actually the trigger for synaptic depression. This insight led to the search for the mechanisms of homosynaptic long-term depression (LTD) in the cerebral cortex (see Bear, 2003) for review.

Even before the discovery of LTD (Dudek and Bear, 1992) it was recognized that synaptic weakening must result from the release of the neurotransmitter glutamate at excitatory synapses (Bear *et al.*, 1987). The discovery that glutamate could directly activate a class of G protein-coupled receptors – subsequently called metabotropic glutamate receptors (mGluRs) – suggested one potential mechanism for LTD (Bear, 1988). Decades later, we

now understand that there are multiple forms of LTD. In fact, the LTD mechanism that is responsible for amblyopia is dependent on NMDA receptors rather than mGluRs (Yoon *et al.*, 2009). Nonetheless, the mGluR hypothesis was eventually tested in the cerebellum, hippocampus, and elsewhere; and indeed, activation of these receptors is one important trigger for LTD (Luscher and Huber, 2010).

### From mGluR-LTD to FXS

There are 8 mGluRs in the genome, and these are divided into three structurally and functionally related groups, numbered 1–3. LTD is triggered in the hippocampus (and elsewhere) by activation of group 1 mGluRs, particularly the receptor designated mGluR5. A simple paradigm to induce LTD is brief application of the selective agonist, DHPG (dihydroxyphenylglycine), but LTD can also be induced by glutamate released in response to patterned electrical activation of synapses (Huber *et al.*, 2001).

The mGluR-LTD resembles homosynaptic LTD triggered by activation of NMDA receptors, which are both expressed by internalization of postsynaptic AMPA-type glutamate receptors (Snyder *et al.*, 2001). However, a distinguishing feature of mGluR-LTD is that it normally requires immediate translation of mRNAs that pre-exist in the dendrites of neurons (Huber *et al.*, 2000). The mGluR-LTD rapidly decays back to baseline if it is induced in the presence of a protein synthesis inhibitor such as cycloheximide.

This requirement for protein synthesis in LTD was surprising, but there were previous indications that mGluRs could regulate protein synthesis. It had been shown biochemically that activation of group 1 mGluRs can stimulate protein synthesis at synapses (Weiler and Greenough, 1993), and some other lasting electrophysiological consequences of mGluR activation had been shown to require protein synthesis (Merlin *et al.*, 1998; Raymond *et al.*, 2000). We now recognize that mGluR5 is part of a molecular machine that ensures that the supply of synaptic proteins keeps up with demand as registered by the release of glutamate at excitatory synapses. Although the mGluR5 receptor triggers several biological responses, one of these is the initiation of new protein synthesis at synapses.

At the turn of the century, the most immediate questions related to how mGluR5 activation regulates protein synthesis at synapses and the identity of the protein species required for LTD. It is here that research on neuroplasticity collided with FXS. Weiler and Greenough had shown in 1997 that one protein synthesized in response to mGluR5 activation was FMRP, the protein missing in FXS (Weiler *et al.*, 1997). We wondered if FMRP might be one of the hypothetical ‘LTD proteins’ and to test this idea we



obtained the *Fmr1* KO mouse. Our hypothesis was that without *Fmr1* mRNA at synapses there would be impaired LTD in the hippocampus. Surprisingly, however, the experiments revealed the opposite phenotype: LTD was exaggerated in the KO (Huber *et al.*, 2002).

Earlier findings *in vitro* suggested that FMRP binds mRNA and inhibits translation (Laggerbauer *et al.*, 2001; Li *et al.*, 2001). Thus to account for our LTD results we proposed that mGluR5 stimulation triggers the synthesis of LTD proteins and in addition, synthesis of FMRP. We imagined that FMRP normally feeds back to *inhibit* further synthesis of LTD proteins, an example of the familiar biochemical principle of end-product inhibition. Without FMRP, protein synthesis proceeds unchecked and, consequently, more LTD is expressed in the *Fmr1* KO.

### The mGluR theory of FXS

In addition to contributing to LTD, it was known by 2002 that mGluR-dependent protein synthesis has varied effects at different types of synapse (Merlin *et al.*, 1998; Raymond *et al.*, 2000; Vanderklish and Edelman, 2002). This led me to wonder what the consequences might be if group 1 mGluR functions were exaggerated throughout the nervous system in the absence of the negative regulation provided by FMRP. This was a spine tingling moment. It dawned on me that it was possible that many symptoms of FXS could be related to exaggerated responses to mGluR5 (and mGluR1, the other group 1 mGluR). These might include cognitive impairment, anxiety, epilepsy, and even irritable bowel; mGluRs might be a thread that could connect widely varied symptoms of the disease. The exciting and obvious implication was that inhibitors of group 1 mGluR signaling might provide a disease-altering therapy for FXS.

Of course, this was an extremely speculative idea, based on little more than our LTD findings in the *Fmr1* KO mice. The conservative course would have been to keep the idea to ourselves and work quietly to test it before going public. However, we quickly realized that this path would take us years. Because of the tremendous therapeutic possibilities, we were compelled to share this idea immediately with other researchers and enlist their help to test it. Accordingly I presented the 'mGluR theory' at a small meeting of fragile X experts in April, 2002 and the next year I helped organize a meeting of mGluR experts to introduce them to FXS (see Bear *et al.*, 2004) for review). These communities accepted the challenge to test the idea, and this has greatly accelerated progress.

Good theories are based on simple, concrete, and testable assumptions, and ours was that in the absence of FMRP exaggerated responses to group

1 mGluR activation (particularly protein synthesis) are pathogenic and responsible for the major neurological and psychiatric symptoms of the disease. This proposal of excessive protein synthesis downstream of mGluR5 has now been confirmed in several studies of the *Fmr1* KO mouse (Aschrafi *et al.*, 2005; Qin *et al.*, 2005; Dolen *et al.*, 2007; Osterweil *et al.*, 2010). Moreover, other electrophysiological and biochemical consequences of mGluR-activation, including epileptogenesis (Chuang *et al.*, 2005), LTP priming (Auerbach and Bear), cerebellar LTD (Koekkoek *et al.*, 2005), and glutamate receptor internalization (Nakamoto *et al.*, 2007) have also been found to be altered in the KO, consistent with increased protein synthesis.

The most important consequence of the theory, of course, is that multiple aspects of FXS should be improved by reducing signaling via mGluR5. This hypothesis has been tested in animal models of fragile X using two approaches, one genetic and the other pharmacological. The genetic approach was to reduce signaling via mGluR5 by crossing a mutant mouse line that expresses only 50% the WT level of mGluR5 (the *Grm5*<sup>+/-</sup> mouse) with the *Fmr1* KO (Dolen *et al.*, 2007). Remarkably, reducing mGluR5 in the *Fmr1* KO mouse was sufficient to correct 7 of 8 fragile X phenotypes examined, including seizures, hippocampal synaptic plasticity, ocular dominance plasticity, protein synthesis, and dendritic spine density. A similar approach was taken in the fruit fly model of fragile X with similar results (Pan and Broadie, 2007; Pan *et al.*, 2008; Repicky and Broadie, 2009). These experiments validate the theoretical concept that mGluR5 and FMRP act in functional opposition, and that defects caused by the loss of FMRP can be ameliorated by reducing signaling via mGluR5.

The genetic experiments reveal that mGluR5 is indeed a potential therapeutic drug target, and this idea has been extensively tested in animal experiments using a compound called MPEP (2-methyl-6-(phenylethynyl)-pyridine), a negative allosteric modulator of mGluR5 (Gasparini *et al.*, 1999). A dramatic early demonstration of the utility of MPEP was provided by Yan *et al.* (2005), who showed that a particularly severe fragile X phenotype in mice, audiogenic seizure, could be prevented by acute MPEP treatment. In a contemporaneous study McBride *et al.* (2005) showed that chronic drug treatment could correct both neuroanatomical and behavioral defects in the fruit fly model of fragile X. Importantly, they saw improvements even when treatment was begun in adult flies. Subsequent work from a number of laboratories using both mouse and fly models have strongly supported the conclusion that mGluR5 inhibitors can ameliorate many diverse fragile X phenotypes (reviewed by Krueger and Bear, 2011). The fact that this approach works in species as distantly related as flies and mice suggests that

mGluR5 and FMRP have an evolutionarily conserved relationship, which greatly boosts confidence that a similar approach can be successful in humans with FXS.

These studies have ushered in a new era in fragile X. Few would have believed it would be possible to develop a small molecule therapy that could substantially improve the outcome of a genetic defect in brain development. Tests of the mGluR theory over the past 10 years have shown beyond question that new, disease-altering treatments are indeed possible. This has inspired a search for additional potential therapeutics in fragile X and some very interesting new targets have emerged, including enzymes ‘downstream’ from mGluR5 (*e.g.*, Bilousova *et al.*, 2009; Min *et al.*, 2009) and ‘upstream’ neurotransmitter receptors that regulate the release of glutamate in the brain (*e.g.*, Chang *et al.*, 2008).

### Clinical trials

2011 is an auspicious moment. Exploratory ‘phase 2’ human clinical trials have now been completed using compounds designed to dampen mGluR5 activation or signaling (Berry-Kravis *et al.*, 2008a; Berry-Kravis *et al.*, 2008b; Berry-Kravis *et al.*, 2009; Erickson *et al.*, 2010; Jacquemont *et al.*, 2011). These include fenobam and AFQ056 (mGluR5 inhibitors), lithium (inhibitor of enzymes downstream of mGluR5), and arbaclofen (agonist of GABA-B receptors that reduce glutamate release). The results have been sufficiently encouraging that two compounds, AFQ056 and arbaclofen, have advanced into larger phase 3 trials. If successful, these studies could lead to regulatory approval of these drugs for the treatment of fragile X syndrome in children and adults. Needless to say, we await the outcome of these studies with great anticipation. Results should be available by the end of 2012.

Discussions of clinical trials often lead to two questions: (1) when must treatment begin to be effective, and (2) what aspects of human FXS do we hope to improve. These issues are critical because they can mean the difference between success and failure of a clinical trial, even if the approach is fundamentally correct. If treatment must begin in infancy to alter the trajectory of brain development, then trials initiated in young adults may fail simply because a ‘critical period’ has been missed. This presents a particular risk for compounds that are entering human trials for the first time, because regulatory agencies are appropriately cautious about allowing treatment in young children before there is a thorough understanding of potential toxicity. Fortunately the good news emerging from animal studies is that it does appear that measurable improvements still occur when treatments are begun after adolescence.

The other risk, applying to all new treatments, is that the wrong ‘end-points’ are chosen to assess drug efficacy. The endpoints that lead to regulatory approval are those that improve the quality of life for the affected individuals and their families, which are not easily measured reproducibly. Although we take great pride in the rescue of various synaptic defects in animals, it remains an open question precisely how these findings will translate to behavior in humans. Mouse behavior, in my opinion, does not provide much guidance because of dramatic differences in brain and behavioral complexity, and in cognitive capability. We hope that the measures that have appeared to respond in the exploratory trials will show robust, statistically significant improvements in the phase 3 trials.

Based on the strength of the animal research, I am confident that if we can start the correct treatment(s) at the correct time, treat for the correct duration and at the correct dose, and if we measure the correct outcome, clinical trials in fragile X will be successful and we will be able to provide substantial benefit to the affected individuals. Of course, that is a lot of ‘ifs’ so we must be prepared to tolerate some failure before we triumph. But triumph we will.

### **New hope for developmental brain disorders**

In this brief review I have highlighted the explosive progress in FXS that occurred when the streams of genetics and neurobiology mixed together. This is only one example, however. The study of genetically engineered animal models of several other human syndromes associated with ASD and ID have also yielded insights that suggest the possibility of meaningful drug therapy, with benefits even when that therapy is begun in adulthood (Silva and Ehninger, 2009). Moreover, it has also become apparent that many genetic mutations associated with ASD and ID may affect common biochemical signaling pathways (Kelleher and Bear, 2008). Thus, there is reason to hope that a treatment developed for a ‘rare’ cause of ASD and ID like FXS may be beneficial for others, even before we fully understand what these other causes are.

It is important to add, however, that while drug therapies might correct disruptions in synaptic biochemistry, they will never substitute for quality sensory experience and education. We imagine the drug treatment will unlock the potential for substantial gains in cognitive and social behaviors. But this potential will only be realized when pharmacotherapy is combined with appropriate cognitive and behavioral therapies that exploit life-long neuroplasticity.

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## Literature cited

- Aschrafi A, Cunningham BA, Edelman GM, Vanderklish PW (2005) The fragile X mental retardation protein and group I metabotropic glutamate receptors regulate levels of mRNA granules in brain. *Proc Natl Acad Sci USA* 102:2180–2185.
- Auerbach BD, Bear MF (2010) Loss of the fragile X mental retardation protein decouples metabotropic glutamate receptor dependent priming of long-term potentiation from protein synthesis. *J Neurophysiol* 104:1047–1051.
- Bear MF (1988) Involvement of excitatory amino acid receptor mechanisms in the experience-dependent development of visual cortex. In: *Recent Advances in Excitatory Amino Acid Research* (Lehman J, Turski L, eds), pp. 393–401. New York: Liss.
- Bear MF (2003) Bidirectional synaptic plasticity: from theory to reality. *Philos Trans R Soc Lond B Biol Sci* 358:649–655.
- Bear MF, Cooper LN, Ebner FF (1987) A physiological basis for a theory of synapse modification. *Science* 237:42–48.
- Bear MF, Huber KM, Warren ST (2004) The mGluR theory of fragile X mental retardation. *Trends Neurosci* 27:370–377.
- Berry-Kravis E, Sumis A, Hervey C, Nelson M, Porges SW, Weng N, Weiler IJ, Greenough WT (2008a) Open-label treatment trial of lithium to target the underlying defect in fragile X syndrome. *J Dev Behav Pediatr* 29:293–302.
- Berry-Kravis E, Sumis A, Hervey C, Nelson M, Porges SW, Weng N, Weiler IJ, Greenough WT (2008b) Open-label treatment trial of lithium to target the underlying defect in fragile X syndrome. *J Dev Behav Pediatr* 29:293–302.
- Berry-Kravis EM, Hessler D, Coffey S, Hervey C, Schneider A, Yuhass J, Hutchison J, Snape M, Tranfaglia M, Nguyen DV, Hagerman R (2009) A pilot open-label single-dose trial of fenobam in adults with fragile X syndrome. *J Med Genet.*
- Bienenstock E, Cooper L, Munro P (1982) Theory for the development of neuron selectivity: orientation specificity and binocular interaction in visual cortex. *J Neurosci* 2:32–48.
- Bilousova TV, Dansie L, Ngo M, Aye J, Charles JR, Ethell DW, Ethell IM (2009) Minocycline promotes dendritic spine maturation and improves behavioural performance in the fragile X mouse model. *J Med Genet* 46:94–102.
- Chang S, Bray SM, Li Z, Zarnescu DC, He C, Jin P, Warren ST (2008) Identification of small molecules rescuing fragile X syndrome phenotypes in *Drosophila*. *Nat Chem Biol* 4:256–263.
- Chuang SC, Zhao W, Bauchwitz R, Yan Q, Bianchi R, Wong RKS (2005) Prolonged Epileptiform Discharges Induced by Altered Group I Metabotropic Glutamate Receptor-Mediated Synaptic Responses in Hippocampal Slices of a Fragile X

- Mouse Model. *J Neurosci* 25:8048-8055.
- Dolen G, Osterweil E, Rao BSS, Smith GB, Auerbach BD, Chattarji S, Bear MF (2007) Correction of Fragile X Syndrome in Mice. *Neuron* 56:955-962.
- Dudek S, Bear MF (1992) Homosynaptic long-term depression in area CA1 of hippocampus and effects of N-methyl-D-aspartate receptor blockade. *Proc Natl Acad Sci USA* 89:4363-4367.
- Dutch Belgian Fragile X Consortium, Bakker CE, Verheij C, Willemsen R, van der Helm R, Oerlemans F, Vermey M, Bygrave A, Hoogeveen A, Oostra BA, Reyniers E, De Boule K, D'Hooge R, Cras P, van Velzen D, Nagels G, Martin JJ, De Deyn PP, Darby JK, Willems PJ (1994) Fmr1 knockout mice: A model to study fragile X mental retardation. *Cell* 78:23-33.
- Erickson CA, Mullett JE, McDougale CJ (2010) Brief Report: Acamprosate in Fragile X Syndrome. *J Autism Dev Disord*.
- Frenkel MY, Bear MF (2004) How monocular deprivation shifts ocular dominance in visual cortex of young mice. *Neuron* 44:917-923.
- Gasparini F, Lingenhöhl K, Stoeckl N, Flor PJ, Heinrich M, Vranesic I, Biollaz M, Allgeier H, Heckendorn R, Urwyler S, Varney MA, Johnson EC, Hess SD, Rao SP, Saccaan AI, Santori EM, Veliçelebi G, Kuhn R (1999) 2-Methyl-6-(phenylethynyl)-pyridine (MPEP), a potent, selective and systemically active mGlu5 receptor antagonist. *Neuropharmacology* 38:1493-1503.
- Huber KM, Kayser MS, Bear MF (2000) Role for rapid dendritic protein synthesis in hippocampal mGluR-dependent long-term depression. *Science* 288:1254-1257.
- Huber KM, Roder JC, Bear MF (2001) Chemical induction of mGluR5- and protein synthesis-dependent long-term depression in hippocampal area CA1. *J Neurophysiol* 86:321-325.
- Huber KM, Gallagher SM, Warren ST, Bear MF (2002) Altered synaptic plasticity in a mouse model of fragile X mental retardation. *Proc Natl Acad Sci USA* 99:7746-7750.
- Jacquemont S *et al.* (2011) Epigenetic modification of the FMR1 gene in fragile X syndrome is associated with differential response to the mGluR5 antagonist AFQ056. *Sci Transl Med* 3:64ra61.
- Kelleher RJ, Bear MF (2008) The Autistic Neuron: Troubled Translation? *Cell* 135:401-406.
- Koekkoek SKE *et al.* (2005) Deletion of FMR1 in Purkinje Cells Enhances Parallel Fiber LTD, Enlarges Spines, and Attenuates Cerebellar Eyelid Conditioning in Fragile X Syndrome. *Neuron* 47:339-352.
- Krueger DD, Bear MF (2011) Toward fulfilling the promise of molecular medicine in fragile X syndrome. *Annu Rev Med* 62:411-429.
- Laggerbauer B, Ostareck D, Keidel EM, Ostareck-Lederer A, Fischer U (2001) Evidence that fragile X mental retardation protein is a negative regulator of translation. *Hum Mol Genet* 10:329-338.
- Li Z, Zhang Y, Ku L, Wilkinson KD, Warren ST, Feng Y (2001) The fragile X mental retardation protein inhibits translation via interacting with mRNA. *Nucleic Acids Res* 29:2276-2283.
- Lubs H (1969) A marker X chromosome. *Am J Hum Genet* 21:231-244.
- Luscher C, Huber KM (2010) Group 1 mGluR-dependent synaptic long-term depression: mechanisms and implications for circuitry and disease. *Neuron* 65:445-459.
- Martin JP, Bell J (1943) A pedigree of mental defect showing sex-linkage. *J Neurol Psychiatry* 6:154-157.
- McBride SMJ, Choi CH, Wang Y, Liebelt D, Braunstein E, Ferreira D, Sehgal A, Siwicki KK, Dockendorff TC, Nguyen HT, McDonald TV, Jongens TA (2005) Pharmacological Rescue of Synaptic Plasticity, Courtship Behavior, and Mushroom Body Defects in a *Drosophila*



- Model of Fragile X Syndrome. *Neuron* 45:753-764.
- Merlin LR, Bergold PJ, Wong RK (1998) Requirement of protein synthesis for group I mGluR-mediated induction of epileptiform discharges. *J Neurophysiol* 80:989-993.
- Min WW, Yuskaitis CJ, Yan Q, Sikorski C, Chen S, Jope RS, Bauchwitz RP (2009) Elevated glycogen synthase kinase-3 activity in Fragile X mice: Key metabolic regulator with evidence for treatment potential. *Neuropharmacology* 56:463-472.
- Nakamoto M, Nalavadi V, Epstein MP, Narayanan U, Bassell GJ, Warren ST (2007) Fragile X mental retardation protein deficiency leads to excessive mGluR5-dependent internalization of AMPA receptors. *Proc Natl Acad Sci USA* 104:15537-15542.
- Osterweil EK, Krueger DD, Reinhold K, Bear MF (2010) Hypersensitivity to mGluR5 and ERK1/2 leads to excessive protein synthesis in the hippocampus of a mouse model of fragile X syndrome. *J Neurosci* 30:15616-15627.
- Pan L, Broadie KS (2007) Drosophila Fragile X Mental Retardation Protein and Metabotropic Glutamate Receptor A Convergenly Regulate the Synaptic Ratio of Ionotropic Glutamate Receptor Subclasses. *J Neurosci* 27:12378-12389.
- Pan L, Woodruff III E, Liang P, Broadie K (2008) Mechanistic relationships between Drosophila fragile X mental retardation protein and metabotropic glutamate receptor A signaling. *Mol Cell Neurosci* 37:747-760.
- Qin M, Kang J, Burlin TV, Jiang C, Smith CB (2005) Postadolescent Changes in Regional Cerebral Protein Synthesis: An In Vivo Study in the Fmr1 Null Mouse. *J Neurosci* 25:5087-5095.
- Raymond CR, Thompson VL, Tate WP, Abraham WC (2000) Metabotropic glutamate receptors trigger homosynaptic protein synthesis to prolong long-term potentiation. *J Neurosci* 20:969-976.
- Repicky S, Broadie K (2009) Metabotropic Glutamate Receptor-Mediated Use-Dependent Down-Regulation of Synaptic Excitability Involves the Fragile X Mental Retardation Protein. *J Neurophysiol* 101:672-687.
- Rittenhouse CD, Shouval HZ, Paradiso MA, Bear MF (1999) Monocular deprivation induces homosynaptic long-term depression in visual cortex. *Nature* 397:347-350.
- Silva AJ, Ehninger D (2009) Adult reversal of cognitive phenotypes in neurodevelopmental disorders. *J Neurodev Disord* 1:150-157.
- Snyder EM, Philpot BD, Huber KM, Dong X, Fallon JR, Bear MF (2001) Internalization of ionotropic glutamate receptors in response to mGluR activation. *Nat Neurosci* 4:1079-1085.
- Vanderklish PW, Edelman GM (2002) Dendritic spines elongate after stimulation of group 1 metabotropic glutamate receptors in cultured hippocampal neurons. *Proc Natl Acad Sci U S A* 99:1639-1644.
- Verkerk AJMH *et al.* (1991) Identification of a gene (FMR-1) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome. *Cell* 65:905-914.
- Weiler IJ, Greenough WT (1993) Metabotropic glutamate receptors trigger postsynaptic protein synthesis. *Proc Natl Acad Sci U S A* 90:7168-7171.
- Weiler IJ, Irwin SA, Klintsova AY, Spencer CM, Brazelton AD, Miyashiro K, Comery TA, Patel B, Eberwine J, Greenough WT (1997) Fragile X mental retardation protein is translated near synapses in response to neurotransmitter activation. *Proc Natl Acad Sci USA* 94:5395-5400.
- Wiesel T, Hubel D (1963) Single-cell responses in striate cortex of kittens deprived of vision in one eye. *J Neurophysiol* 26:1003-1017.
- Yan QJ, Rammal M, Tranfaglia M, Bauchwitz RP (2005) Suppression of two major



- Fragile X Syndrome mouse model phenotypes by the mGluR5 antagonist MPEP. *Neuropharmacology* 49:1053-1066.
- Yoon BJ, Smith GB, Heynen AJ, Neve RL, Bear MF (2009) Essential role for a long-term depression mechanism in ocular dominance plasticity. *Proc Natl Acad Sci U S A* 106:9860-9865.

# THE HUMAN GENOME DIVERSITY AND THE SUSCEPTIBILITY TO AUTISM SPECTRUM DISORDERS

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## Introduction

The diagnosis of autism is based on impairments in reciprocal social communication and stereotyped behaviors. The term “autism spectrum disorders” (ASD) is used to refer to any patient that meets these diagnostic criteria. But beyond this unifying definition lies an extreme degree of clinical heterogeneity, ranging from profound to moderate impairments. Indeed, autism is not a single entity, but rather a complex phenotype thought to be caused by different types of defects in common pathways, producing similar behavioral phenotypes. The prevalence of ASD overall is about 1/100, but closer to 1/300 for typical autism [1]. ASD are more common in males than females with a 4:1 ratio [2, 3].

The first twin and family studies performed in last quarter of the 20<sup>th</sup> century conclusively described ASD as the most ‘genetic’ of neuropsychiatric disorders, with concordance rates of 82–92% in monozygotic (MZ) twins versus 1–10% in dizygotic (DZ) twins; sibling recurrence risk is 6% [2, 3]. However, recent studies have indicated that the concordance for ASD in DZ twins might be higher (>20%) than previously reported [4]. Furthermore the concordance for ASD in MZ could also be lower than originally suggested [5, 6]. All these studies pointed at a larger part of the environment and/or epigenetic factors in the susceptibility to ASD. For example, in a twin study using structured diagnostic assessments (Autism Diagnostic Interview – Revised and Autism Diagnostic Observation Schedule), a large proportion of the variance in liability was explained by shared environmental factors (55%; 95% CI, 9%–81% for autism and 58%; 95% CI, 30%–80% for ASD) in addition to moderate genetic heritability (37%; 95% CI, 8%–84% for autism and 38%; 95% CI, 14%–67% for ASD). However, most likely due to the high genetic and clinical heterogeneity of autism/ASD, the very large confidence interval of the results makes the gene/environment debate still unresolved.

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From a cognitive perspective, 15 to 70% of children diagnosed as suffering from ASD have intellectual disabilities [7], and it is now understood that autism symptoms can be caused either by gene mutations or by chromosomal aberrations. In approximately 10–25% of the affected individuals, autism is ‘syndromic’, i.e. occurring in a child with a known genetic or environmental toxin disorder, such as fragile X, tuberous sclerosis, neurofibromatosis, valproic syndrome, or autism caused by brain herpes simplex infection [2, 7].

In the last years, various independent studies and large-scale international efforts have identified a growing number of candidate genes for ASD and suggest a set of mechanisms that could underlie the ASD phenotype. In this chapter, I will briefly review the recent advance in understanding the human genome diversity and the genes that increase the risk of ASD. Finally, I will expose recent genetic and functional results supporting that an alteration in synaptic homeostasis could be one of the mechanisms leading to ASD.

### The human genome diversity

The human genome project was launched in the mid-1980s and consequently the first genetic and physical maps were presented in the mid-1990s. But it was only in 2001 that both the academic institutions and the private company *Celera Genomics* achieved the first (almost) complete sequence of the human genome [8, 9]. Ten years after, the 19<sup>th</sup> version of the human genome assembly (hg19) is available with less gaps and errors than the first release. The human genome is made of 3.102 billion base pairs (the so-called ATGC bases) and contains approximately 33000 genes (among them 21000 are coding for proteins). The comparison of the human genomes with those of other species such as (*pan troglodyte* and *mus musculus*) led to the identification of genomic sequences that were highly conserved during evolution. This comparison could provide great helps in identifying gene sequences within the raw sequence (exons and introns) as well as conserved regulatory elements (promoters, enhancers, silencers...). On the other hand, the identification of rapidly evolving regions could point at compelling candidate genes that could have played crucial roles in shaping phenotypic differences between species. More recently, the genome of *Homo neanderthalensis* could also inform us on the recent genomic events that appeared in the homo lineage.

However, both the academic and the *Celera Genomics* sequences were obtained from the collection of the DNA of very few individuals. For the academic sequence the majority of the DNA fragments were obtained from a genomic DNA library (RP-11) originating from one donor after a request for volunteers that was advertised in a local USA newspaper, *The Buffalo News*. For the *Celera Genomics* sequence, DNA from five different individ-

uals was used for sequencing. The lead scientist of Celera Genomics at that time, Craig Venter, later acknowledged (in a public letter to the journal *Science*) that his DNA was one of 21 samples in the pool, five of which were selected for use.

Therefore, if these initial sequences allowed researchers to do genomic comparison between species and to map genes, very little was known on the genetic diversity between humans. Ascertaining this variability was the next step required to better understand the history of human populations and to identify the variations that contribute to the heredity of human physical traits such as height as well as to the genetic risk factors for frequent diseases such as diabetes and cardiovascular disorders. In order to ascertain the human genetic variability, two main international consortia were launched. First, in 2002, the HapMap project had the goal to identify the most frequent variations within human populations (<http://hapmap.ncbi.nlm.nih.gov/>). In parallel, different groups identified genomic imbalances (loss or gain of genetic materials) within the genome and therefore produced maps of these events (<http://projects.tcag.ca/variation/>). Then, thanks to the recent improvements in sequencing technology ('next-gen' sequencing platforms) that have sharply reduced the cost of sequencing, the 1000 Genomes Project was launched in 2008 (<http://www.1000genomes.org/>). The first goal of this project was to sequence the genomes of a large number of people and therefore to provide a comprehensive resource on human genetic variation.

Geneticists usually use the term polymorphism when the genetic variation is observed in more than 1% of the population and the term variant when the frequency of this variation is below 1%. The majority of the variations identified in one individual are inherited and shared by other individuals in the population and in his/her family. However, the results of the first phase of the 1000 genomes project indicate that approximately 30 variations ( $10^{-8}$ ) are present in the genome of one individual and absent in his/her parents [10]. These variant called *de novo* are very few, but they can have dramatic consequences when they affect genes with crucial biological function.

The molecular bases of human genetic diversity can be divided into two major classes. Single Nucleotides Polymorphisms (SNP) are defined as variations of single bases in the genome (see Fig. 1, p. 253). An SNP can be frequently observed in a given population or only present in few individuals (<1%). A very broad estimation of the human genetic diversity has indicated that, in average, one SNP/1200 bp is observed between two humans. This makes an average of 3 million SNP differences between two individuals. To date, the last release of dbSNP (build 132) contains 30.44 million human SNPs (<http://www.ncbi.nlm.nih.gov/projects/SNP/>). The second class of

variation is called Copy Number Variant (CNV). CNVs are defined as a loss or a gain of genetic material of more than 1000 bp compared with the reference genome. As SNPs, CNVs can be observed in a limited number of individuals or at high frequency (also sometimes called CNP for Copy Number Polymorphism).

These genetic data are very useful, but one of the main challenges for biologists remains to ascertain the consequences of these genetic variations at the phenotypic level. While, it is expected that a large proportion of these variations will be neutral with no functional consequences, some variations can contribute to phenotypic differences between individuals. On average, each person is found to carry approximately 250 to 300 loss-of-function variants in annotated genes and 50 to 100 variants previously implicated in inherited disorders [10]. In addition, SNPs can affect the regulation of a gene or a CNV can delete or duplicate one copy of a gene with dramatic consequences at the functional level. One general rule is that variations with high frequency in the population tend to have lower functional effect compared with those rarely observed or that appeared *de novo*. However, there are numerous exceptions and functional studies should be undertaken to address the functional consequence of the variations. To address the role of these variants on gene expression, analyses comparison between SNP and expression data are performed to detect expression quantitative trait loci (eQTL). Finally, the interaction between variations remains largely unknown despite that it might be crucial to understand the genotype-phenotype relationship in complex traits. Indeed, two variations each one with low affect when apart could within the same genome have a dramatic consequence at the phenotypic level (a phenomenon called epistasis).

### **Genetic variations and the modes of inheritance of ASD**

Due to the absence of classical Mendelian inheritance, ASDs were first thought to be a polygenic trait involving many genes, each ones with low effect. Therefore, model free linkage studies, such as affected sib-pair analyses, were performed to identify susceptibility genes. Many genomic regions were detected, but only a restricted number of loci were replicated in independent scans (e.g., chromosome 7q31 and 17q11). To homogenize the genetic and phenotypic data and to gain higher statistical power, collaborative efforts were initiated, such as the autism genome project (AGP), that genotyped 1496 sib-pair families using the Affymetrix 10K single nucleotide polymorphisms (SNP) array [11]. Nevertheless, no genome-wide significant loci could be detected, and the signals on chromosome 7q31 and 17q11 were lost. The absence of relevant targets identified by linkage studies prompted geneticists to

use an alternative method: association studies with dense SNP arrays. In theory, association studies are sensitive to allelic heterogeneity whereas linkage studies are not. Nevertheless, association studies provide major advantages compared with linkage studies. First, studies can include large sample of patients since they are not restricted to multiplex families with two or more affected children. Second, the genomic regions associated with the trait are much narrower than in linkage studies, due to loss of strong linkage disequilibrium between relatively close genomic regions. In addition, SNP arrays can be used to detect structural variants such as CNVs [12].

By using these approaches, several genes were associated with ASD. A list of 190 genes is available at AutDB, a public, curated, web-based, database for autism research (<http://www.mindspec.org/autdb.html>). However, most of these genes remain only candidates since their association was not always confirmed by replication and/or functional validation. Depending on the impact of the mutation on the risk for ASD (a property call penetrance), two main categories of genes can be made. In the first category, genes or loci appear to have a high penetrance, but are mutated in a limited number of individuals (sometime a single individual). In this category, variations are mostly composed of *de novo* or rare point mutations, CNVs and cytogenetically detected deletions/duplications (Table 1). The second category of genes includes the so-called susceptibility genes to ASD (Table 2). Here, the variations are mostly composed of SNPs or inherited CNVs observed in the general population and associated with low risk for ASD. Especially, in this category of genes, the association with ASD should be taken with great care, since the three largest genome-wide association studies (GWAS) performed on more than 1000 patients in each study could not detect the same genes associated with ASD [13–15]. Nevertheless, if these results seem negative, some relevant results were obtained providing a better understanding on the diverse causes of ASD.

### **Abnormal level of synaptic proteins**

Several lines of evidence indicate that mutations in genes regulating various aspects of synaptogenesis and neuronal circuit formation (see Fig. 2, p. 254) are associated with an increased risk for ASD. Among these, several genes seem to regulate the level of proteins at the synapse. Two X-linked genes, *MeCP2* and *FMR1*, are involved in autism ‘secondary’ to Rett and fragile X syndromes, respectively. *MeCP2* (Fig. 2B, p. 254) is a protein that directly and/or indirectly regulates neurotrophic factors, such as Brain Derived Neurotrophic factor (BDNF), by binding to methylated DNA [16]. Deletions or mutations of *MECP2* are associated with Rett syndrome in females, whereas

Table 1. Genes associated with high risk for ASD

Gene	Chromosome	Function	Evidence	Inheritance	Diagnosis	Reference
<i>FMR1</i>	Xq27	Synaptic translation	Mutations	<i>de novo</i> (permutations)	ASD, Fragile X syndrome	71
<i>MECP2</i>	Xq26	Chromatin remodeling	CNV, mutations	<i>de novo</i> (rarely inherited)	ASD, Rett syndrome	72
<i>TSC1</i>	9q34.13	mTOR / PI3K pathway	CNV, mutations	<i>de novo</i> , inherited	ASD, Tuberous sclerosis	73
<i>TSC2</i>	16p13.3	mTOR / PI3K pathway	CNV, mutations	<i>de novo</i> , inherited	ASD, Tuberous sclerosis	73
<i>NF1</i>	17q11.2	mTOR / PI3K pathway	CNV, mutation	<i>de novo</i> , inherited	ASD, Neurofibromatosis	74
<i>PTEN</i>	10q23.31	mTOR / PI3K pathway	CNV, mutations	<i>de novo</i> , inherited	ASD, Cowden syndrome	75
<i>CACNA1C</i>	12p13.33	Calcium channel	Mutation	<i>de novo</i>	ASD, Timothy syndrome	76
<i>DPPYD</i>	1p21.3	Pyrimidine base biosynthesis	CNV	<i>de novo</i>	ASD	59
<i>RFXWD2</i>	1q25.1-q25.2	Ubiquitination	CNV	<i>de novo</i> , inherited	ASD	22
<i>NRXN1</i>	2p16.3	Synaptic CAM	CNV, mutations, SNP	<i>de novo</i> , inherited	ASD, SCZ	11, 77
<i>CNTN4</i>	3p26.3	Synaptic CAM	CNV	Inherited	ASD, MR	22, 57, 58, 78
<i>MEF2C</i>	5q14.3	Transcription factor	CNV, mutations	<i>de novo</i>	MR, Seizures	27
<i>SYNGAP1</i>	6p21.3	Synaptic Ras GAP	CNV	<i>de novo</i>	ASD, MR	45
<i>CNTNAP2</i>	7q35-7q36.1	Synaptic CAM	CNV, rare variants *	Inherited	ASD, MR, SCZ, TS,	37, 54-56, 79, 80
<i>DPP6</i>	7q36.2	dipeptidyl-peptidase activity	CNV	<i>de novo</i> , inherited	ASD	59
<i>DLGAP2</i>	8p23.3	Synaptic scaffold	CNV	<i>de novo</i>	ASD	59
<i>ASTN2</i>	9q33.1	Neuron-Glial Interaction	CNV	Inherited	ASD, SCZ, ADHD	22
<i>SHANK2</i>	11q13	Synaptic scaffold	CNV	<i>de novo</i>	ASD	45
<i>NBEA</i>	13q13.2	Synaptic protein	Translocation	<i>de novo</i>	ASD	81
<i>UBE3A</i>	15q11-q13	Ubiquitination	CNV	<i>de novo</i> , inherited	ASD	22
<i>SHANK3 (del 22q13)</i>	22q13	Synaptic scaffold	CNV, mutations	<i>de novo</i> , inherited	ASD, MR, SCZ	43, 44, 82
<i>NLGN3</i>	Xq13.1	Synaptic CAM	Mutation	Inherited	ASD	83
<i>IL1RAPL1</i>	Xp21.3-p21.2	Synaptic receptor	CNV, mutations	<i>de novo</i> , inherited	ASD, MR	84
<i>NLGN4</i>	Xp22	Synaptic CAM	CNV, mutations	<i>de novo</i> , inherited	ASD, MR, TS	83
<i>PTCHD1</i>	Xp22.11	Hedgehog receptor activity	CNV	Inherited	ASD	59
<i>GRI43</i>	Xp25	Synaptic receptor	CNV	Inherited	ASD	51

ASD Autism Spectrum Disorder; SCZ Schizophrenia; MR Mental Retardation; ADHD Attention-Deficit Hyperactivity Disorder; MDC1D congenital muscular dystrophy; BP Bipolar, TS Tourette syndrome; \* in contrast to mutations, the functional role of the rare variants was not confirmed.



Table 2. Proposed susceptibility genes for ASD

Gene	Chromosome	Function	Evidence	Diagnosis	References
<i>ASMT</i>	PAR1	Melanin pathway	Inherited CNV, SNPs, mutations	ASD	85,87
<i>DISC1/DISC2</i>	1q42.2	Axonal growth	Inherited CNV	ASD, SCZ	88
<i>TSNAX</i>	1q42.2	Cell differentiation	Inherited CNV	ASD, SCZ	88
<i>DPP10</i>	2q14.1	Dipeptidyl-peptidase activity	Inherited CNV	ASD	88
<i>CNTN3</i>	3p12.3	Synaptic CAM	Inherited CNV	ASD	59
<i>FBXO40</i>	3q13.3	Unknown function	Inherited CNV P = 3.3 x 10 <sup>-3</sup>	ASD	58
<i>SLC9A9</i>	3q24	Transporter	Inherited CNV, mutations	ASD, ADHD, MR	22
<i>PCDH10</i>	4q28	Synaptic CAM	Inherited CNV	ASD	58
<i>PARK2</i>	6q26	Ubiquitination	Inherited CNV P = 3.3 x 10 <sup>-3</sup>	ASD, PD	58
<i>INMP2L</i>	7q31.1	Mitochondrial protease	Inherited CNV	ASD, TS, ADHD	22
<i>PCDH9</i>	13q21	Synaptic CAM	Inherited CNV	ASD	89
<i>MDGA2</i>	14q21.3	GPI anchor protein	Inherited CNV P = 1.3 x 10 <sup>-4</sup>	ASD	90
<i>BZRAP1</i>	17q22	Benzodiazepine receptor binding	Inherited CNV P = 2.3 x 10 <sup>-5</sup>	ASD	90
<i>PLD5</i>	1q43	Phospholipase D	SNP rs2196826 P = 1.1 x 10 <sup>-8</sup>	ASD	15
<i>SLC25A12</i>	2q31.1	Synaptic receptor	SNP rs2056202 P = 1 x 10 <sup>-3</sup>	ASD	91,92
<i>CDH9/CDH10</i>	5p14.2	Synaptic CAM	SNP rs4307059 P = 3.4 x 10 <sup>-8</sup>	ASD	13
<i>SEMA3A</i>	5p15.2	Axonal guidance	SNP rs10513025 P = 2 x 10 <sup>-7</sup>	ASD	14
<i>TAS2R1</i>	5p15.2	Receptor	SNP rs10513025 P = 2 x 10 <sup>-7</sup>	ASD	14
<i>GRIK2</i>	6q16.3	Synaptic receptor	SNP rs3213607 P = 0.02	ASD	50
<i>POU6F2</i>	7p14.1	Transcription factor	SNP rs1025862 P = 4.4 x 10 <sup>-7</sup>	ASD, SCZ, OCD, MR	15
<i>RELN</i>	7q22.1	Axonal guidance	GCG repeat in the 5'UTR P <0.05	ASD, BP	93
<i>NRCAM</i>	7q31.1	Synaptic receptor	SNP rs2300045 P =0.017	ASD	94
<i>MEET</i>	7q31.2	Tyrosine kinase	SNP rs1858830 P = 2 x 10 <sup>-3</sup>	ASD	21
<i>EN2</i>	7q36.3	Transcription factor	SNP rs1861972 P = 9 x 10 <sup>-3</sup>	ASD	95
<i>STS81A2</i>	15q26.1	N-glycan processing	SNP rs3784730 P = 4 x 10 <sup>-7</sup>	ASD	15
<i>GRIN2A</i>	16p13.2	Synaptic receptor	SNP rs1014531 P =2.9 x 10 <sup>-7</sup>	ASD, SCZ	96
<i>ABAT</i>	16p13.2	Enzyme	SNP rs1731017 P = 1 x 10 <sup>-3</sup>	ASD, GABA-AT Deficiency	96
<i>SLC6A4</i>	17q11.2	Serotonin Transporter	Meta analysis P >0.05	ASD, OCD	97
<i>ITGB3</i>	17q21.3	Cell-matrix adhesion	SNP Leu33Pro P = 8.2 x 10 <sup>-4</sup>	ASD	98
<i>TLE2 / TLE6</i>	19p13	Wnt receptor signaling pathway	SNP rs480693 P =7.8 x 10 <sup>-5</sup>	ASD, FHM2, AHC	99
<i>MACROD2</i>	20p12	Unknown function	SNP rs4141463 P = 2 x 10 <sup>-8</sup>	ASD	15

ASD Autism Spectrum Disorder; SCZ Schizophrenia; PD Parkinson Disease; TS Tourette syndrome; ADHD Attention-Deficit Hyperactivity Disorder; MR Mental Retardation; FHM2 Familial Hemiplegic Migraine 2; AHC Alternating Hemiplegia of Childhood; OCD Obsessive-Compulsive Disorder; BP Bipolar Disorder.

duplications of *MeCP2* are associated with mental retardation and ASD in males and psychiatric symptoms, including generalized anxiety, depression, and compulsions in females [17]. FMRP (Fig. 2A, B, p. 254) is a selective RNA-binding protein that transports mRNA into dendrites and regulates the local translation of some of these mRNAs at synapses in response to activation of metabotropic glutamate receptors (mGluRs). In the absence of FMRP, there is an excess and a dysregulation of mRNA translation leading to altered protein synthesis dependent plasticity [18].

Mutations of other genes associated with ASD seem to affect the level of synaptic proteins by dysregulating overall cellular translation [18]. Patients with neurofibromatosis, tuberous sclerosis, or Cowden/Lhermitte Duclos syndromes have a higher risk of having ASD than the general population. These disorders are caused by dominant mutations in the tumor suppressor genes *NF1*, *TSC1/TSC2* and *PTEN* (Fig. 2, p. 254). These proteins act in a common pathway as negative effectors of the rapamycin-sensitive *mTOR*-raptor complex, a major regulator of mRNA translation and cellular growth in mitotic cells [18]. The mutations observed in ASD have been predicted to enhance the *mTORC1* complex, which could lead to abnormal synaptic function due to an excess of protein synthesis. Interestingly loss of *Tsc1/Tsc2* or *Pten* in mice results in neuronal hypertrophy [19], and patients presenting mutations in *NF1*, *TSC1/TSC2* and *PTEN* have a higher risk for macrocephaly. Further modulation of the *PTEN* and *mTOR* pathways is exerted by serotonin and the proto-oncogene cMET, two pathways that were also associated with ASD [20, 21].

Consistent with the hypothesis of a relationship between abnormal levels of synaptic proteins in ASD, many studies have reported mutations in genes involved in synaptic protein ubiquitination, including *UBE3A*, *PARK2*, *RFWD2* and *FBXO40* [22] (Fig. 2A, p. 254). Protein degradation through ubiquitination proceeds through the ligation of ubiquitin to the protein to be degraded. This post-translational modification directs the ubiquitinated proteins to cellular compartments or to degradation into the proteasome. The ligation of ubiquitin is reversible and could be used to regulate specific protein levels at the synapse. In mice, many proteins of the post-synaptic density, including the mouse orthologs of the ASD-associated SHANK proteins, have been demonstrated to be targeted by ubiquitination in an activity-dependent homeostatic manner [23]. Ubiquitination involves activating enzymes (E1), conjugating enzymes (E2) and ligases (E3). Substrate specificity is usually provided by the E3 ligases, which typically have substrate-binding sites. *UBE3A* (also called E6-AP) is an E3 ligase encoded by an imprinted gene (only expressed from the maternal copy) and is responsible

for Angelman syndrome [24]. In ASD, *de novo* maternal duplications of chromosome 15q11-q13 including *Ube3A* have been observed in 1–3% of the patients [24]. It is still not clear whether *Ube3A* alone contributes to the risk of ASD, since other candidate genes are also duplicated on chromosome 15q11-q13; however, its role at the synapse has been recently demonstrated in mice [25, 26]. In cultured hippocampal neurons *Ube3A* is localized at the pre- and post-synaptic compartments, but also at the nucleus. Experience-driven neuronal activity induces *Ube3A* transcription, and *Ube3A* then regulates excitatory synapse development by controlling the degradation of Arc, a synaptic protein that promotes the internalization of the AMPA subtype of glutamate receptors [26]. This might have many consequences for synaptic structure, as suggested by *Ube3A* maternal-deficient mice, which exhibit abnormal dendritic spine development, including spine morphology, number and length [25], and a reduced number of AMPA receptors at excitatory synapses [26].

Finally, the transcription factor *MEF2C* (Fig. 2B, p. 254), involved in the regulation of the number of synapses appears to be a risk factor for intellectual disability [27], and could therefore also be associated with ASD. Taken together, the genetic results obtained in humans and the functional studies mostly obtained in mice suggest that different independent mechanisms could alter the level of synaptic proteins; however, the actual nature of the impaired synaptic function(s), and its association with ASD phenotype remains to be characterized.

### **Abnormal formation of neuronal circuits in ASD**

The main category of genes associated with ASD is related to the development and the function of neuronal circuits [28]. At the synaptic membranes, cell adhesion molecules, such as NLGNs and NRXNs (Fig. 2, p. 254) are major organizers of excitatory glutamatergic and inhibitory GABAergic synapses, and contribute to the activity-dependent formation of neuronal circuits in mice [29]. Mutations identified in patients with ASD were found to alter the ability of NLGNs to trigger synapse formation in cultured neuronal cells [30, 31]. The disorders associated with NLGN-NRXN mutations can greatly vary among individuals, and this appears to be the case even for subjects of the same family, carrying the same mutation. Mutations of the X-linked *Nlgn4X* have been associated with mental retardation [32], typical autism [31, 33], Asperger syndrome [34] and more recently with Tourette syndrome [35]. In one case, a *Nlgn4X* deletion was observed in a male with normal intelligence and apparently no autistic features [36]. *Nrxn1*, by contrast, has been implicated in disor-

ders such as schizophrenia and Pitt-Hopkins-like syndrome, but has been also found in asymptomatic carriers [37].

Interestingly, *Nlgn* and *Nrxn* might also play a role in social interaction in other species than humans without affecting overall cognitive functions. Mutant mice carrying a R451C *Nlgn3* mutation displayed an increased number of GABAergic synapses and inhibitory currents [38], normal [39] to reduced social interaction [38] and a reduction of ultrasonic vocalization in pups [39]. The knockout mice for *Nlgn4* displayed reduced social interactions and ultrasonic vocalizations at the adult stage [40]. By contrast, mutant knock-in *Nlgn3* and knock-out *Nlgn4* displayed enhanced to normal learning compared with wild-type mice [38, 40]. Furthermore, in the mouse model for fragile X, an enhanced *Nlgn1* expression improved social behavior, whereas no effect on learning and memory was observed [41]. Finally, in the honeybee, sensory deprived animals had a lower level of *Nlgn1* expression, but a generally increased level of the *Nlgn2-5* and *Nrxn1* expression compared with hive bees [42].

Postsynaptic density plays a major role in the organization and plasticity of the synapse, and mutations affecting scaffolding proteins, such as *SHANK2*, *SHANK3* and *DLGAP2*, are recurrently found in ASD [43–45]. Deletions at 22q13 and mutations of *SHANK3* could be present in more than 1–2% of ASD patients (Box 1) [43, 44, 46]. Shank proteins are a family of three members, which are crucial components of the postsynaptic density. Together with their binding partners, they have been shown, *in vitro*, to regulate the size and shape of dendritic spines [47]. They also link glutamate receptors to the cytoskeleton and variations in genes regulating cytoskeletal dynamics were associated with mental retardation and ASD [45, 48].

The role of neurotransmitter transporters and receptors in the susceptibility to ASD is still unclear. Because of the abnormally high levels of serotonin in ASD patients [20], the serotonin transporter *SLC6A4* was extensively analyzed, and the results pointed toward dimensional rather than categorical roles for *SLC6A4* in stereotypic behaviors [49]. For glutamate, only weak associations for *GRIK2* were detected [50], and a duplication of the X-linked *GRIA3* receptor gene was observed in a patient presenting typical autism [51]. Concerning GABA, the most robust findings concern the duplication of the GABA receptor subunit gene-cluster on chromosome 15q11–13 and the observation of maternal over-transmission of a rare variant of the GABA(A) receptor beta3 subunit gene (*GABRB3*) [52].

Finally, proteins, related to axonal growth and synaptic identity, are now also suspected to play a role in ASD. Semaphorins are membrane or secreted proteins (Fig. 2, p. 254) that influence axon outgrowth and pruning, synap-

togenesis and the density and maturation of dendritic spines. SNPs located close to the semaphorin *SEMA5A* were associated with ASD in a large cohort [14]. Independently, the level of *SEMA5A* mRNA was found to be lower in brain-tissue and B-lymphoblastoid cell lines from patients with ASD compared with controls [53]. The contactin family of proteins is involved in axonal guidance as well as in the connection between axons and glial cells, and ASD patients have been found to have deletions of the contactin genes *CNTN3* and *CNTN4* and the contactin associated protein *CNTNAP2* [54–58]. In addition, inherited CNVs or SNPs have been found in other cell-adhesion proteins – cadherins (*CDH9*, *CDH10*, *CDH18*) and protocadherins *PCDH9* and *PCDH10* [13, 58, 59] – which might contribute to the susceptibility to ASD by altering neuronal identity.

### **Abnormal synaptic homeostasis in ASD**

Different homeostatic mechanisms allow neuronal cells to maintain an optimal level of neuronal activity despite global changes in the overall activity of the network [60–62]. Recent evidence suggests that homeostasis plays a role in the adaptation of synaptic plasticity by changing levels of activity [23, 60], and might be also associated with the downscaling of synaptic weights during sleep [61]. During development and the first years of life, activity plays an important role in the refinement of brain connections, and many results suggest that these processes are under homeostatic control at the synapse [63]. The genes and the mechanisms that we have surveyed in this chapter might disrupt synaptic homeostasis at various levels [64]. The synthesis and degradation of different postsynaptic density proteins has been shown to vary as a function of activity [23]. Mutations in ubiquitin-dependent degradation could directly interfere with this process, as would also be the case if mutations are present in scaffolding genes such as the Shank family. Synaptic homeostasis has been shown to depend on local protein synthesis, on  $\text{Ca}^{2+}$  concentration and on a tight regulation between the pre- and the post synaptic sides of the synaptic contact mediated by cell adhesion molecules such as Nlgn and Nrnx [65]. Finally, synaptic homeostasis is not independent from cellular homeostasis and therefore should be affected by mutations altering gene expression level as well as neuronal numbers and shape such as mutations related to the mTOR pathway.

If synaptic homeostasis is altered in ASD, environmental factors that influence this regulatory process could also modulate its severity. As reviewed elsewhere [20, 66], abnormal serotonin and/or melatonin levels and altered sleep or circadian rhythms might constitute risk factors for ASD [67]. Sleep has been proposed as an important mechanism to regulate synaptic home-

ostasis. During wakefulness there appears to be a global increase in the strength of excitatory synapses, scaled down during sleep to a baseline level [61, 68], a mechanism that can play an important role in learning and memory [69]. In addition to mutations of genes directly involved in synaptic processes, we have recently proposed that, in some cases, ASD could result from the interplay between abnormalities in synaptic and clock genes, and that restoring circadian rhythms might therefore be beneficial for the patients and their families [66].

Most of the genes considered in this review are thought to be expressed throughout the brain; however, neuroimaging studies seem to converge into a stereotypical network of brain regions where differences between ASD and control populations can be detected. These two results would not need to be in contradiction, if different brain networks were differently resilient to variations in synaptic homeostasis (see Fig. 3, p. 255). From an evolutionary standpoint, brain networks involved in more recently acquired cognitive skills, such as language or complex social behavior, might have less compensatory mechanisms compared with more ancient biological functions that have been shaped by a much stronger selective pressure.

### **Concluding remarks and perspectives**

It is a matter of time for geneticists to be able to obtain whole genome sequences of ASD patients. Exploring epigenetic alterations should be also more feasible in the near future, thanks to the availability of brain tissue samples and stem cells from patients. Animal models based on genetic results are now under scrutiny in many laboratories and the consequence of the mutations and their reversibility is analyzed from cell to behavior. However, more than ever we need to recognize the inherent heterogeneity of the genetic correlates of ASD. A true understanding of the relationship between genetic mutations and ASD phenotype will not be possible if we persist in considering autism as a binary value in our analyses. Advancement in the research on ASD requires the expertise from different fields, but only clinicians and psychiatrists will be able to determine what we are actually looking at (i.e. the autism phenotype or, rather, the different autism phenotypes). Future studies should tell if increasing sample size or meta-analyses, phenotypic stratification, pathway analyses and SNP x SNP interactions can identify common variants associated with sub groups of patients with ASD. Indeed, to date, it is not clear how many loci can regulate synaptic homeostasis and how these variants interact with each other to modulate the risk for ASD [70]. A better knowledge of these genetic interactions will be necessary to understand the complex inheritance pattern of ASD.

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## References

1. Fernell, E., and Gillberg, C. (2010) Autism spectrum disorder diagnoses in Stockholm preschoolers. *Res Dev Disabil* 31, 680–685.
2. Freitag, C.M. (2007) The genetics of autistic disorders and its clinical relevance: a review of the literature. *Mol Psychiatry* 12, 2–22.
3. Abrahams, B.S., and Geschwind, D.H. (2008) Advances in autism genetics: on the threshold of a new neurobiology. *Nat Rev Genet* 9, 341–355.
4. Hallmayer, J., et al. (2011) Genetic Heritability and Shared Environmental Factors Among Twin Pairs With Autism. *Arch Gen Psychiatry*.
5. Lichtenstein, P., et al. (2010) The Genetics of Autism Spectrum Disorders and Related Neuropsychiatric Disorders in Childhood. *Am J Psychiatry* 167, 1–7.
6. Ronald, A., et al. (2010) A twin study of autism symptoms in Sweden. *Mol Psychiatry*.
7. Gillberg, C., and Coleman, M. (2000) *The biology of the autistic syndromes*. Oxford University Press.
8. Lander, E.S., et al. (2001) Initial sequencing and analysis of the human genome. *Nature* 409, 860–921.
9. Venter, J.C., et al. (2001) The sequence of the human genome. *Science* 291, 1304–1351.
10. Durbin, R.M., et al. (2010) A map of human genome variation from population-scale sequencing. *Nature* 467, 1061–1073.
11. Szatmari, P., et al. (2007) Mapping autism risk loci using genetic linkage and chromosomal rearrangements. *Nat Genet* 39, 319–328.
12. Cook, E.H., Jr., and Scherer, S.W. (2008) Copy-number variations associated with neuropsychiatric conditions. *Nature* 455, 919–923.
13. Wang, K., et al. (2009) Common genetic variants on 5p14.1 associate with autism spectrum disorders. *Nature* 459, 528–533.
14. Weiss, L.A., et al. (2009) A genome-wide linkage and association scan reveals novel loci for autism. *Nature* 461, 802–808.
15. Anney, R., et al. (2010) A genomewide scan for common risk variants nominates phospholipase D and polysialyl-transferase proteins for a role in autism. *submitted*.
16. Chahrour, M., et al. (2008) MeCP2, a key contributor to neurological disease, activates and represses transcription. *Science* 320, 1224–1229.
17. Ramocki, M.B., et al. (2009) Autism and other neuropsychiatric symptoms are prevalent in individuals with MeCP2 duplication syndrome. *Ann Neurol* 66, 771–782.
18. Kelleher, R.J., 3rd, and Bear, M.F. (2008) The autistic neuron: troubled translation? *Cell* 135, 401–406.
19. Tavazoie, S.F., et al. (2005) Regulation of neuronal morphology and function by the tumor suppressors Tsc1 and Tsc2. *Nat Neurosci* 8, 1727–1734.
20. Cook, E.H., and Leventhal, B.L. (1996) The serotonin system in autism. *Curr Opin Pediatr* 8, 348–354.



21. Campbell, D.B., *et al.* (2006) A genetic variant that disrupts MET transcription is associated with autism. *Proc Natl Acad Sci U S A* 103, 16834-16839.
22. Glessner, J.T., *et al.* (2009) Autism genome-wide copy number variation reveals ubiquitin and neuronal genes. *Nature* 459, 569-573.
23. Ehlers, M.D. (2003) Activity level controls postsynaptic composition and signaling via the ubiquitin-proteasome system. *Nat Neurosci* 6, 231-242.
24. Schanen, N.C. (2006) Epigenetics of autism spectrum disorders. *Hum Mol Genet* 15 Spec No 2, R138-150.
25. Dindot, S.V., *et al.* (2008) The Angelman syndrome ubiquitin ligase localizes to the synapse and nucleus, and maternal deficiency results in abnormal dendritic spine morphology. *Hum Mol Genet* 17, 111-118.
26. Greer, P.L., *et al.* (2010) The Angelman Syndrome Protein Ube3A Regulates Synapse Development by Ubiquitinating Arc. *Cell* 140, 704-716.
27. Le Meur, N., *et al.* (2009) MEF2C haploinsufficiency caused either by microdeletion of the 5q14.3 region or mutation is responsible for severe mental retardation with stereotypic movements, epilepsy and/or cerebral malformations. *J Med Genet*.
28. Bourgeron, T. (2009) A synaptic trek to autism. *Curr Opin Neurobiol* 19, 231-234.
29. Sudhof, T.C. (2008) Neuroligins and neurexins link synaptic function to cognitive disease. *Nature* 455, 903-911.
30. Chih, B., *et al.* (2004) Disorder-associated mutations lead to functional inactivation of neuroligins. *Hum Mol Genet* 13, 1471-1477.
31. Zhang, C., *et al.* (2009) A neuroligin-4 missense mutation associated with autism impairs neuroligin-4 folding and endoplasmic reticulum export. *J Neurosci* 29, 10843-10854.
32. Laumonnier, F., *et al.* (2004) X-linked mental retardation and autism are associated with a mutation in the NLGN4 gene, a member of the neuroligin family. *Am J Hum Genet* 74, 552-557.
33. Jamain, S., *et al.* (2003) Mutations of the X-linked genes encoding neuroligins NLGN3 and NLGN4 are associated with autism. *Nature Genetics* 34, 27-29.
34. Jamain, S., *et al.* (2003) Mutations of the X-linked genes encoding neuroligins NLGN3 and NLGN4 are associated with autism. *Nat Genet* 34, 27-29.
35. Lawson-Yuen, A., *et al.* (2008) Familial deletion within NLGN4 associated with autism and Tourette syndrome. *Eur J Hum Genet* 16, 614-618.
36. Macarov, M., *et al.* (2007) Deletions of VCX-A and NLGN4: a variable phenotype including normal intellect. *J Intellect Disabil Res* 51, 329-333.
37. Zweier, C., *et al.* (2009) CNTNAP2 and NRXN1 are mutated in autosomal-recessive Pitt-Hopkins-like mental retardation and determine the level of a common synaptic protein in Drosophila. *Am J Hum Genet* 85, 655-666.
38. Tabuchi, K., *et al.* (2007) A neuroligin-3 mutation implicated in autism increases inhibitory synaptic transmission in mice. *Science* 318, 71-76.
39. Chadman, K.K., *et al.* (2008) Minimal aberrant behavioural phenotypes of Neuroligin-3 R451C knockin mice. *Autism Research* 1, 147-158.
40. Jamain, S., *et al.* (2008) Reduced social interaction and ultrasonic communication in a mouse model of monogenic heritable autism. *Proc Natl Acad Sci U S A* 105, 1710-1715.
41. Dahlhaus, R., and El-Husseini, A. (2009) Altered Neuroligin expression is involved in social deficits in a mouse model of the Fragile X Syndrome. *Behav Brain Res*.
42. Biswas, S., *et al.* (2010) Sensory regulation of neuroligins and neurexin I in the honeybee brain. *PLoS One* 5, e9133.

43. Durand, C.M., *et al.* (2007) Mutations in the gene encoding the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders. *Nat Genet* 39, 25-27.
44. Moessner, R., *et al.* (2007) Contribution of SHANK3 mutations to autism spectrum disorder. *Am J Hum Genet* 81, 1289-1297.
45. Pinto, D., *et al.* (2010) Functional impact of global rare copy number variation in autism spectrum disorder. *Nature* (In press).
46. Gauthier, J., *et al.* (2009) Novel *de novo* SHANK3 mutation in autistic patients. *Am J Med Genet B Neuropsychiatr Genet* 150B, 421-424.
47. Roussignol, G., *et al.* (2005) Shank expression is sufficient to induce functional dendritic spine synapses in aspiny neurons. *J Neurosci* 25, 3560-3570.
48. Persico, A.M., and Bourgeron, T. (2006) Searching for ways out of the autism maze: genetic, epigenetic and environmental clues. *Trends Neurosci* 29, 349-358.
49. Sutcliffe, J.S., *et al.* (2005) Allelic heterogeneity at the serotonin transporter locus (SLC6A4) confers susceptibility to autism and rigid-compulsive behaviors. *Am J Hum Genet* 77, 265-279.
50. Jamain, S., *et al.* (2002) Linkage and association of the glutamate receptor 6 gene with autism. *Molecular Psychiatry* 7, 302-310.
51. Jacquemont, M.L., *et al.* (2006) Array-based comparative genomic hybridisation identifies high frequency of cryptic chromosomal rearrangements in patients with syndromic autism spectrum disorders. *J Med Genet* 43, 843-849.
52. Delahanty, R.J., *et al.* (2009) Maternal transmission of a rare GABRB3 signal peptide variant is associated with autism. *Mol Psychiatry*.
53. Melin, M., *et al.* (2006) Constitutional downregulation of SEMA5A expression in autism. *Neuropsychobiology* 54, 64-69.
54. Alarcon, M., *et al.* (2008) Linkage, association, and gene-expression analyses identify CNTNAP2 as an autism-susceptibility gene. *Am J Hum Genet* 82, 150-159.
55. Arking, D.E., *et al.* (2008) A common genetic variant in the neurexin superfamily member CNTNAP2 increases familial risk of autism. *Am J Hum Genet* 82, 160-164.
56. Bakkaloglu, B., *et al.* (2008) Molecular cytogenetic analysis and resequencing of contactin associated protein-like 2 in autism spectrum disorders. *Am J Hum Genet* 82, 165-173.
57. Roohi, J., *et al.* (2009) Disruption of contactin 4 in three subjects with autism spectrum disorder. *J Med Genet* 46, 176-182.
58. Morrow, E.M., *et al.* (2008) Identifying autism loci and genes by tracing recent shared ancestry. *Science* 321, 218-223.
59. Marshall, C.R., *et al.* (2008) Structural variation of chromosomes in autism spectrum disorder. *Am J Hum Genet* 82, 477-488.
60. Turrigiano, G.G. (1999) Homeostatic plasticity in neuronal networks: the more things change, the more they stay the same. *Trends Neurosci* 22, 221-227.
61. Tsononi, G., and Cirelli, C. (2003) Sleep and synaptic homeostasis: a hypothesis. *Brain Res Bull* 62, 143-150.
62. Macleod, G.T., and Zinsmaier, K.E. (2006) Synaptic homeostasis on the fast track. *Neuron* 52, 569-571.
63. Turrigiano, G.G., and Nelson, S.B. (2004) Homeostatic plasticity in the developing nervous system. *Nat Rev Neurosci* 5, 97-107.
64. Ramocki, M.B., and Zoghbi, H.Y. (2008) Failure of neuronal homeostasis results in common neuropsychiatric phenotypes. *Nature* 455, 912-918.
65. Yu, L.M., and Goda, Y. (2009) Dendritic signalling and homeostatic adaptation. *Curr Opin Neurobiol* 19, 327-335.

66. Bourgeron, T. (2007) The possible interplay of synaptic and clock genes in autism spectrum disorders. *Cold Spring Harb Symp Quant Biol* 72, 645-654.
67. Melke, J., et al. (2008) Abnormal Melatonin Synthesis in Autism Spectrum Disorders. *Mol Psychiatry* May 15.
68. Miller, G. (2009) Neuroscience. Sleeping to reset overstimulated synapses. *Science* 324, 22.
69. Stickgold, R., and Walker, M.P. (2005) Memory consolidation and reconsolidation: what is the role of sleep? *Trends Neurosci* 28, 408-415.
70. Toro, R., et al. (2010) Key role for gene dosage and synaptic homeostasis in autism spectrum disorders. *Trends Genet*, in press.
71. Garber, K.B., et al. (2008) Fragile X syndrome. *Eur J Hum Genet* 16, 666-672.
72. Amir, R.E., et al. (1999) Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. *Nature Genetics* 23, 185-188.
73. Wiznitzer, M. (2004) Autism and tuberous sclerosis. *J Child Neurol* 19, 675-679.
74. Rosser, T.L., and Packer, R.J. (2003) Neurocognitive dysfunction in children with neurofibromatosis type 1. *Curr Neurol Neurosci Rep* 3, 129-136.
75. Butler, M.G., et al. (2005) Subset of individuals with autism spectrum disorders and extreme macrocephaly associated with germline PTEN tumour suppressor gene mutations. *J Med Genet* 42, 318-321.
76. Splawski, I., et al. (2006) CACNA1H mutations in autism spectrum disorders. *J Biol Chem* 281, 22085-22091.
77. Feng, J., et al. (2006) High frequency of neurexin 1beta signal peptide structural variants in patients with autism. *Neurosci Lett* 409, 10-13.
78. Fernandez, T., et al. (2008) Disruption of Contactin 4 (CNTN4) results in developmental delay and other features of 3p deletion syndrome. *Am J Hum Genet* 82, 1385.
79. Verkerk, A.J., et al. (2003) CNTNAP2 is disrupted in a family with Gilles de la Tourette syndrome and obsessive compulsive disorder. *Genomics* 82, 1-9.
80. Friedman, J.I., et al. (2008) CNTNAP2 gene dosage variation is associated with schizophrenia and epilepsy. *Mol Psychiatry* 13, 261-266.
81. Castermans, D., et al. (2003) The neurobeachin gene is disrupted by a translocation in a patient with idiopathic autism. *J Med Genet* 40, 352-356.
82. Gauthier, J., et al. (2008) Novel de novo SHANK3 mutation in autistic patients. *Am J Med Genet B Neuropsychiatr Genet*
83. Jamain, S., et al. (2003) Mutations of the X-linked genes encoding neuroligins NLGN3 and NLGN4 are associated with autism. *Nat Genet* 34, 27-29
84. Piton, A., et al. (2008) Mutations in the calcium-related gene IL1RAPL1 are associated with autism. *Hum Mol Genet* 17, 3965-3974.
85. Melke, J., et al. (2008) Abnormal melatonin synthesis in autism spectrum disorders. *Mol Psychiatry* 13, 90-98.
86. Cai, G., et al. (2008) Multiplex ligation-dependent probe amplification for genetic screening in autism spectrum disorders: Efficient identification of known microduplications and identification of a novel microduplication in ASMT. *BMC Med Genomics* 1, 50.
87. Toma, C., et al. (2007) Is ASMT a susceptibility gene for autism spectrum disorders? A replication study in European populations. *Mol Psychiatry* 12, 977-979.
88. Williams, J.M., et al. (2009) A 1q42 deletion involving DISC1, DISC2, and TSNAX in an autism spectrum disorder. *Am J Med Genet A* 149A, 1758-1762.
89. Petek, E., et al. (2007) Molecular and genomic studies of IMMP2L and mutation

- screening in autism and Tourette syndrome. *Mol Genet Genomics* 277, 71–81
90. Bucan, M., *et al.* (2009) Genome-wide analyses of exonic copy number variants in a family-based study point to novel autism susceptibility genes. *PLoS Genet* 5, e1000536.
  91. Turunen, J.A., *et al.* (2008) Mitochondrial aspartate/glutamate carrier SLC25A12 gene is associated with autism. *Autism Res* 1, 189–192.
  92. Ramoz, N., *et al.* (2004) Linkage and association of the mitochondrial aspartate/glutamate carrier SLC25A12 gene with autism. *Am J Psychiatry* 161, 662–669.
  93. Skaar, D.A., *et al.* (2005) Analysis of the RELN gene as a genetic risk factor for autism. *Mol Psychiatry* 10, 563–571.
  94. Bonora, E., *et al.* (2005) Mutation screening and association analysis of six candidate genes for autism on chromosome 7q. *Eur J Hum Genet* 13, 198–207.
  95. Benayed, R., *et al.* (2005) Support for the homeobox transcription factor gene ENGRAILED 2 as an autism spectrum disorder susceptibility locus. *Am J Hum Genet* 77, 851–868.
  96. Barnby, G., *et al.* (2005) Candidate-gene screening and association analysis at the autism-susceptibility locus on chromosome 16p: evidence of association at GRIN2A and ABAT. *Am J Hum Genet* 76, 950–966.
  97. Devlin, B., *et al.* (2005) Autism and the serotonin transporter: the long and short of it. *Mol Psychiatry* 10, 1110–1116.
  98. Weiss, L.A., *et al.* (2006) Variation in ITGB3 is associated with whole-blood serotonin level and autism susceptibility. *Eur J Hum Genet* 14, 923–931.
  99. Kilpinen, H., *et al.* (2009) Linkage and linkage disequilibrium scan for autism loci in an extended pedigree from Finland. *Hum Mol Genet* 18, 2912–2921.

## Databases used in this review

DECIPHER v4.3

<https://decipher.sanger.ac.uk/application/>

Autism Genetic Database (AGD)

<http://wren.bcf.ku.edu/>

Autism CNV Database

[http://projects.tcag.ca/autism\\_500k/](http://projects.tcag.ca/autism_500k/)

AutDB

[www.mindspec.org/autdb.html](http://www.mindspec.org/autdb.html)

BioGPS

<http://biogps.gnf.org/#goto=welcome>

UCSC Genome browser

<http://genome.ucsc.edu>

# NEUROSCIENCE, EDUCATION, AND LEARNING DISABILITIES

■ ALBERT M. GALABURDA

We are entering an age in which knowledge about the brain in general, and the mind in particular,<sup>1</sup> will inform policy. Genetics already informs policy, which is curious since advances in genetics are significantly more recent than advances in the brain sciences, including cognitive science, and the distance between genes and behavior is long and complex, often making poor predictions from the former to the latter. Too much has been learned about brain structure and function (including mental structure and function), their development and involution throughout the life span, and their deterioration after injury and illness, to ignore in fields such as the law, education, economics, even the humanities and others relevant to human happiness and human progress. For example, biological brain markers exist to help predict the cognitive development of children, and much is known about how children, even infants, learn (Benarós, Lipina, Segretin, Hermida, & Jorge, 2010; Berrettini, 2005; Bloom & Weisberg, 2007; Kebir, Tabbane, Sengupta, & Joobar, 2009; Morley & Montgomery, 2001; Plomin & Craig, 2001; van Belzen & Heutink, 2006). Likewise, not only genetic characteristics, but also brain structural and functional markers exist that help diagnose and design treatments for developmental disorders affecting perception, cognition, and behavior, although this is still to be considered a nascent area of research (Benarós, *et al.*, 2010; Eckert, 2004; Keenan, Thangaraj, Halpern, & Schlaug, 2001; Zamarian, Ischebeck, & Delazer, 2009; Zatorre, 2003). In this brief and focused review, I will outline some of the progress made in the field of learning disabilities, particularly the biology of developmental dyslexia, which has the potential to grow into a mature neuroscience of education.

## Advances in genetics and neuroscience

Advances in the neurosciences and genetics have a bearing on the future of education. Starting with genetics, just as the field of pharmacogenomics looms near (Lee & Mudaliar, 2009; Service, 2005), which means that soon

<sup>1</sup> Note that here I use the word 'mind' as part of the concept of brain, whereby brain also consists of structures and functions that lie outside the mind, e.g., regulation of blood pressure, temperature control, endocrine homeostasis, etc.

we will be able to know with better confidence which medications work with which people and how to minimize undesirable side effects after examining specific genetic characteristics of a given individual, we can anticipate with equal certainty that genetics will allow us to know what educational programs work better for what children. This is not pie in the sky; instead, I am referring to empirical data correlating learning styles (presentation and testing formats, speed of learning, cognitive strengths and weaknesses, etc.) with single nucleotide polymorphisms or haplotypes in genetically characterized human populations. However, the empirical research still needs to be done, which means that new resources must be allocated to this type of research, which in turn depends on the priority society gives to education. This is laborious research requiring large Ns in the samples, culturally normed psychological batteries and/or well circumscribed and highly reproducible cognitive/behavioral endophenotypes, as well as genomic analyses with high throughput and low cost. But, even assuming that this difficult to obtain knowledge can be gathered, it is still a substantial challenge to develop curricula based on it and train educators to apply them and measure their outcome, both at short and long-term follow up times.

In addition to genetics, knowledge from neuroscience also lends itself to applications to education, and I would hypothesize that the predictive value of neuroscience data to learning is apt to be, on the average, greater than that of genetic data. This is explained simply by the fact that the distance between brain and behavior is shorter than that between developmental genes and behavior, where there is much time and many possible strategies for compensation. But neuroscience is a broad subject, ranging from genetic expression in neural tissues, where predictive value is more closely shared with other aspects of genetics, to downstream pathways in cells, the formation of circuits and networks, cognitive psychology dealing with the structure of sensory-perceptual, cognitive, and behavioral representations and processes in the mind, where mental structures are much more closely paired with observed behavior. Thus, for example, the best prediction for dyslexia is not the presence of a risk allele, or even a deviant manifestation of brain asymmetry, but rather the presence of metaphonological weakness. Moreover, each of these levels has a developmental history that must be taken into consideration, as abnormal neural structures during development are possibly compatible with substantial compensation or worsening later on.

Neuroscience knowledge at low levels, involving gene expression and signaling pathways, has potential for helping develop functional chemical markers for learning style – for instance relating to ligands and receptors that are activated on PET or MRI scans during particular tasks – as well as drugs that

can enhance learning, diminish forgetting, improve attention, etc. (Eisdorfer, Nowlin, & Wilkie, 1970; Greely *et al.*, 2008; Marshall, 2004; Young & Colpaert, 2009). At the highest levels of cognitive psychology, knowledge about the structure and development of the mind can serve to devise better formats and timings for presenting educational materials (Roederer & Moody, 2008; Watson & Sanderson, 2007; Yeh, Merlo, Wickens, & Brandenburg, 2003). At the mid-levels, knowledge of structural and functional anatomy, particularly as obtained by high resolution *in vivo* imaging of the brain anatomy or by activation studies under specific cognitive and sensory-perceptual challenges, can serve not only for identifying variant anatomies associated with disability or advantage and deviant location and size of activation under specific tasks, but also to assess the effects of learning, unlearning, and the treatment of learning disorders and other disorders of cognitive function (Blair & Diamond, 2008; Draganski & May, 2008; Shaywitz & Shaywitz, 2008). However, it should be made clear that these markers are unlikely to jump up and declare themselves, as often the most obvious findings are not visible if one does not have a prediction for their existence. For instance, for decades the obvious asymmetry of the planum temporale was missed, until von Economo and Horn looked for it (Economo & Horn, 1930).

Ultimately, it is difficult and probably ill-advised to separate genetics from neuroscience, and indeed from all other branches of human biology, when thinking about the elements that contribute to learning in children and adults. A healthy mind begins with healthy genes, continues with healthy brain development, and ends with a healthy cognitive and emotional environment conducive to learning, which in turn depend on a social and political system that takes the health and education of children seriously. Healthy brain development starts with a healthy pregnancy (healthy genes and intrauterine environment) and continues with good nutrition, a culturally enriched and energetic family environment, public health measures aimed at arresting infections and toxic exposures, minimization of violence and personal loss, and the preservation of culture and the desire to pass it on and improve it through child education. Positive exposure at any of these levels propagates quickly to the other levels and augments the odds that these other levels will also be positive; injury at any of these levels also propagates quickly to the other levels. Thus toxic exposures can damage genes (Wallace, 2005; Yamashita & Matsumoto, 2007) and family stress and violence can kill hippocampal neurons, even when the affected individual has not suffered direct, visible physical injury (Eiland & McEwen, 2010). Ultimately, then, it is not possible to think of genetics, neuroscience, and education, without thinking of society as a whole.



## Cultural bases of developmental dyslexia

Dyslexia has from the start been defined as a difficulty with learning to read and with reaching normal reading competency (Fletcher, 2009; Lyon & Moats, 1997), and continues to be so in the schools and in the lay literature, sometimes reduced to the inaccurate observation that it consists mainly of reading and writing in mirror (Terepocki, Kruk, & Willows, 2002). Recently, however, *endophenotypes*, such as phonological awareness or magnocellular function, increasingly have entered scientific jargon to stand for dyslexia after studies associating these features of reading disorders with genetic and/or neurobiological characteristics have been productive (Bishop, 2009; Fisher & DeFries, 2002; Fisher & Francks, 2006; Igo, *et al.*, 2006; Kebir, *et al.*, 2009; Roeske, *et al.*; C.M. Stein, *et al.*, 2006; J. Stein, 2001). 'Dyslexia', in fact, may have become an outdated term, just as 'diabetes' standing alone is an outdated term now replaced by 'diabetes mellitus, types one or two', 'gestational diabetes' and 'diabetes insipidus', with substantial biological differences among them.

Although biological differences among dyslexics, such as being identified by differences in one single nucleotide polymorphism or another, have not as yet served to differentiate among different behavioral forms of dyslexia (but see, by comparison, neurophysiological markers (Lachmann, Berti, Kujala, & Schroger, 2005)), it is possible that this differentiation will become clear in the near future, once the appropriate behavioral endophenotypes are identified. This limitation notwithstanding, efforts to understand purely environmental, cultural factors in dyslexia continue to take place and shed light onto the relationship between dyslexia and culture. Thus, for instance, the structure of the native language determines the incidence, prevalence, and behavioral characteristics of dyslexia (Huessy, 1967; Paulesu *et al.*, 2001; Ziegler & Goswami, 2005; Ziegler, Perry, MaWyatt, Ladner, & Schulte-Korne, 2003). For instance, whereas in languages with opaque orthographies, such as English, most dyslexics, particularly young ones, read slowly and make phonological errors (e.g., reading 'symphony' for 'sympathy'), in languages such as Finnish and Italian, where the orthography is transparent, only slow reading and poor spelling are seen (Angelelli, Notarnicola, Judica, Zoccolotti, & Luzzatti; Holopainen, Ahonen, & Lyytinen, 2001; Kiuru *et al.*; Serrano & Defior, 2008). On the other hand, learning a foreign language is a challenge for dyslexics anywhere (Downey, Snyder, & Hill, 2000; Sparks, Patton, Ganschow, Humbach, & Javorsky, 2006).

There is a longstanding debate as to whether dyslexia should be defined independently from intelligence, or should take intelligence into account. Although it is not possible in this brief chapter to review this complex sub-

ject, I want to make some comments that may be relevant to the subject of education, dyslexia, and neuroscience (for a more general recent review, please see (Gustafson & Samuelsson, 1999)). Intelligence, as we measure it, is influenced not only by differences in aptitude, motivation, attention, and alertness, but also by accumulated knowledge, which depends on several factors, including family and societal encouragement, opportunity, and support. In literate societies, dyslexia interferes with the acquisition of knowledge, since a large proportion of this knowledge is received *via* the written word, and dyslexics, on average, read less. This need not be true in societies where knowledge is imparted by different means, such as by imitation and story telling. Thus, it is difficult to separate intelligence, as we measure it, from a reading disorder. Even the portions of the intelligence test dealing with non-verbal skills and achievement depend in part on verbal abilities, since this is the medium through which instructions are given for skill acquisition and skill testing. In general, non-verbal abilities are found to be normal in dyslexic children (Del Giudice *et al.*, 2000, but c.f. Eden, Stein, Wood, & Wood, 1996; Eden, Wood, & Stein, 2003; Russeler, Scholz, Jordan, & Quaiser-Pohl, 2005), and, in fact, they may be underestimated during testing (Attree, Turner, & Cowell, 2009; Gotestam, 1990).

Even as dyslexia interferes with the measurement of intelligence, intelligence could interfere with the measurement of dyslexia, especially if the measures focus on reading speed and reading comprehension. Thus, a dyslexic endowed with a powerful memory will be helped with decoding text because he will be better able to guess at words he is having difficulty decoding based on prior knowledge. This type of dyslexic would read text quite well, even if he would trip when reading a word list, where he does not derive benefit from semantic, syntactic, and pragmatic cues. Similarly, a dyslexic endowed with a well-tuned attention and executive system will be able to better manage information during the original experience of acquisition and subsequent retrieval stages, such that he will be less dependent on his phonological abilities to derive meaning from text. Does this mean that his phonological abilities are stronger than those of a child who is less able? Actually, they could even be weaker, as these are independent mental faculties; but it is clear that the intelligent child with relatively mild phonological deficits will do best, and may actually defy detection and diagnosis, while the less intelligent child with severe phonological deficits will do worst. Thus, the core system mainly responsible for dyslexia, the phonological module or access to it (Ramus & Szenkovits, 2008), is independent of intelligence, in that it can be either strong or weak in intelligent and less intelligent children; thus, the influence of intelligence on the ultimate clin-

ical manifestations of a weak phonological module is difficult to ignore. What this also says is that, just as we have been able to think of and implement different enrichment programs for normally developing children according to their level of intelligence, we should likewise not treat all dyslexic children equally, and should be receptive to thinking of ways of enriching their educational experience through especially designed educational programs. Similarly, children with weaker memory and executive functions should not be expected to learn most efficiently using educational systems that have been designed without concern for the diversity of intellectual skills. This is not a matter of the influence of neuroscience on education, but rather on the importance of developmental psychology for education.

### **Neuroscience of dyslexia**

There are two lines of research that characterize the neuroscience of dyslexia. First, there are imaging studies *in vivo* on dyslexics that investigate how the brain activates when performing language, reading and other cognitive tasks, which have shown differences between them and appropriate reading controls (e.g. Demonet, Taylor, & Chaix, 2004; Pugh *et al.*, 2000). Similarly, *in vivo* imaging studies have been able to show anatomical differences between dyslexic and control brains (see, for instance, Chang *et al.*, 2007; Leonard & Eckert, 2008; Pernet, Andersson, Paulesu, & Demonet, 2009). The main usefulness of knowing about these anatomical and physiological differences is their potential for (1) helping in the early diagnosis of dyslexia, before the clinical deficits are evident, so that preventive and treatment approaches can be implemented, and (2) contributing to the classification of the disorder into subtypes that may respond to different forms of prevention and treatment. For these two objectives to be reached, it appears that the most important factor is to deploy the neuroscience tools much earlier in development, at a time when the forerunners of the dyslexic cognitive and behavioral phenotypes are not well known and may look very different from the cognitive and behavioral picture at the usual time of diagnosis. However, early identification has remained a challenge, although some progress is being achieved (Benasich *et al.*, 2006; Facioetti *et al.*; Goswami *et al.*; Lyytinen *et al.*, 2004; Raschle, Chang, & Gaab; van der Lely & Marshall). Thus, for quite some time investigators have been studying younger siblings of dyslexic children, who are considered to be at an increased risk of developing dyslexia, based on early investigations demonstrating familial aggregation (DeFries, Singer, Foch, & Lewitter, 1978). More recent genetic studies using linkage and genomewide association have identified several risk alleles, some of which have gained additional strength

through replication studies in various populations and larger numbers (for recent reviews, see Fisher & Francks, 2006; Galaburda, LoTurco, Ramus, Fitch, & Rosen, 2006; Scerri & Schulte Korne; Smith, 2007). Thus, of these *KIAA0319*, *DCDC2*, and *DYX1C1* predict for increase risk of developing dyslexia, but, as with other complex traits, account for a small proportion of the dyslexic population. It is expected that additional genes will be found and associations strengthened in larger numbers as the field of genetic epidemiology continues to advance, which has been the case over the past decade. Less likely to succeed, in my view, will be our ability to link specific genetic mutations or variants to subtypes of dyslexia, since it is likely to be the case, and there is some evidence for this (Galaburda, *et al.*, 2006), that multiple genes affected participate in the same molecular pathways, thus leading ultimately to both shared brain variants and cognitive phenotypes.

### **The dyslexic brain**

Even though dyslexia, as defined, is diagnosed during the time when a child is learning to read, usually between 5 and 7 years of age, the brain changes that seem to predispose to the learning disorder are present from a time before birth (Galaburda & Kemper, 1979; Galaburda, Sherman, Rosen, Aboitiz, & Geschwind, 1985; Chang *et al.*, 2007). The first anatomical studies of dyslexia, performed on autopsy brains, disclosed evidence of neuronal migration abnormalities. These studies were limited by the fact that the number of human brains examined at autopsy was small and because additional autopsy studies were not published by others, most likely as a result of the difficulty in obtaining these brains and funding this type of research, rather than because of the finding of non confirmatory results. As a way to get around the limitations of the human autopsy studies, Galaburda and colleagues searched for and discovered mouse mutants that exhibited similar neuronal migration anomalies, and which also had learning deficits (Rosen, Sherman, & Galaburda, 1989; Rosen, Sherman, Mehler, Emsbo, & Galaburda, 1989; Sherman, Galaburda, Behan, & Rosen, 1987; Sherman, Morrison, Rosen, Behan, & Galaburda, 1990; Sherman, Stone, Press, Rosen, & Galaburda, 1990; Sherman, Stone, Rosen, & Galaburda, 1990). These early animal studies were very useful for establishing the relationship between focal neuronal migration anomalies, abnormal circuits, and abnormal learning behaviors, but lacked the ability to establish causal relationships among these findings. However, a stronger causal association between neuronal migration anomalies and learning deficits was established after these investigators learned to create neuronal migrational anomalies in otherwise normal animals. After induction of anomalies, these otherwise normal an-

imals exhibited anatomical and behavioral changes that modeled some aspects of dyslexia in humans (Herman, Galaburda, Fitch, Carter, & Rosen, 1997; Rosen, Burstein, & Galaburda, 2000; Rosen, Herman, & Galaburda, 1999; Rosen, Mesples, Hendriks, & Galaburda, 2006; Rosen, Press, Sherman, & Galaburda, 1992; Rosen, Sherman, & Galaburda, 1994, 1996; Rosen, Sigel, Sherman, & Galaburda, 1995; Rosen, Waters, Galaburda, & Denenberg, 1995; Rosen, Windzio, & Galaburda, 2001). Specifically, the rats that were thus treated showed difficulties processing certain sounds (Clark, Rosen, Tallal, & Fitch, 2000; Fitch, Breslawski, Rosen, & Chrobak, 2008; Herman, *et al.*, 1997; Peiffer, Friedman, Rosen, & Fitch, 2004; Peiffer, Rosen, & Fitch, 2002, 2004; Threlkeld *et al.*, 2007), and it was concluded that similar anatomical abnormalities in humans might also cause auditory processing deficits that could predispose to phonological deficits during and after language acquisition.

Additional work in rats with induced neuronal migration abnormalities were shown to exhibit abnormal thalamic architecture and abnormal axonal connections between the thalamus and the cortex (Herman, *et al.*, 1997; Livingstone, Rosen, Drislane, & Galaburda, 1991; Rosen, *et al.*, 2000; Rosen, *et al.*, 2006), in addition to abnormal cortical architecture and cortico-cortical connections both within and between the hemispheres. This, coupled with neurophysiological studies that showed aberrant acoustic representations in the rat's auditory cortex (Escabi, Higgins, Galaburda, Rosen, & Read, 2007; Higgins, Escabi, Rosen, Galaburda, & Read, 2008), suggested that an altered thalamocortical relationship might be behind the abnormal auditory behaviors in this rat model of dyslexia. Further details were uncovered by this research, such as male-female differences in these thalamic changes, with female thalami showing an absent response to induction of cortical neuronal migration accompanied by absent abnormalities in acoustic processing. Thus, part of the gender difference reported in dyslexia could be explained by gender-differences in the response to cortical injury, as it concerns cortico-thalamic organization.

### **Genes and the dyslexic brain**

The earlier rodent models of abnormal auditory behaviors resulting from early damage to the cerebral cortex and secondary thalamic changes helped to understand the relationship between developmental cortical abnormalities and abnormal auditory processing, although it remained an incomplete dyslexia model for two reasons. First, abnormal auditory processing is not universally found among dyslexics, so experts argued that it is not necessary for dyslexia to occur, and, by extension, the acoustic deficits in the rat are ir-

relevant. Less clear is the answer to whether the presence of abnormal auditory processing during development is sufficient for dyslexia to occur. The fact that acoustic deficits are not found in all dyslexics may be related to the time of testing. Thus, most studies have looked at older children, and it can be argued that the hypothesized acoustic deficits improve with age and may not be diagnosable in a substantial proportion of older children. The work of April Benasich in babies (Benasich, *et al.*, 2006) and results from Holly Fitch's lab in rodents (Peiffer, Friedman, *et al.*, 2004; Threlkeld, *et al.*, 2007) would tend to support this hypothesis. Regarding the second question, whether abnormal auditory processing is sufficient for dyslexia to follow during development, the answer can be more cavalier. Recall, above, that in some languages and in certain cognitive states, e.g., high level of intelligence, and languages with transparent orthographies, the presence of even substantial precursors for dyslexia may not result in dyslexia, at least one that could easily be diagnosed during the school years. Thus, at present, these represent the best arguments for continuing to model dyslexia in rodents, by linking neuronal migration anomalies to abnormal auditory processing. However, this type of research is not a substitution for developmental research targeting infants even in the perinatal period and looking for early evidence of sound processing deficits and abnormal phonological acquisition. Despite the differences between rodents and humans, it is expected the animal research can help guide the types of questions that may be asked in clinical research searching for early markers of dyslexia risk in humans.

That said, the second reason for the rodent lesion model's remaining an incomplete animal model of dyslexia is the fact that injury to the brain has never been found to underlie developmental dyslexia (but see Downie, Frisk, & Jakobson, 2005). On the other hand, epidemiological evidence for a cause of dyslexia<sup>2</sup> has implicated gene mutations or gene variants, thus suggesting that appropriate genetic animal models may shed additional light linking brain and behavior in a causal manner. We have recently developed such animal models in our laboratories, taking advantage of the publication of risk dyslexia alleles in several human populations. Of these alleles, we have worked on the rodent dyslexia risk gene homologs *dyx1c1*, *dcdc2*, and *kiaa0319* (Burbridge *et al.*, 2008; Currier, Etchegaray, Haight, Galaburda, & Rosen, 2011; Peschansky *et al.*, 2010; Rosen *et al.*, 2007; Szalkowski *et al.*, 2010; Threlkeld, *et al.*, 2007). An interesting and most relevant discovery is

<sup>2</sup> Of course, such genetic studies do not establish causality, but make it more likely that a causal relationship exists.

the development of neuronal migration anomalies to the cerebral cortex after silencing any of the three genes by performing intrauterine electroporation of inhibiting short hairpin ribonucleic acid (shRNA) plasmids during the period of neuronal migration to the cortex. The details of these malformations need not be given in this brief review, and it suffices to state that neurons fail to migrate and remain in the subcortex, or migrate abnormally within the cortical layers. The anatomical phenotype partly resembles the migration anomalies described either in autopsy studies or in *in vivo* neuroimaging. Additional important details are still lacking in this model, such as the status of cortical connections to the thalamus and other cortical areas, and the physiological properties of the neurons and networks associated with the malformations. The establishment of abnormalities in these circuits would go a long way in helping explain the behavioral changes associated with the malformations in this model system. However, relatively little information is available on the cognitive/behavioral consequences of inducing malformations by RNA silencing, but delays in processing acoustic information and other deficits have been documented, and in cases where the hippocampus is involved, memory deficits are present, too (Fitch, *et al.*, 2008; Szalkowski, *et al.*, 2010; Threlkeld, *et al.*, 2007). Thus, we already have a model whereby manipulation of candidate genes produces anatomical abnormalities equivalent to those found in dyslexic brains, whereby auditory and memory dysfunction can occur as a result.

In summary, although much more detailed knowledge needs still to be derived in the pathways between abnormal or variant genes and the school failure that is characterized by difficulty with learning to read and achieving normal reading competency, some consistent developmental factors seem to be common. The candidate risk genes that have been published have central nervous system functions and play a role in neuronal migration to the cortex. Previous research has indicated that disorder of neuronal migration to the cortex can be associated with abnormal cortico-cortical connectivity and abnormal acoustic mapping in the cerebral cortex. Related research has shown that the abnormal cortico cortical anatomy and physiology may be the crucial factor underlying deficits in sound and phonological processing in dyslexia.

### **Neuroscience and education**

A neuroscience of learning disorders can contribute to the development of a complete neuroscience of education. For a successful education of children to take place, it is important to know how the mind and brain work, how they achieve mature functioning after a period of developmental



change, and how genes and environments modulate this growth, on-line functioning, and ultimate achievement. As with any biological process, we expect variation in the developmental trajectories and in ultimate achievement, but we do not know as yet what the normal ranges of variation are. We are slightly familiar with the fact that there is variation far outside the normal range, causing cases of genius, cases of learning disability, and occasionally combinations of both. We have very little knowledge about how this happens, and what are the interactions among genes, brains, behaviors, and environments in these situations. However, this type of knowledge is tractable, if enough resources are thrown in the direction of developmental neuroscience and cognitive science, as well as for a scientifically based educational research program. Such an effort is not only expected to shed light on better ways to educate children, with or without learning disabilities, but also are likely to uncover wonderful mysteries about the development of the human mind, the sources of genius and creativity, and the range of human potential.

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## References

- Angelelli, P., Notarnicola, A., Judica, A., Zoccolotti, P., & Luzzatti, C. (2010). Spelling impairments in Italian dyslexic children: phenomenological changes in primary school. *Cortex*, 46(10), 1299-1311.
- Attree, E.A., Turner, M.J., & Cowell, N. (2009). A virtual reality test identifies the visuospatial strengths of adolescents with dyslexia. *Cyberpsychol Behav*, 12(2), 163-168.
- Benarós, S., Lipina, S.J., Segretin, M.S., Hermida, M.J., & Jorge, J.A. (2010). Neuroscience and education: towards the construction of interactive bridges. *Revista de Neurología*, 50(3), 179-186.
- Benasich, A.A., Choudhury, N., Friedman, J.T., Realpe Bonilla, T., Chojnowska, C., & Gou, Z. (2006). The infant as a prelinguistic model for language learning impairments: predicting from event related potentials to behavior. *Neuropsychologia*, 44(3), 396-411.
- Berrettini, W.H. (2005). Genetic bases for endophenotypes in psychiatric disorders. *Dialogues Clin Neurosci*, 7(2), 95-101.
- Bishop, D.V. (2009). Genes, cognition, and communication: insights from neurodevelopmental disorders. *Ann NY Acad Sci*, 1156, 1-18.
- Blair, C., & Diamond, A. (2008). Biological processes in prevention and intervention: the promotion of self-regulation as a means of preventing school failure. *Dev Psychopathol*, 20(3), 899-911.
- Bloom, P., & Weisberg, D.S. (2007). Childhood origins of adult resistance to science. *Science*, 316(5827), 996-997.
- Burbridge, T.J., Wang, Y., Volz, A.J., Peschansky, V.J., Lisann, L., Galaburda, A.M., et

- al. (2008). Postnatal analysis of the effect of embryonic knockdown and overexpression of candidate dyslexia susceptibility gene homolog *Dcdc2* in the rat. *Neuroscience*, 152(3), 723-733.
- Chang, B.S., Katzir, T., Liu, T., Corriveau, K., Barzillai, M., Apse, K.A., et al. (2007). A structural basis for reading fluency: white matter defects in a genetic brain malformation. *Neurology*, 69(23), 2146-2154.
- Clark, M.G., Rosen, G.D., Tallal, P., & Fitch, R.H. (2000). Impaired processing of complex auditory stimuli in rats with induced cerebrocortical microgyria: An animal model of developmental language disabilities. *J Cogn Neurosci*, 12(5), 828-839.
- Currier, T.A., Etchegaray, M.A., Haight, J.L., Galaburda, A.M., & Rosen, G.D. (2011). The effects of embryonic knockdown of the candidate dyslexia susceptibility gene homologue *Dyx1c1* on the distribution of GABAergic neurons in the cerebral cortex. *Neuroscience*, 172, 535-546.
- DeFries, J.C., Singer, S.M., Foch, T.T., & Lewitter, F.I. (1978). Familial nature of reading disability. *Br J Psychiatry*, 132, 361-367.
- Del Giudice, E., Trojano, L., Fragassi, N.A., Posteraro, S., Crisanti, A.F., Tanzarella, P., et al. (2000). Spatial cognition in children. II. Visuospatial and constructional skills in developmental reading disability. *Brain Dev*, 22(6), 368-372.
- Demonet, J.F., Taylor, M.J., & Chaix, Y. (2004). Developmental dyslexia. *Lancet*, 363(9419), 1451-1460.
- Downey, D.M., Snyder, L.E., & Hill, B. (2000). College students with dyslexia: persistent linguistic deficits and foreign language learning. *Dyslexia*, 6(2), 101-111.
- Downie, A.L., Frisk, V., & Jakobson, L.S. (2005). The impact of periventricular brain injury on reading and spelling abilities in the late elementary and adolescent years. *Child Neuropsychol*, 11(6), 479-495.
- Draganski, B., & May, A. (2008). Training induced structural changes in the adult human brain. *Behav Brain Res*, 192(1), 137-142.
- Eckert, M. (2004). Neuroanatomical markers for dyslexia: a review of dyslexia structural imaging studies. *Neuroscientist*, 10(4), 362-371.
- von Economo, C., & Horn, L. (1930). Ueber windungsrelief, masse und rindenarchitektonik der supratemporalflaeche, ihre individuellen und ihre seitenunterschiede. *Zeitschrift fuer die Gesamte Neurologie und Psychiatrie*, 130, 678-757.
- Eden, G.F., Stein, J.F., Wood, H.M., & Wood, F.B. (1996). Differences in visuospatial judgement in reading-disabled and normal children. *Percept Mot Skills*, 82(1), 155-177.
- Eden, G.F., Wood, F.B., & Stein, J.F. (2003). Clock drawing in developmental dyslexia. *J Learn Disabil*, 36(3), 216-228.
- Eiland, L., & McEwen, B.S. (2010). Early life stress followed by subsequent adult chronic stress potentiates anxiety and blunts hippocampal structural remodeling. *Hippocampus*, Sept. 16 [Epub ahead of print].
- Eisdorfer, C., Nowlin, J., & Wilkie, F. (1970). Improvement of learning in the aged by modification of autonomic nervous system activity. *Science*, 170(964), 1327-1329.
- Escabi, M.A., Higgins, N.C., Galaburda, A.M., Rosen, G.D., & Read, H.L. (2007). Early cortical damage in rat somatosensory cortex alters acoustic feature representation in primary auditory cortex. *Neuroscience*, 150(4), 970-983.
- Facoetti, A., Trussardi, A.N., Ruffino, M., Lorusso, M.L., Cattaneo, C., Galli, R., et al. (2010). Multisensory spatial attention deficits are predictive of phonological decoding skills in developmental dyslexia. *J Cogn Neurosci*, 22(5), 1011-1025.
- Fisher, S.E., & DeFries, J.C. (2002). Developmental dyslexia: genetic dissection of a complex cognitive trait. *Nat Rev Neurosci*, 3(10), 767-780.

- Fisher, S.E., & Francks, C. (2006). Genes, cognition and dyslexia: learning to read the genome. *Trends Cogn Sci*, 10(6), 250-257.
- Fitch, R.H., Breslawski, H., Rosen, G.D., & Chrobak, J.J. (2008). Persistent spatial working memory deficits in rats with bilateral cortical microgyria. *Behav Brain Funct*, 4, 45.
- Fletcher, J.M. (2009). Dyslexia: The evolution of a scientific concept. *J Int Neuropsychol Soc*, 15(4), 501-508.
- Galaburda, A.M., & Kemper, T.L. (1979). Cytoarchitectonic abnormalities in developmental dyslexia: a case study. *Ann Neurol*, 6(2), 94-100.
- Galaburda, A.M., LoTurco, J., Ramus, F., Fitch, R.H., & Rosen, G.D. (2006). From genes to behavior in developmental dyslexia. *Nat Neurosci*, 9(10), 1213-1217.
- Galaburda, A.M., Sherman, G.F., Rosen, G.D., Aboitiz, F., & Geschwind, N. (1985). Developmental dyslexia: four consecutive patients with cortical anomalies. *Ann Neurol*, 18(2), 222-233.
- Goswami, U., Wang, H.L., Cruz, A., Fosker, T., Mead, N., & Huss, M. (2011). Language universal sensory deficits in developmental dyslexia: English, Spanish, and Chinese. *J Cogn Neurosci*, 23(2), 325-337.
- Gotestam, K.O. (1990). Lefthandedness among students of architecture and music. *Percept Mot Skills*, 70(3 Pt 2), 1323-1327; discussion 1345-1326.
- Greely, H., Sahakian, B., Harris, J., Kessler, R.C., Gazzaniga, M., Campbell, P., et al. (2008). Towards responsible use of cognitive-enhancing drugs by the healthy. *Nature*, 456(7223), 702-705.
- Gustafson, S., & Samuelsson, S. (1999). Intelligence and dyslexia: implications for diagnosis and intervention. *Scand J Psychol*, 40(2), 127-134.
- Herman, A.E., Galaburda, A.M., Fitch, R.H., Carter, A.R., & Rosen, G.D. (1997). Cerebral microgyria, thalamic cell size and auditory temporal processing in male and female rats. *Cereb Cortex*, 7(5), 453-464.
- Higgins, N.C., Escabi, M.A., Rosen, G.D., Galaburda, A.M., & Read, H.L. (2008). Spectral processing deficits in belt auditory cortex following early postnatal lesions of somatosensory cortex. *Neuroscience*, 153(2), 535-549.
- Holopainen, L., Ahonen, T., & Lyytinen, H. (2001). Predicting delay in reading achievement in a highly transparent language. *J Learn Disabil*, 34(5), 401-413.
- Huessy, H.R. (1967). The comparative epidemiology of reading disability in German and English speaking countries. *Acta Paedopsychiatr*, 34(9), 273-277.
- Igo, R.P., Jr., Chapman, N.H., Berninger, V.W., Matsushita, M., Brkanac, Z., Rothstein, J.H., et al. (2006). Genomewide scan for real-word reading subphenotypes of dyslexia: novel chromosome 13 locus and genetic complexity. *Am J Med Genet B Neuropsychiatr Genet*, 141B(1), 15-27.
- Kebir, O., Tabbane, K., Sengupta, S., & Joobar, R. (2009). Candidate genes and neuropsychological phenotypes in children with ADHD: review of association studies. *J Psychiatry Neurosci*, 34(2), 88-101.
- Keenan, J.P., Thangaraj, V., Halpern, A.R., & Schlaug, G. (2001). Absolute pitch and planum temporale. *Neuroimage*, 14(6), 1402-1408.
- Kiuru, N., Haverinen, K., Salmela Aro, K., Nurmi, J.E., Savolainen, H., & Holopainen, L. (2011). Students With Reading and Spelling Disabilities: Peer Groups and Educational Attainment in Secondary Education. *J Learn Disabil*, 44(6), 556-569.
- Lachmann, T., Berti, S., Kujala, T., & Schroger, E. (2005). Diagnostic subgroups of developmental dyslexia have different deficits in neural processing of tones and phonemes. *Int J Psychophysiol*, 56(2), 105-120.
- Lee, S.S., & Mudaliar, A. (2009). Medicine. Racing forward: the Genomics and Per-

- sonalized Medicine Act. *Science*, 323(5912), 342.
- Leonard, C.M., & Eckert, M.A. (2008). Asymmetry and dyslexia. *Dev Neuropsychol*, 33(6), 663-681.
- Livingstone, M.S., Rosen, G.D., Drislane, F.W., & Galaburda, A.M. (1991). Physiological and anatomical evidence for a magnocellular defect in developmental dyslexia. *Proc Natl Acad Sci U S A*, 88(18), 7943-7947.
- Lyon, G.R., & Moats, L.C. (1997). Critical conceptual and methodological considerations in reading intervention research. *J Learn Disabil*, 30(6), 578-588.
- Lyytinen, H., Aro, M., Eklund, K., Erskine, J., Guttorm, T., Laakso, M.L., et al. (2004). The development of children at familial risk for dyslexia: birth to early school age. *Ann Dyslexia*, 54(2), 184-220.
- Marshall, E. (2004). Forgetting and remembering. A star-studded search for memory enhancing drugs. *Science*, 304(5667), 36-38.
- Morley, K.I., & Montgomery, G.W. (2001). The genetics of cognitive processes: candidate genes in humans and animals. *Behav Genet*, 31(6), 511-531.
- Paulesu, E., Demonet, J.F., Fazio, F., McCrory, E., Chanoine, V., Brunswick, N., et al. (2001). Dyslexia: cultural diversity and biological unity. *Science*, 291(5511), 2165-2167.
- Peiffer, A.M., Friedman, J.T., Rosen, G.D., & Fitch, R.H. (2004). Impaired gap detection in juvenile microgyric rats. *Brain Res Dev Brain Res*, 152(2), 93-98.
- Peiffer, A.M., Rosen, G.D., & Fitch, R.H. (2002). Rapid auditory processing and MGN morphology in microgyric rats reared in varied acoustic environments. *Brain Res Dev Brain Res*, 138(2), 187-193.
- Peiffer, A.M., Rosen, G.D., & Fitch, R.H. (2004). Sex differences in rapid auditory processing deficits in microgyric rats. *Brain Res Dev Brain Res*, 148(1), 53-57.
- Pernet, C., Andersson, J., Paulesu, E., & Demonet, J.F. (2009). When all hypotheses are right: a multifocal account of dyslexia. *Hum Brain Mapp*, 30(7), 2278-2292.
- Peschansky, V.J., Burbridge, T.J., Volz, A.J., Fiondella, C., Wissner Gross, Z., Galaburda, A.M., et al. (2010). The effect of variation in expression of the candidate dyslexia susceptibility gene homolog Kiaa0319 on neuronal migration and dendritic morphology in the rat. *Cereb Cortex*, 20(4), 884-897.
- Plomin, R., & Craig, I. (2001). Genetics, environment and cognitive abilities: review and work in progress towards a genome scan for quantitative trait locus associations using DNA pooling. *British Journal of Psychiatry Suppl.*, 40(s41-48).
- Pugh, K.R., Mencl, W.E., Jenner, A.R., Katz, L., Frost, S.J., Lee, J.R., et al. (2000). Functional neuroimaging studies of reading and reading disability (developmental dyslexia). *Ment Retard Dev Disabil Res Rev*, 6(3), 207-213.
- Ramus, F., & Szenkovits, G. (2008). What phonological deficit? *Q J Exp Psychol (Colchester)*, 61(1), 129-141.
- Raschle, N.M., Chang, M., & Gaab, N. (2011). Structural brain alterations associated with dyslexia predate reading onset. *Neuroimage*, 57(3), 742-749.
- Roederer, M., & Moody, M.A. (2008). Polychromatic plots: graphical display of multidimensional data. *Cytometry A*, 73(9), 868-874.
- Roeske, D., Ludwig, K.U., Neuhoﬀ, N., Becker, J., Bartling, J., Bruder, J., et al. (2011). First genome wide association scan on neurophysiological endophenotypes points to trans-regulation effects on SLC2A3 in dyslexic children. *Mol Psychiatry*, 16(1), 97-107.
- Rosen, G.D., Bai, J., Wang, Y., Fiondella, C.G., Threlkeld, S.W., LoTurco, J.J., et al. (2007). Disruption of neuronal migration by RNAi of *Dyx1c1* results in neocortical and hippocampal malformations. *Cereb Cortex*, 17(11), 2562-2572.

- Rosen, G.D., Burstein, D., & Galaburda, A.M. (2000). Changes in efferent and afferent connectivity in rats with induced cerebrocortical microgyria. *J Comp Neurol*, 418(4), 423-440.
- Rosen, G.D., Herman, A.E., & Galaburda, A.M. (1999). Sex differences in the effects of early neocortical injury on neuronal size distribution of the medial geniculate nucleus in the rat are mediated by perinatal gonadal steroids. *Cereb Cortex*, 9(1), 27-34.
- Rosen, G.D., Mesples, B., Hendriks, M., & Galaburda, A.M. (2006). Histometric changes and cell death in the thalamus after neonatal neocortical injury in the rat. *Neuroscience*, 141(2), 875-888.
- Rosen, G.D., Press, D.M., Sherman, G.F., & Galaburda, A.M. (1992). The development of induced cerebrocortical microgyria in the rat. *J Neuropathol Exp Neurol*, 51(6), 601-611.
- Rosen, G.D., Sherman, G.F., & Galaburda, A.M. (1989). Interhemispheric connections differ between symmetrical and asymmetrical brain regions. *Neuroscience*, 33(3), 525-533.
- Rosen, G.D., Sherman, G.F., & Galaburda, A.M. (1994). Radial glia in the neocortex of adult rats: effects of neonatal brain injury. *Brain Res Dev Brain Res*, 82(1-2), 127-135.
- Rosen, G.D., Sherman, G.F., & Galaburda, A.M. (1996). Birthdates of neurons in induced microgyria. *Brain Res*, 727(1-2), 71-78.
- Rosen, G.D., Sherman, G.F., Mehler, C., Emsbo, K., & Galaburda, A.M. (1989). The effect of developmental neuropathology on neocortical asymmetry in New Zealand black mice. *Int J Neurosci*, 45(3-4), 247-254.
- Rosen, G.D., Sigel, E.A., Sherman, G.F., & Galaburda, A.M. (1995). The neuroprotective effects of MK-801 on the induction of microgyria by freezing injury to the newborn rat neocortex. *Neuroscience*, 69(1), 107-114.
- Rosen, G.D., Waters, N.S., Galaburda, A.M., & Denenberg, V.H. (1995). Behavioral consequences of neonatal injury of the neocortex. *Brain Res*, 681(1-2), 177-189.
- Rosen, G.D., Windzio, H., & Galaburda, A.M. (2001). Unilateral induced neocortical malformation and the formation of ipsilateral and contralateral barrel fields. *Neuroscience*, 103(4), 931-939.
- Russeler, J., Scholz, J., Jordan, K., & Quaiser Pohl, C. (2005). Mental rotation of letters, pictures, and three dimensional objects in German dyslexic children. *Child Neuropsychol*, 11(6), 497-512.
- Scerri, T.S., & Schulte Korne, G. (2010). Genetics of developmental dyslexia. *Eur Child Adolesc Psychiatry*, 19(3), 179-197.
- Serrano, F., & Defior, S. (2008). Dyslexia speed problems in a transparent orthography. *Ann Dyslexia*, 58(1), 81-95.
- Service, R.F. (2005). Pharmacogenomics. Going from genome to pill. *Science*, 308(5730), 1858-1860.
- Shaywitz, S.E., & Shaywitz, B.A. (2008). Paying attention to reading: the neurobiology of reading and dyslexia. *Dev Psychopathol*, 20(4), 1329-1349.
- Sherman, G.F., Galaburda, A.M., Behan, P.O., & Rosen, G.D. (1987). Neuroanatomical anomalies in autoimmune mice. *Acta Neuropathol*, 74(3), 239-242.
- Sherman, G.F., Morrison, L., Rosen, G.D., Behan, P.O., & Galaburda, A.M. (1990). Brain abnormalities in immune defective mice. *Brain Res*, 532(1-2), 25-33.
- Sherman, G.F., Stone, J.S., Press, D.M., Rosen, G.D., & Galaburda, A.M. (1990). Abnormal architecture and connections disclosed by neurofilament staining in the cerebral cortex of autoimmune mice. *Brain Res*, 529(1-2), 202-207.
- Sherman, G.F., Stone, J.S., Rosen, G.D., & Galaburda, A.M. (1990). Neocortical VIP neurons are increased in the hemisphere containing focal cerebrocortical microdysgenesis in New Zealand Black mice. *Brain Res*, 532(1-2), 232-236.

- Smith, S.D. (2007). Genes, language development, and language disorders. *Ment Retard Dev Disabil Res Rev*, 13(1), 96–105.
- Sparks, R.L., Patton, J., Ganschow, L., Humber, N., & Javorsky, J. (2006). Native language predictors of foreign language proficiency and foreign language aptitude. *Ann Dyslexia*, 56(1), 129–160.
- Stein, C.M., Millard, C., Kluge, A., Miscimarra, L.E., Cartier, K.C., Freebairn, L.A., et al. (2006). Speech sound disorder influenced by a locus in 15q14 region. *Behav Genet*, 36(6), 858–868.
- Stein, J. (2001). The magnocellular theory of developmental dyslexia. *Dyslexia*, 7(1), 12–36.
- Szalkowski, C.E., Hinman, J.R., Threlkeld, S.W., Wang, Y., Lepack, A., Rosen, G.D., et al. (2010). Persistent spatial working memory deficits in rats following in utero RNAi of *Dyx1c1*. *Genes Brain Behav*, 10(2), 244–252.
- Terepocki, M., Kruk, R.S., & Willows, D.M. (2002). The incidence and nature of letter orientation errors in reading disability. *J Learn Disabil*, 35(3), 214–233.
- Threlkeld, S.W., McClure, M.M., Bai, J., Wang, Y., LoTurco, J.J., Rosen, G.D., et al. (2007). Developmental disruptions and behavioral impairments in rats following in utero RNAi of *Dyx1c1*. *Brain Res Bull*, 71(5), 508–514.
- van Belzen, M.J., & Heutink, P. (2006). Genetic analysis of psychiatric disorders in humans. *Genes Brain Behav*, 5 Suppl 2, 25–33.
- van der Lely, H.K., & Marshall, C.R. (2010). Assessing component language deficits in the early detection of reading difficulty risk. *J Learn Disabil*, 43(4), 357–368.
- Wallace, D.R. (2005). Overview of molecular, cellular, and genetic neurotoxicology. *Neurol Clin*, 23(2), 307–320.
- Watson, M.O., & Sanderson, P. (2007). Designing for attention with sound: challenges and extensions to ecological interface design. *Hum Factors*, 49(2), 331–346.
- Yamashita, H., & Matsumoto, M. (2007). Molecular pathogenesis, experimental models and new therapeutic strategies for Parkinson's disease. *Regen Med*, 2(4), 447–455.
- Yeh, M., Merlo, J.L., Wickens, C.D., & Brandenburg, D.L. (2003). Head up versus head down: the costs of imprecision, unreliability, and visual clutter on cue effectiveness for display signaling. *Hum Factors*, 45(3), 390–407.
- Young, A.M., & Colpaert, F.C. (2009). Recall of learned information may rely on taking drug again. *Nature*, 457(7229), 533.
- Zamarian, L., Ischebeck, A., & Delazer, M. (2009). Neuroscience of learning arithmetic evidence from brain imaging studies. *Neuroscience and Biobehavioral Reviews*, 33(6), 909–925.
- Zatorre, R.J. (2003). Absolute pitch: a model for understanding the influence of genes and development on neural and cognitive function. *Nat Neurosci*, 6(7), 692–695.
- Ziegler, J.C., & Goswami, U. (2005). Reading acquisition, developmental dyslexia, and skilled reading across languages: a psycholinguistic grain size theory. *Psychol Bull*, 131(1), 3–29.
- Ziegler, J.C., Perry, C., Ma Wyatt, A., Ladner, D., & Schulte Korne, G. (2003). Developmental dyslexia in different languages: language specific or universal? *J Exp Child Psychol*, 86(3), 169–193.



# INTERACTING EXPERIENTIAL AND GENETIC EFFECTS ON HUMAN NEUROCOGNITIVE DEVELOPMENT

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Recent advances in brain imaging now allow for the investigation of the neural bases of cognitive processes important for academic achievement, and the effects of environmental and genetic factors on the development of these processes. Similar methods are used to characterize neuroplasticity, or the ‘changeability’ of brain processes following different kinds of experience. This research has shown that neuroplasticity confers the possibility for brain systems important for academic achievement to be both enhanceable when experiences are good and also vulnerable to deficit if experiences are not adequate. An understanding of the development of these systems, and in particular of the time periods during development when these effects of experience are maximal, can provide important evidence-based information for parents, educators, and policymakers, who can use evidence from this research to inform the development of evidence-based curricula. Here we describe basic research in our laboratory on the neuroplasticity of selective attention. Selective attention plays a critical role in all aspects of learning and memory. Also, as described below, systems important for selective attention are both vulnerable in children from lower socioeconomic status (SES) households (and thus at risk for school failure) and at the same time they display a high degree of enhanceability for example following sensory deprivation within one modality (Stevens and Neville, in press). Therefore we are testing the hypotheses that attention itself is trainable, and that attention acts as a ‘force multiplier’ that amplifies abilities across different domains of cognition/thinking/skills. If attention does act across domains of processing, then training attention should result in gains across a number of domains important for academic success. As discussed below, in this research we also examine the interacting roles of genetics and experience on the development of attention.

## Socioeconomic status

A substantial and growing literature documents the consequences of growing up in different childhood environments on cognitive development and academic achievement (for recent review, see Raizada & Kishiyama,



2010) These environmental differences are typically quantified using measures of socio-economic status (SES), a variable usually quantified by measuring household differences in parental education level, occupational prestige, and income (Ensminger & Fothergill, 2003). While this is the most common method for measuring SES, many other, correlated, factors contribute to differences in household environments related to SES, including prenatal care, stress, physical health and nutrition, substance abuse, parenting attitudes, and school and neighborhood characteristics (Bornstein & Bradley, 2003).

While ‘unpacking’ SES through the assessment of the individual effects of these factors is at present underexplored, the aggregate effect of SES on academic achievement is substantial. Numerous studies, using assessments such as standardized test scores, grades, and graduation rates, have found that children from lower SES backgrounds are at risk for school failure or reduced academic achievement (e.g., Duncan, Brooks-Gunn, & Klebanov, 1994; McLoyd, 1998; Walker, Greenwood, Hart, & Carta, 1994). Research on academic achievement has shown that children from lower SES backgrounds are both under-identified and under-represented in advanced, rigorous coursework of any kind (for review, see Burney & Beilke, 2008). As discussed below, research in developmental cognitive neuroscience has shifted the focus to specific cognitive skills which are central to academic achievement. One such skill is attention.

### **Neuroplasticity of attention**

While attention is a complex construct, most researchers agree on several distinct components of attention. Selective attention is the ability to orient to targeted stimuli and select particular signals for further processing, an ability that depends both on enhancing the signal of interest and suppressing unattended distractors. Alerting is the ability to maintain an alert and focused state, either transiently or in a sustained manner (Posner & Rothbart, 2007). Executive function includes cognitive flexibility, inhibitory control, and working memory (Diamond, 2006). Of these components, selective attention is of particular importance in enabling the neuroplasticity of different brain systems. For example, in monkeys, experience-dependent changes to brain regions important for hearing and touch have been documented; however, these changes do not occur with mere exposure, but rather only when attention is directed toward relevant stimuli (Recanzone, Schreiner, & Merzenich, 1993). Given this, and the central role of attention in learning more generally, the study of the development and neuroplasticity of selective attention is a key focus of research in our laboratory.

In this research a key method we employ is the recording of event-related brain potentials (ERPs), a non-invasive electrophysiological measure of neural processing. The ERP technique enables researchers to 'eavesdrop' on the electrical signals that neurons send when they are processing information. It is similar to the way using a stethoscope enables one to 'eavesdrop' on the functions of the heart. Silver 'buttons' are sewn into a hat worn by the child, and they pick up and amplify the electrical 'brain waves' associated with the task in which the children are asked to engage. Thus, ERPs provide an on-line, multidimensional index of cognitive processes with a temporal resolution of milliseconds in which no overt behavioral response is required, and thus are well suited for use with young children.

Using this methodology we have examined the effects of sustained, selective attention on neural processing using a child-friendly experimental paradigm adapted from well-tested paradigms developed in adults (Hillyard, *et al.*, 1973). In this approach attention is manipulated while keeping physical stimuli, arousal levels, and task demands constant (i.e., the 'Hillyard principle'). For example, competing streams of stimuli are presented (e.g., two different trains of auditory stimuli delivered to different ears), with participants alternating attention to one stream at a time in order to detect rare events in the attended stream. By comparing the brain response to the same physical stimuli (e.g., tones or flashes of light) when a participant is paying attention to these stimuli versus when the participant is attending the other stream, the effects of selective attention can be quantified. Studies of adults using such paradigms have found consistently that selective attention amplifies the neural response to attended stimuli: the electrical response is twice as large to the same physical stimuli when attended versus ignored, and this enhancement occurs by at least 100 milliseconds (Hillyard, Hink, Schwent, & Picton, 1973; Luck, Woodman, & Vogel, 2000; Mangun & Hillyard, 1990). This early attentional modulation is in part domain-general in that it is observed across multiple sensory modalities (e.g., auditory, visual, tactile) and in selection based on different attributes of stimuli, such as timing or location in space. In addition, ERPs can separately index processes of signal enhancement (larger response for attended stimuli) and distractor suppression (reduced response for unattended stimuli).

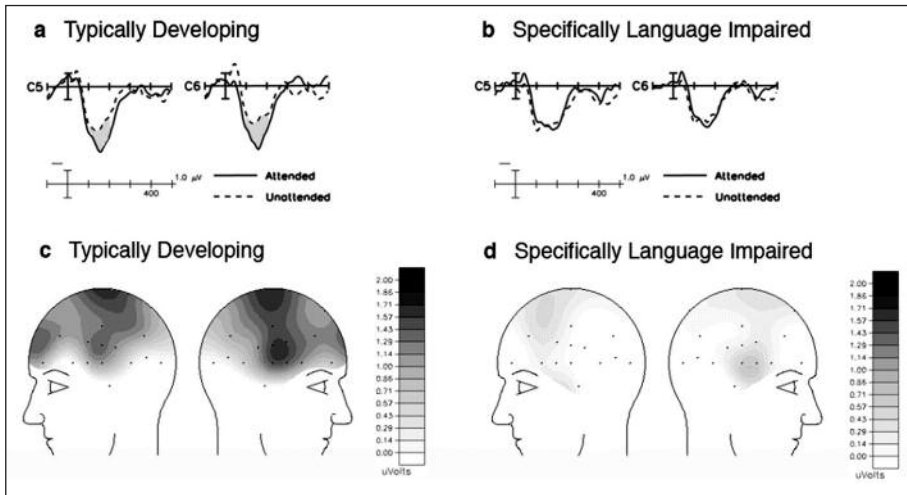
In several studies we have documented the neuroplasticity of this early attentional modulation in the form of enhancements that accompany profoundly different kinds of early experience. In adults born deaf we observe enhancements of this early attentional modulation of visual stimuli compared to hearing adults. Furthermore these effects are specific to the peripheral, but not central, visual field (Bavelier, *et al.*, 2001; Bavelier, *et al.*,

2000; Neville & Lawson, 1987). Similarly, in studies of auditory spatial attention among congenitally blind adults, we observe enhancements of the early attentional modulation compared to sighted adults and these are also specific to peripheral auditory space (Röder, *et al.*, 1999). In a recent study, we have observed that these enhancements of the early attentional modulation are not present in adults blinded later in life, suggesting that early neural mechanisms for selective attention may show the greatest neuroplasticity (i.e., be both enhanceable and vulnerable) earlier in development (Fieger, Röder, Teder-Sälejärvi, Hillyard, & Neville, 2006).

In line with this hypothesis, recent behavioral studies suggest that children at-risk for school failure, including those with poor language or reading abilities or from lower socioeconomic backgrounds, exhibit deficits in aspects of attention including filtering and noise exclusion (Atkinson, 1991; Cherry, 1981; Lipina, Martelli, Vuelta, & Colombo, 2005; Noble, Norman, & Farah, 2005; Sperling, Lu, Manis, & Seidenberg, 2005; Stevens, Sanders, Andersson, & Neville, 2006; Ziegler, Pech-Georgel, George, Alanio, & Lorenzi, 2005). These attentional deficits are found across linguistic and nonlinguistic domains within the auditory and visual modalities, suggesting that the deficits are domain general.

In order to further pursue this hypothesis, we have used ERPs to examine the neural mechanisms of selective attention in typically developing, young children and in groups of children at-risk for school failure. We developed a child-friendly paradigm based on those used with adults in which two different children's stories were presented concurrently, one each from speakers to the left and right of the participant while the participant was asked to attend to one story and ignore the other. Superimposed on the stories were auditory probes to which ERPs were recorded. Typically-developing adults tested with this paradigm showed the early attentional modulation described above (Coch, Sanders, & Neville, 2005). Children as young as three years of age also showed an early attentional modulation within the first 100 milliseconds of processing (Sanders, Stevens, Coch, & Neville, 2006), suggesting that with sufficient cues, children as young as three years of age are able to attend selectively to one of two auditory streams and that doing so doubles the amplitude of neural activity within the attended stream and reduces that of the unattended stream within 100 milliseconds of processing.

We have employed this paradigm to examine selective auditory attention in children with specific language impairment (SLI) aged six to eight years and typically developing control children matched for age, gender, nonverbal IQ, and SES (Stevens, Sanders, & Neville, 2006). As shown in Figure 1



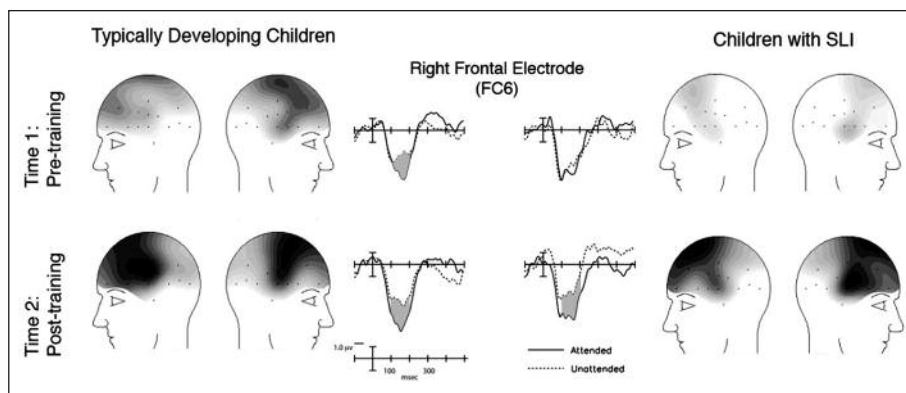
**Figure 1.** Data from the selective auditory attention ERP paradigm showing the early attentional modulation between 100-200 milliseconds. This modulation is the difference between attended and unattended stimuli, (a) in typically developing children ( $p = .001$ ; shaded area) and (b) in children with specific language impairment ( $p > 0.4$ ). Voltage maps of this early attentional modulation show where on the scalp this modulation (darker areas) is present: (c) in typically developing children a large, broadly distributed effect and (d) in children with specific language impairment no modulation with attention. Data from Stevens, *et al.* (2006). Permission pending from Brain Research.

a, c, by 100 milliseconds, typically developing children in this study showed an early attentional modulation as observed in our larger samples of typically developing children. In contrast, children with SLI showed no evidence of neural modulation with attention, despite behavioral performance indicating that they were performing the task as directed (Fig. 1, b, d). These results suggested that deficits in neural mechanisms for attention may in part underlie language difficulties in at least some children with SLI.

In a related line of research, we examined the neural mechanisms of selective attention in children from different SES backgrounds. Previous behavioral studies indicated that children from lower SES backgrounds experience difficulty with selective attention, and particularly in tasks of executive function and in those tasks that require filtering irrelevant information or suppressing automatic responses (Farah, *et al.*, 2006; Lupien, King, Meaney, & McEwen, 2001; Mezzacappa, 2004; Noble, McCandliss, & Farah, 2007; Noble, *et al.*, 2005). Using the same task described above, we observed that children from lower SES backgrounds showed reduced effects of selective attention on neural processing compared to children from higher SES back-

grounds (Fig. 2) (Stevens, Lauinger, & Neville, 2009). These deficits arose from a reduced ability to filter irrelevant information. It has been hypothesized that early deficits in such foundational skills could have consequences for later development and learning (Mezzacappa, 2004; Noble, Norman, & Farah, 2005; Stevens, Lauinger, & Neville, 2009). Since attention acts as a force-multiplier with the possibility to enhance processing across multiple domains, these consequences would likely be reflected in low performance across multiple academic domains. This is consistent with the literature documenting the risk for reduced academic achievement in lower SES children.

Thus, together with the studies of deaf and blind adults described above, studies of children with SLI and of children from lower SES backgrounds point to two sides of the plasticity of early mechanisms of attention. That is, these mechanisms possess considerable neuroplasticity and show both enhancements and vulnerabilities in different populations. This raises the hypothesis that early environmental enrichment in the form of interventions can protect and enhance the plastic and thus potentially vulnerable neurocognitive systems in children with, or at risk for, developmental deficits.



**Figure 2.** Data from the selective auditory attention ERP paradigm showing the early attentional modulation between 100-200 milliseconds in three- to eight-year-old children from different socioeconomic backgrounds. This modulation is the difference between attended and unattended stimuli (shaded) in children from higher socioeconomic backgrounds (upper panel) and lower socioeconomic backgrounds (lower panel). The early attentional modulation is significantly larger in children from higher socioeconomic backgrounds ( $p = .001$ ). Data from Stevens, *et al.*, 2009. Permission pending from Developmental Science.

## Effects of genetics

While the findings that foundational skills such as selective attention vary as a function of SES are compelling, because they are correlational they do not permit the inference that factors related to different SES environments *cause* these differences. Another reasonable hypothesis is that both environmental differences and the cognitive differences associated with lower SES status are the result of shared genetic information between parents and children. One way to investigate this is to directly examine effects of genetic variation on specific aspects of cognition such as selective attention.

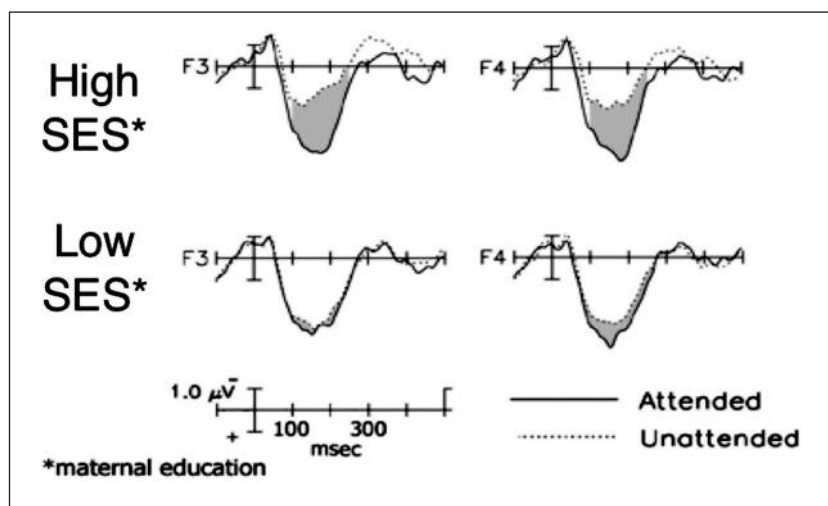
A growing literature documents the impact of variation in genes important in the transport, reception, and metabolism of neurotransmitters which have diverse effects on cognitive function, all of which are implicated in attention (for review, see Savitz, Solms, & Ramesar, 2006). We have examined the effects of variability in types, or alleles, of genes important for the function of neurotransmitters such as dopamine and serotonin on behavioral measures of cognition and the ERP index of selective attention described above. These results showed that in 3- to 5-year-old children, performance on both behavioral measures of cognition and the effects of selective attention on neural processing vary as a function of the variants of certain genes (Bell, *et al.*, 2008; Bell, Voelker, Braasch, & Neville, under review). For example, children with a certain variant of a gene associated with the transport of the chemical dopamine had reduced early attentional modulation (as described above). This same genetic variant has been linked with increased rates of ADHD (Fan, Fossella, Sommer, Wu, & Posner, 2003; Parasuraman, Greenwood, Kumar, & Fosella, 2005; Rueda, Rothbart, McCandliss, Saccamanno, & Posner, 2005; Savitz, *et al.*, 2006). However, as discussed below, these genetic effects interact with characteristics of the environment. Moreover, to date we have not observed any distributional differences in alleles between higher and lower SES children.

## Interventions

Another way to approach the question of the direction of the relation between environments and SES is to directly manipulate the environment. Given the research reviewed above showing that mechanisms of selective attention are both vulnerable and enhanceable early in development, we have been investigating the possibility that attention itself is trainable. Further, given the results that attention skills are predictive of academic achievement, this research is also testing the hypothesis that training attention will result in gains across cognitive domains important for academic success.

In one study we found that, after six weeks of high-intensity (100 min/day) training with a computerized intervention program designed to

improve language skills, both children with SLI and typically developing children who received training showed both increases in standardized measures of receptive language as well as increases in the early attentional modulation following training (Stevens, Fanning, Coch, Sanders, & Neville, 2008) (Fig. 3). Similar gains were not observed in a group of typically developing children who did not receive the training, but were also tested and re-tested after six weeks (Stevens, *et al.*, 2008). In a second study, we examined the neural mechanisms of selective attention in kindergarten children who were either on-track in preliterate skills or at-risk for reading failure. They were studied at the beginning and following the first semester of kindergarten, with the at-risk group receiving supplemental instruction with a reading intervention (Stevens, Currin, *et al.*, 2008; Stevens, *et al.*, in press). The at-risk group raised their performance on behavioral measures of preliterate skills close to that of the on-track group by the end of the year and also showed larger increases in early attentional modulation. In both cases, increases in the early attentional modulation were accompanied



**Figure 3.** Data from the selective auditory attention ERP paradigm showing the early attentional modulation between 100-200 milliseconds in typically developing (TD) children and children with specific language impairment (SLI) before and after six weeks of daily, 100-minute computerized language training. Voltage maps of this early attentional modulation show where on the scalp this modulation (darker areas) is present. Following training, both children with SLI ( $p < .05$ ) and typically developing children ( $p < .1$ ) showed evidence of increased early attentional modulation which were larger than those made in a no-treatment control group ( $p < .01$ ). This group showed no change in the early attentional modulation when retested after a comparable time period ( $p = 0.96$ ). Data from Stevens, *et al.*, in press, *Journal of Learning Disabilities*. Permission pending.



by behavioral changes in other domains also targeted by the training programs, including language and preliteracy skills.

In our latest research, we have developed and implemented attention-training programs informed by basic research on the neuroplasticity of attention. We recently compared two models of an eight-week attention training program for preschool children in a randomized trial including children participating in half-day Head Start classrooms; the details of this study are discussed elsewhere (Stevens, *et al.*, 2010). The two programs, *Attention Boost for Children* (ABC) and *Parents and Children Making Connections – Highlighting Attention* (PCMC-A), both included a child-training component, as well as a family-based training component for parents, caregivers, and siblings (hereafter ‘parents’) of Head Start children.

For both the child and parent components, theory-informed and research-based activities and instructional methods were used to train attention and/or foster a less stressful and more cognitively stimulating home environment. The two programs differed in their relative emphasis (parent-versus child-training) and method of delivery (primarily outside of versus during the school day). The ABC model emphasized child-directed training in small groups (4–6 children: 2 adults). Child sessions lasted 40 minutes/day, four days per week, for eight weeks, and were held as pull-out sessions during the regular Head Start day. Across the eight-week program period, parents received three small group sessions lasting 90 minutes and four support phone calls, held in alternating weeks. The PCMC-A model emphasized parent training in eight weekly, two-hour classes that occurred in the evenings or on weekends, with seven phone calls from the instructor between meetings. The extended hours spent with parents in PCMC-A allowed for more in-depth instructional techniques. The child-directed portion of PCMC-A was an abbreviated version of the ABC child component (eight-session format versus 32-session). Child sessions were 50 minutes in duration and held concurrently with adult sessions.

The child component included a set of small group activities designed to increase self-awareness, self-monitoring, and self-regulation of attention and emotion states. In line with cognitive models of attention, the activities targeted aspects of attention including general alertness, selective attention (including the suppression of distractions), working memory, and switching between tasks. Activities also focused on the awareness of what it means and feels like to pay attention and strategies for emotion regulation, such as the use of full, deep breaths to calm down when feeling frustrated or upset.

The parent-directed component of both interventions included strategies delivered in small group format to address the goals of (a) family stress

regulation with predictability, planning, and problem solving strategies, (b) consistent family structure with contingency-based discipline strategies, (c) cognitive instruction using visualization strategies (e.g., picture notes), (d) language enrichment strategies, and (e) knowledge of age-appropriate behavior and achievement across multiple domains, with a focus on attention. Parents also received information on the attention activities their children participate in, with suggestions for home-based implementation to provide further practice.

Prior to and following the eight-week program period, outcomes were assessed in both children and parents. Assessments of children included laboratory measures of cognition (nonverbal IQ, receptive language, preliteracy skills, and executive functioning) and parent and teacher ratings of children's social skills and problem behaviors. Assessments of parents included self-report measures of stress and parenting confidence/ability as well as direct observations of parents' language use and interaction behaviors with their children.

Across measures of both child and parent outcomes, strong support was found for the PCMC-A model relative to the ABC model. The more parent-focused program was associated with greater gains in nonverbal IQ and receptive language scores for children, as well as higher ratings of social skills and lower ratings of problem behaviors by parents. The more parent-focused program was also associated with higher levels of parents' perceived confidence and ability in parenting, as well as lower levels of parenting stress. Parents' functional language and interaction behaviors with their children additionally showed greater enhancements following the more parent-emphasized model of training. Taken together, these data support both the positive role of early childhood programs in supporting preschool children's attention and early school readiness skills, as well as the powerful role of parents and families in providing effective and comprehensive programs for children.

### **Gene-environment interactions**

As discussed above, we have documented genetic effects on behavioral measures of cognition and an ERP measure of selective attention in preschool children from lower SES backgrounds. However, recent studies suggest that such genetic effects display plasticity that is dependent on and modified by environmental input including parenting quality, parental interventions, and small group interventions (e.g., Caspi, *et al.*, 2003; Caspi, *et al.*, 2002; Bakermans-Kranenburg & van Ijzendoorn, 2006; Bakermans-Kranenburg, van Ijzendoorn, Pijlman, Mesman, & Juffer, 2008; Sheese, Voelker, Rothbart & Posner, 2007). This is consistent with a vast and growing liter-

ature from studies of animals and humans documenting the processes by which environmental conditions in early life can up- and down-regulate gene expression and thus influence the phenotype over the lifetime of the individual (i.e., gene-environment interactions; for recent review, see Meaney, 2010).

A growing body of evidence suggests that environmental factors interact with, and actually modify, genetic effects on aspects of brain function and behavior. To investigate the degree to which the genetic effects we have reported may be modified by environmental input, we have recently begun to examine the effects of our interventions in preschoolers on behavioral measures of cognition and our ERP measure of selective attention as a function of genetic variability (Dennis, Bell, & Neville, in preparation; unpublished observations from our laboratory). We have observed interactions between groups of children who possess different variants of certain genes and their performance gains on behavioral measures of language, early literacy, and other cognitive measures, as well as the effects of selective attention on neural processing. Interestingly, in several cases the genetic variants associated with lower group pre-intervention scores were also associated with greater group gains as a function of the intervention, suggesting that these genetic variants confer a sensitivity to the environment such that environmental enrichment in the form of focused intervention may be particularly powerful. While further research is necessary, this raises the intriguing possibility that in the future genetic information could serve as a valuable tool in modifying learning environments and teaching strategies to better support children's cognitive and academic development. Indeed, a framework to guide future educational policy recently put forth recognizes the potential to leverage cutting-edge biodevelopmental research to inspire fresh thinking in educational policy (Shonkoff, 2010).

## Conclusions

The importance of children's early school readiness skills has coincided with a burgeoning interest in training programs to support these skills in preschool aged children. While many programs emphasize child-only models of attention training, the present study supports more family-centered models of preschool intervention that incorporate parents and caregivers in more than a peripheral way. These findings also underscore the important role of parents and caregivers in providing a nurturing environment to support children's developing attention and school readiness skills, and their capacity to support meaningful change in the lives of their children.

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## References

- Atkinson, J. (1991). Review of human visual development: Crowding and dyslexia. In J. Cronly-Dillon & J. Stein (eds.), *Vision and Visual Dysfunction* (Vol. 13, pp. 44-57).
- Bakermans-Kranenburg, M., & Van Ijzendoorn, M.H. (2006). Gene-environment interaction of the dopamine D4 receptor (DRD4) and observed maternal insensitivity predicting externalizing behavior in preschoolers. *Developmental Psychobiology*, 48, 406-409.
- Bakermans-Kranenburg, M., Van Ijzendoorn, M.H., Pijlman, F.T.A., Mesman, J., & Femmie, J. (2008). Experimental evidence for differential susceptibility: Dopamine D4 receptor polymorphism (DRD4VNTR) moderates intervention effects on toddlers' externalizing behavior in a randomized controlled trial. *Developmental Psychology*, 44, 293-300.
- Bavelier, D., Brozinsky, C., Tomann, A., Mitchell, T., Neville, H., & Liu, G. (2001). Impact of early deafness and early exposure to sign language on the cerebral organization for motion processing. *Journal of Neuroscience*, 21(22), 8931-8942.
- Bavelier, D., Tomann, A., Hutton, C., Mitchell, T., Liu, G., Corina, D., et al. (2000). Visual attention to the periphery is enhanced in congenitally deaf individuals. *Journal of Neuroscience*, 20(17), 1-6.
- Bell, T., Batterink, L., Currin, L., Pakulak, E., Stevens, C., & Neville, H. (2008). Genetic influences on selective auditory attention as indexed by ERPs. Paper presented at the Cognitive Neuroscience Society, San Francisco, CA.
- Bell, T., Voelker, P., Braasch, M., & Neville, H.J. (under review). *Genetic variation and cognition in young children*.
- Bornstein, M.H., & Bradley, R.H. (2003). *Socioeconomic status, parenting, and child development*. Paper presented at the Monographs in parenting series, Mahwah, N.J.
- Burney, V.H., & Beilke, J.R. (2008). The Constraints of Poverty on High Achievement. *Journal for the Education of the Gifted*, 31(3), 171-197.
- Caspi, A., McClay, J., Moffitt, T., Mill, J., Martin, J., Craig, I.W., et al. (2002). Role of genotype in the cycle of violence in maltreated children. *Science*, 297(5582), 851-854.
- Caspi, A., Sugden, K., Moffitt, T.E., Taylor, A., Craig, I.W., Harrington, H.L., et al. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science*, 301(5631), 386-389.
- Cherry, R. (1981). Development of selective auditory attention skills in children. *Perceptual and Motor Skills*, 52, 379-385.
- Coch, D., Sanders, L.D., & Neville, H.J. (2005). An event-related potential study of selective auditory attention in children and adults. *Journal of Cognitive Neuroscience*, 17(4), 605-622.
- Dennis, A., Bell, T., & Neville, H. (in preparation). *Gene by environment interaction in cognition in young children: Effects of genetic variation on sensitivity to focused intervention*.

- Diamond, A. (2006). The early development of executive functions. In E. Bialystok & F. Craik (eds.), *Lifespan Cognition: Mechanisms of Change* (pp. 70-95): Oxford University Press.
- Duncan, G.J., Brooks-Gunn, J., & Klebanov, P.K. (1994). Economic deprivation and early childhood development. *Child Development*, 65(2), 296-318.
- Ensminger, M.E., & Fothergill, K. (2003). *A decade of measuring SES: What it tells us and where to go from here*: Bornstein, Marc H. (ed.); Bradley, Robert H. (ed.).
- Fan, J., Fossella, J., Sommer, T., Wu, Y., & Posner, M.I. (2003). Mapping the genetic variation of executive attention onto brain activity. *Proceedings of the National Academy of Science, USA*, 100(12), 7406-7411.
- Farah, M., Shera, D., Savage, J., Betancourt, L., Giannetta, J., Brodsky, N., et al. (2006). Childhood poverty: Specific associations with neurocognitive development. *Brain Research*, 1110, 166-174.
- Fieger, A., Röder, B., Teder-Sälejärvi, Hilliard, S.A., & Neville, H.J. (2006). Auditory spatial tuning in late onset blind humans. *Journal of Cognitive Neuroscience*, 18(2), 149-157.
- Hillyard, S., Hink, R.F., Schwent, V.L., & Picton, T.W. (1973). Electrical signals of selective attention in the human brain. *Science*, 182(4108), 177-179.
- Lipina, S., Martelli, M., Vuelta, B., & Colombo, J. (2005). Performance on the A-not-B task of Argentinian infants from unsatisfied and satisfied basic needs homes. *Interamerican Journal of Psychology*, 39, 49-60.
- Luck, S.J., Woodman, G.F., & Vogel, E.K. (2000). Event-related potential studies of attention. *Trends in Cognitive Sciences*, 4(11), 432-440.
- Lupien, S.J., King, S., Meaney, M.J., & McEwen, B.S. (2001). Can poverty get under your skin? Basal cortisol levels and cognitive function in children from low and high socioeconomic status. *Development and Psychopathology*, 13, 653-676.
- Mangun, G., & Hillyard, S. (1990). Electrophysiological studies of visual selective attention in humans. In A. Scheibel & A. Wechsler (eds.), *Neurobiology of Higher Cognitive Function* (pp. 271-295). New York: Guilford Publishers.
- McLoyd, V.C. (1998). Socioeconomic disadvantage and child development. *American Psychologist*, 53(2), 185-204.
- Meaney, M.J. (2010). Epigenetics and the biological definition of gene x environment interactions. *Child Development*, 81(1), 41-79.
- Mezzacappa, E. (2004). Alerting, orienting, and executive attention: developmental properties and sociodemographic correlates in epidemiological sample of young, urban children. *Child Development*, 75(5), 1373-1386.
- Neville, H.J., & Lawson, D. (1987). Attention to central and peripheral visual space in a movement detection task: An event-related potential and behavioral study. II. Congenitally deaf adults. *Brain Research*, 405, 268-283.
- Noble, K., McCandliss, B., & Farah, M. (2007). Socioeconomic gradients predict individual differences in neurocognitive abilities. *Developmental Science*, 10, 464-480.
- Noble, K.G., Norman, M.F., & Farah, M.J. (2005). Neurocognitive correlates of socioeconomic status in kindergarten children. *Dev Sci*, 8(1), 74-87.
- Parasuraman, R., Greenwood, P.M., Kumar, R., & Fossella, J. (2005). Behind heritability: Neurotransmitter genes differentially modulate visuospatial attention and working memory. *Psychological Science*, 16, 200-207.
- Posner, M., & Rothbart, M.K. (2007). Research on attention networks as a model for the integration of psychological science. *Annual Review of Psychology*, 58, 1-23.
- Raizada, R.D.S., & Kishiyama, M.M. (2010). Effects of socioeconomic status on brain development, and how cognitive neuroscience may contribute to levelling the

- playing field. *Frontiers in Human Neuroscience*, 4.
- Recanzone, G., Schreiner, C., & Merzenich, M. (1993). Plasticity in the frequency representation of primary auditory cortex following discrimination training in adult owl monkeys. *Journal of Neuroscience*, 12, 87-103.
- Röder, B., Teder-Sälejärvi, W., Sterr, A., Rösler, F., Hillyard, S.A., & Neville, H.J. (1999). Improved auditory spatial tuning in blind humans. *Nature*, 400(6740), 162-166.
- Rueda, M., Rothbart, M., McCandliss, B., Saccamanno, L., & Posner, M. (2005). Training, maturation, and genetic influences on the development of executive attention. *Proceedings of the National Academy of Science, USA*, 102, 14931-14936.
- Sanders, L., Stevens, C., Coch, D., & Neville, H.J. (2006). Selective auditory attention in 3- to 5-year-old children: An event-related potential study. *Neuropsychologia*, 44, 2126-2138.
- Savitz, J., Solms, M., & Ramesar, R. (2006). The molecular genetics of cognition: dopamine, COMT and BDNF. *Genes, Brain, and Behavior*, 5, 311-328.
- Sheese, B.E., Voelker, P.M., Rothbart, M.K., & Posner, M.I. (2007). Parenting quality interacts with genetic variation in dopamine receptor D4 to influence temperament in early childhood. *Developmental Psychopathology*, 19(4), 1039-1046.
- Shonkoff, J.P. (2010). Building a new biodevelopmental framework to guide the future of early childhood policy. *Child Dev*, 81(1), 357-367.
- Sperling, A., Lu, Z., Manis, F.R., & Seidenberg, M.S. (2005). Deficits in perceptual noise exclusion in developmental dyslexia. *Nature Neuroscience*, 8, 862-863.
- Stevens, C., Currin, J., Paulsen, D., Harn, B., Chard, D., Larsen, D., et al. (2008). *Kindergarten children at-risk for reading failure: Electrophysiological measures of selective auditory attention before and after the early reading intervention*. Paper presented at the Cognitive Neuroscience Society, San Francisco, CA.
- Stevens, C., Fanning, J., Coch, D., Sanders, L., & Neville, H. (2008). Neural mechanisms of selective auditory attention are enhanced by computerized training: Electrophysiological evidence from language-impaired and typically developing children. *Brain Research* (1205), 55-69.
- Stevens, C., Fanning, J., Klein, S., and Neville, H. (2010). Development and comparison of two models of preschool attention training. *IES 5<sup>th</sup> Annual Research Conference*.
- Stevens, C., Harn, H., Chard, D., Currin, J., Parisi, D., & Neville, H. (in press). Examining the role of attention and instruction in at-risk kindergarteners: Electrophysiological measures of selective auditory attention before and after an early literacy intervention. *Journal of Learning Disabilities*.
- Stevens, C., Lauinger, B., & Neville, H. (2009). Differences in the neural mechanisms of selective attention in children from different socioeconomic backgrounds: An event-related brain potential study. *Developmental Science*, 12(4), 634-646.
- Stevens, C., and Neville, H. (in press). Different profiles of neuroplasticity in human neurocognition. In S. Lipina and M. Sigman (eds.), *Cognitive neuroscience and education*.
- Stevens, C., Sanders, L., Andersson, A., & Neville, H. (2006). *Vulnerability and plasticity of selective auditory attention in children: Evidence from language-impaired and second-language learners*. Paper presented at the Cognitive Neuroscience Society, San Francisco, CA.
- Stevens, C., Sanders, L., & Neville, H. (2006). Neurophysiological evidence for selective auditory attention deficits in children with specific language impairment. *Brain Research*, 1111, 143-152.
- Walker, D., Greenwood, C., Hart, B., &

- Carta, J. (1994). Prediction of school outcomes based on early language production and socioeconomic factors. *Child Development*, 65, 605-621.
- Ziegler, J.C., Pech-Georgel, C., George, F., Alanio, F.X., & Lorenzi, C. (2005). Deficits in speech perception predict language learning impairment. *Proceedings of the National Academy of Science, USA*, 102(39), 14110-14115.



## THE DEVELOPING BRAIN

# THE ARCHITECTURE OF THE BABY BRAIN

■ GHISLAINE DEHAENE-LAMBERTZ

When we think ‘education’, we often have in mind formal teaching delivered at school. Yet, developmental researches have shown that infants are learning since the first days of life. This informal learning within the small family circle is at the basis of what makes us humans. Recognizing other fellow humans, understanding what she/he is saying, telling stories, walking, running, singing, figuring out space and number, recognizing 3D objects, etc., all essential skills, are the consequences of complex learning process which begins very early on. Because of the poverty of the behavioral repertoire during the first months of life, parents and researchers have difficult access to what an infant thinks, feels, and learns. These early learning capacities have thus long been neglected. Thanks to the development of non-invasive brain-imaging techniques, we can now understand the richness of this stage in life, when parents are their child’s natural teachers. These new tools allow a better exploration of infant early capacities and of their cerebral bases. They reveal an early and already complex organization sustaining the first interactions with the outside world far away from the blooming buzzing confusion postulated by William James (1892). On the contrary, the early particular organization of the human brain provides infants with a remarkable tool to learn about the external world.

Humans have not only a long developmental period but also the different cortical regions have different maturational time-courses. This produces physical constraints on the spreading of information within the neural networks that evolve along childhood and endow the child brain with its functional characteristics. The infant brain has been for a long time described as a few islands of functional cortex among a vast space of barely functional immature regions. What brain imaging studies reveal is that all cortical regions are participating in the infant thoughts. However, the effectiveness of local processing and the speed of information spreading may vary from one region to the next thus explaining the particular dynamic of an infant’s cognition. I would like to propose that our approaches on learning and development in humans should take advantage of the better description of the physical brain. Our hypotheses about learning algorithms should be constrained by the neural ‘hardware’, and take into account the computational properties provided at a given age by the activated networks. I will illustrate my point with language acquisition and show how the early brain organization promotes language learning in the human species.

Neuropsychology and brain-imaging studies have clearly defined the regions involved in speech processing in adults. They are largely left-lateralized and comprised the superior temporal and inferior frontal regions connected by two main pathways: first, a dorsal suprasylvian pathway consisting of the arcuate fasciculus and the superior longitudinal fasciculus linking the posterior temporal and inferior parietal region with area 44 and second, a ventral pathway running through the uncinate and the extreme capsule connecting the anterior temporal region with area 45 (Anwander, Tittgemeyer, von Cramon, Friederici, & Knosche, 2007; Frey, Campbell, Pike, & Petrides, 2008). Three models of development of this network can be considered. First, maturational models postulate that initially only the primary and secondary areas are sufficiently mature to respond to the complex and fast stimulus like speech. Brain imaging studies should thus show activations initially limited to the superior temporal region bordering Heschl's gyrus. Then, as maturation progresses, the efficient network converges into the adult's mature pattern giving the child more resources to process speech. In this model the behavioral progression observed during the first three years of life is thus related to the progressive involvement of regions able to deal with more and more complex computations. A connectionist alternative might propose that the infant's brain is heavily connected and that it is the competition between entries in the different regions that stabilizes the network in the adult configuration. This type of model postulates more diffuse activations in infants than in adults, and also that the same behavior may be sustained by different cortical layouts (Johnson, 2001). The third type of models postulates that an evolutionary change in brain organization is the critical factor that has provided humans with the language possibility and that infants are equipped with a toolbox facilitating language acquisition, this toolbox being based on a specific organization of the perisylvian areas.

Combining structural and functional studies, our results are in favor of the third model. They show that language learning is based on a tripod: First, an early asymmetric organization of the perisylvian areas biasing language processing toward the left side; Second, a linguistic network based on local connectivity within the temporal lobe but also involving long-distance connections with the parietal and notably the frontal areas; Third, this linguistic network is in strong interaction with the social system.

## **1. An asymmetric organization of the human brain**

### ***a. Morphological asymmetries***

A striking particularity of the human brain is its asymmetrical organization climaxing around the posterior sylvian region. A torque movement

pushing the right frontal area forward and the left occipital region backward (petalias) bends the midline towards the right (Yakovlev, 1962) and raises the right Sylvian fissure over the left (LeMay, 1984). This creates a prominent shape difference between the left and right posterior temporal regions (Toga & Thompson, 2003; Van Essen, 2005) elongating the left planum temporale (Geschwind & Levitsky, 1968). Another important asymmetry revealed by brain imaging is a deeper right superior temporal sulcus at the base of Heschl's gyrus (Glasel *et al.*, submitted; Ochiai *et al.*, 2004). Finally Heschl's gyrus itself, where the primary auditory area is located, is thicker on the left side even in deaf people (Emmorey, Allen, Bruss, Schenker, & Damasio, 2003), suggesting that this asymmetry is constituent and not the consequence of an exposure to oral language.

Human brain development is also strongly asymmetric. Several right sulci appear one or two weeks earlier than their left counterparts (Chi *et al.*, 1977; Dubois *et al.*, 2008). The raising and shortening of the right sylvian scissure and a larger left *planum temporale* are also observed during the fetal life (Chi, Dooling, & Gilles, 1977; Cunningham, 1892; Wada, Clarke, & Hamm, 1975; Witelson & Pallie, 1973). Thus at birth, the main asymmetries observed in the adult perisylvian are already present, i.e. first the raising and shortening of the right sylvian fissure, due to the Yakovlevian torque, second an elongated left *planum temporale*, third a thicker Heschl's gyrus and finally a deeper right superior temporal sulcus (Figure 1, p. 256, Glasel *et al.*, submitted; Hill *et al.*, 2010)

Some of these asymmetries are also noticed in the primate brain. A longer left sylvian fissure (Yeni-Komshian & Benson, 1976), a larger left *planum temporale* (Cantalupo, Pilcher, & Hopkins, 2003; Gannon, Holloway, Broadfield, & Braun, 1998; Gilissen, 2001; Hopkins *et al.*, 2008), and a leftward asymmetry in the inferior frontal regions (Cantalupo & Hopkins, 2001) have been described. No study has looked to the newly described deeper right STS. By contrast, the right frontal-left occipital torque is not observed in chimpanzees while the left occipital petalia is clearly seen in gorillas (Gilissen, 2001). However, when present, these asymmetries are never as systematic and strong as in humans, emphasizing that perisylvian regions have been the target of an evolutionary pressure increasing these characteristics in the human lineage.

Several genes with an asymmetric expression in the human brain have been described. For example, LMO4 is asymmetrically expressed toward the right side in the human brain between 12 and 14 weeks of gestation (Sun *et al.*, 2005). Although during convolution development gene expression has become globally symmetric (Johnson *et al.*, 2009), 76% of the human genes

are expressed in the fetal brain during the 18 to 23 weeks of gestation, and 44% of these are differentially regulated. It creates an intricate pattern of patchy regions with complex interactions and possibly locally asymmetrical gene expression that can regulate locally the size of the subventricular zone (Kriegstein, Noctor, & Martinez-Cerdeno, 2006) and thus subsequently impacting the shape of the cortical plate. It may also modulate fiber connectivity constraints that might more or less bend connected regions. In our work, we did not find correlation between the different asymmetries (*planum temporale*, Heschl's gyrus and STS). This suggests that these characteristics might be related to separate gene expressions (see Figure 1, p. 256).

***b. Is there a functional impact of these anatomical left-right differences?***

Although structural asymmetries are present early on, do they subserve functional asymmetries? Because of a better recovery from early lesions compared to what is observed in adults, authors such as Lenneberg (1967) have postulated that the brain might be equipotential at the beginning of life. Brain-imaging studies in normal infants have contradicted this hypothesis. In particular, the *planum temporale* shows hemispheric biases depending on the presented stimulus. When exposed to speech stimuli, its activation is greater on the left side in newborns (Pena *et al.*, 2003) and in two-month-old infants (Dehaene-Lambertz, Dehaene, & Hertz-Pannier, 2002; Dehaene-Lambertz *et al.*, 2010). This is not related to a bigger structure producing stronger activation for any auditory stimulus, responses to piano melodies being symmetric in both planum (see Figure 2, p. 256) (Dehaene-Lambertz *et al.*, 2010). Asymmetries toward the right side have also been observed with non-speech stimuli (Perani *et al.*; Telkemeyer *et al.*, 2009) and when abnormal speech (flattened or hummed speech) has been compared to normal speech (Homae, Watanabe, Nakano, Asakawa, & Taga, 2006). By contrast, Dehaene-Lambertz *et al.* (2002) did not observe difference in lateralization between the same sentences presented forward and backward. Although the prosodic information in backward speech is not usable by infants (e.g. they cannot discriminate backward French from backward Russian whereas they can do it with normal sentences), some phonetic information is preserved (e.g. fricatives, vowels) and the fast acoustic transitions characteristic of a speech stimulus are still present in backward speech but not in the hummed speech used by Homae *et coll.* (2006). Thus, this early bias toward the left side for speech stimuli can be related to the fast transitions present in this type of signal.

Indeed, at birth there is already an asymmetry at the cochlear level revealed by larger left otoacoustic emissions for tones and larger right otoacoustic

emissions for clicks (Sininger & Cone-Wesson, 2004). Because these otoacoustic emissions are modulated by the olivocochlear efferent neurons, which can themselves be modulated by the contralateral auditory cortex (Perrot *et al.*, 2006), it is not possible to disentangle a cortical or subcortical origin for these peripheral asymmetries. In adults, it is proposed that the left auditory cortex has a better temporal resolution (Boemio, Fromm, Braun, & Poeppel, 2005; Zatorre & Belin, 2001) and integrates incoming signal over short time periods (20–50 ms segments) corresponding roughly to the phoneme length. By contrast, the right auditory cortex preferentially integrating over a longer 100–300 ms time-period would be more sensitive to slower acoustic modulations (Giraud *et al.*, 2007). Because of the weak myelination of axons and the less efficient cortical networks, the infant's brain is relatively slow when compared to the adult's brain. Thus arguments based on a differential processing speed between hemispheres and on a tuning of the oscillatory activity of the left-hemisphere on the time-units of speech should first be tested in infants before being generalized to the early age. Furthermore, acoustical parameters alone are not sufficient to explain all lateralized results. It is known in adults that the perception of tones or vowels for example, can be more or less left-lateralized depending on their linguistic value for the subject {Gandour, 2002 #3262; Jacquemot, 2003 #3123}. Similarly in infants, we have shown that the linguistic (vowel identity) and acoustical value (speaker identity) of the same vowel are processed in parallel respectively in the left and right hemisphere in two-month-old infants (Bristow *et al.*, 2009) although both processing rely on spectral analyses. Thus, as in adults, the acoustical properties of the stimulus are not sufficient to explain the lateralization of the brain responses and we need more functional and structural studies to understand what drives speech processing toward the left side. Structural markers and functional results point at least to an early different developmental trajectory of the right and left hemisphere that precedes and does not follow language development (see Figure 2, p. 256).

## 2. The early linguistic network

During resting, the spontaneous fluctuation of the MRI signal is synchronized across cortical regions and studies in adults have shown consistent patterns of correlated activity in different sensory regions but also in higher cognitive systems. Several studies in infants (Fransson *et al.*, 2009; Fransson *et al.*, 2007) and even preterms (Smyser *et al.*, 2010) have shown networks similar to what observed in adults. These results emphasize the fact that short and long distance connections are not only present but might be functional in the subplate before all neurons are even in place in the cortical

plate (Kostovic & Judas). The observation of regional networks in the earliest time of the preterm period (already around 26 weeks postmenstrual age) also emphasizes that the specific and basic functional organization of the human brain is determined early on during pregnancy contradicting a strong version of constructivist hypotheses.

#### *a. A nested organization in the superior temporal lobe*

Activations paradigms underscore the segregation of the brain in regions dealing with different functional properties. In response to speech, activations do not spread over the entire cortex but remain within the adult linguistic network, i.e. the perisylvian regions. This network involves not only the neighboring regions of the auditory cortex but also extends along the superior temporal region toward the parietal and frontal lobe. These regions are not functionally equivalent but present specific functional properties. First, the superior temporal region can be parsed into distinct regions based on their speed of activation (Dehaene-Lambertz, Hertz-Pannier *et al.*, 2006). The phase of the activation in response to a single sentence increases as one moves from the auditory primary cortex toward the posterior part of the superior temporal gyrus and toward the temporal poles and inferior frontal regions (Broca's area) (see Figure 3, p. 257). Given the size of the delays involved (several seconds), this organization is unlikely to solely reflect synaptic delays. Rather, this temporal gradient of activation might be the result of different cognitive operations that integrate over increasingly larger and possibly more abstract speech units, and may therefore require longer processing time or more sustained activity. We are currently testing this hypothesis in infants, and in adults we observed an increase in the size of the activation with an increase of the prosodic tree (Dehaene-Lambertz *et al.*, in preparation).

Second, the superior temporal can also be parsed in subregions depending on their response to repetition. When a sentence is immediately repeated, a repetition suppression effect is observed in the ventral part of the speech activation in infants (Dehaene-Lambertz *et al.*, 2010). A similar effect is present in adults (Dehaene-Lambertz, Dehaene *et al.*, 2006).

This suppression is interpreted as an indication that the upper region of the temporal lobe codes for acoustics or basic linguistic elements, such as phonemes or syllables, which are constantly changing in a sentence, or that the memory buffer is very short in these regions. By contrast, the lower regions of the superior temporal lobe are able to detect a full-sentence repetition indicating that they are coding at a more global level or that they are able to maintain in memory a specific acoustic/linguistic element during several seconds to detect its repetition.



Finally, the superior temporal sulcus possesses speech cross-modal representation. The presentation of an auditory vowel congruent with previous presentation of an articulatory movement but without sound induced a decrease of the electrical response in comparison with an incongruent situation, again in the lower part of the superior temporal region whereas the upper part is indifferent to the visual information (Bristow *et al.*, 2009). These three experiments pointed to a hierarchy of regions coding for more and more complex sound representations along a dorsal ventral gradient and extending posteriorly toward the parieto-temporal junction and anteriorly toward the temporal pole. This hierarchical architecture of the human temporal lobes presents homologies with that of the monkey brain (Kaas & Hackett, 2000; Pandya & Yeterian, 1990). Thus it is possible that human speech recycles a pre-existing primate system for hierarchical auditory representations (Dehaene & Cohen, 2007). Such a nested organization of processing units with progressively longer temporal window of integration would provide infants with an adequate tool to segment the speech stream in its prosodic components.

Testimonies of the parcellisation of the superior temporal region are also encountered in the microstructure of the cortex. We used the magnetic resonance T2 weighted (T2w) signal as a direct window on the microstructure of the cortex and in particular on its maturation (see Figure 4, p. 257). Maturation processes, i.e. the proliferation of membranes (growth of axons and dendrites, proliferation and differentiation of glia cells), the increase of hydrophobic proteolipids constituting the myelin (Barkovich, 2000) and the deposits of ferritine (Fukunaga *et al.*, 2010), change the ratio of free to bound water and thus decrease the T2w signal. Using an index based on this signal, we have quantified maturation within the linguistic network in 14 1- to 4-month-old infants. There is a clear dorsal-ventral gradient of decreasing maturity along the superior temporal region (*planum temporale* > dorsal STS > ventral STS). Furthermore, there is a significant asymmetry of maturation with the left STS lagging behind the right STS (Leroy *et al.*, 2011). This observation may appear in conflict with the functional studies reported above in which the response to auditory stimuli is largely bilateral over temporal areas. The location of the functional asymmetry is more posterior, over the *planum temporale*. In this area, maturation is symmetric except for a segment close to Heschl's gyrus which is more mature on the right than on the left side. Thus the functional lateralization of the linguistic network does not appear as a direct consequence of a maturational lead of one side over the other. What does it mean? It is an early testimony of the differential fate of these two regions. Indeed, during the whole life-span, the

two superior temporal regions develop and age differently (Paus *et al.*, 1999; Sowell *et al.*, 2003; Sowell *et al.*, 2002). For the moment, we ignore how these structural differences are related to functional properties. However these observations emphasize the different genetic fate of the two STS. Because the STS hosts several important functions beside language such as social contact, biological motion perception and audio-visual integration (Hein & Knight, 2008), further studies are needed to understand how the asymmetric pattern of development of this region may favor the development of the verbal and non-verbal human communication system. One hypothesis might be that the left maturation lag might be useful to allow the environment to shape the linguistic representations (see Figure 4, p. 258).

***b. Long-distance connections: storing sound patterns in the inferior parietal areas and memorizing them in the inferior frontal region***

When infants listen to speech, activations are not limited to the temporal lobe. A larger network involving parietal and frontal areas is recruited providing other useful computational resources. When responses to forward and backward speech are compared, forward speech induces stronger activations in the temporal parietal junction. This region is activated more by words than non-words in adults (Binder *et al.*, 2000) and is described as a dictionary of the auditory forms encountered in the native language. Infants of this age have already learned the prosodic contour of their native language (Dehaene-Lambertz & Houston, 1998) and are able to recognize if a sentence comes or not from their native language. We might thus consider this region as a proto-lexicon of the forms of the native language, which stores the finest unit coded at this age (e.g. intonative contour). In adults, cortex is thicker in this same region either in the most fluent bilingual adults and/or in those who have learned a second language at an early age (Mechelli *et al.*, 2004). This confirms the role of this region in early/fluent language learning.

Another important region is the left inferior frontal region. Two-month-old infants can detect a change of phoneme in a series of syllable even after a 2mn delay (Jusczyk, Kennedy, & Jusczyk, 1995). They are thus able to maintain a series of sounds during a short time as adults are able to remember a phone number the time they dial it. In adults this short-term memory is based on the linguistic dorsal pathway connecting the temporo-parietal junction to the inferior frontal cortex through the arcuate fasciculus. In infants, we also observed that when a sentence or a syllable was repeated, an increase of activity was recorded in the left inferior frontal area for the repeated stimulus (Bristow *et al.*, 2009; Dehaene-Lambertz, Hertz-Pannier *et al.*, 2006). This repetition enhancement effect in the frontal region stands

in contrast with the repetition suppression effect in the superior temporal region and emphasizes the effort done by infants. Repetition enhancement is usually seen in adults when they should keep tracks of the repeated stimuli or when they have difficulties to perceive the stimuli.

In the past the frontal areas were considered immature, unable to sustain an efficient functional activity. This affirmation was based on post-mortem and PET/SPECT studies showing an important gap between these regions and the primary cortices for example. However, these studies are scarce and obtained from post-mortem studies in sick children, or they lack spatial resolution in metabolic studies. They are in contradiction with the results presented above (see also Grossman *et al.*, 2008) reporting anterior prefrontal activity when social cues are perceived by infants. Using the T2w normalized index defined above, we compared the degree of maturation of the frontal and temporal linguistic regions. We were surprised to observe that the most immature region was not the inferior frontal region but the left ventral superior temporal sulcus that stands behind all other structures we measured (see Figure 4, p. 258). The primary cortices (motor, sensory and auditory) are as expected the most mature regions. Then, the inferior frontal sulcus, the precentral and all Broca's rami were classified as belonging to the same intermediate maturational group than the planum. The most immature regions of this network are the dorsal and ventral bank of the superior temporal sulcus (STS), with the more immature region being the left ventral bank of the STS. Thus, there is no inconsistency between the functional and the structural results. It is perfectly explicable to observe infants' inferior frontal areas engaged in functional activities. Moreover, correlation analyses reveal that temporal and frontal regions are not developing independently but show correlated inter-individual variability over and above age-related changes between area 44 and the posterior ventral STS. A similar result has been reported in adolescents using cortical thickness as the variable (Lerch *et al.*, 2006). Covariations in cortical microstructure between distant brain areas have thus been proposed as revealing the architecture of the human brain (Chen, He, Rosa-Neto, Germann, & Evans, 2008).

Anterior and posterior linguistic regions are linked by the arcuate fasciculus through the dorsal linguistic pathway. Diffusion tensor imaging MR sequences can be used to follow the maturation of white matter tracts. As myelination progresses, water diffusivity decreases and fractional anisotropy (FA) increases inside the tracts. We measured an asymmetry in the parietal segment of the arcuate with an increase of FA in the left relative to the right tract, suggesting a faster myelination or a more compact tract on the left. This asymmetry was correlated with the asymmetry in maturation in the grey matter of area 44 and the posterior STS (see Figure 5, p. 258).

To summarize, we observe correlations between the maturation of regions belonging to the dorsal linguistic pathway. This dorsal pathway might thus provide the neural substrate behind the enhancement of activity observed in Broca's area when syllables (Bristow *et al.*, 2009) and sentences (Dehaene-Lambertz, Hertz-Pannier *et al.*, 2006) are repeated. Language acquisition has been mainly described as a bottom-up process with a progressive tuning to the characteristics of the native language through statistical analyses of the speech input. Can the early involvement of this dorsal pathway change our view? What new type of computational resources can this system provide? The arcuate fasciculus is prominent in humans compared to other primates (Rilling *et al.*, 2008) and is notably involved in the phonological loop underlying working memory. Working memory is not only useful for adults to remember a phone number but might be crucial at the beginning of language acquisition to increase the duration of the auditory buffer offering a longer temporal window to analyze the speech signal. The dorsal pathway also provides infants with an early interface between speech perception and production systems, through area 44, which is tightly connected with the motor and somato-sensory areas (Petrides & Pandya, 2006). Thus area 44 can be seen as a functional hub, containing amodal phonetic templates informed by auditory, visual, motor and proprioceptive stimuli. This crossroad region is thus at a correct location to fulfill two functions. First, it might drive infants' motor productions by sending mismatched signals about the auditory gap between the produced sound and the internal templates. Second, it might strengthen the auditory representations of the native phonetic contrasts through the infants' efforts to imitate the caregiver's productions and to decrease the gap with the target. Indeed, infants are rapidly engaged in social contact, seeking eye contact and imitating adults' movements, such as mouth opening from birth on. They also rapidly begin to emit sounds during these social interactions or in response to heard speech stimuli, that progressively fit better and better with the model (Kuhl & Meltzoff, 1996). Scott *et al.* (2009) have proposed that the inferior frontal region is crucial as conversational turn-taking in adults. Thus a virtuous circle would be precociously established between frontal and temporal areas through the arcuate to reinforce frequently used phonetic representations in perception and production. Congruent with this hypothesis, Imada *et al.* (2006), using MEG, reported a progressive emergence of a frontal response in response to a vowel in neonates, 6- and 12-month-old infants. This active and progressive attunement of amodal representations in area 44 might be supported by individual neurons described by Rizzolatti and his collaborators in macaques as motor neurons (Kohler *et al.*, 2002; Rizzolatti & Craighero, 2004).

### 3. Interactions with the social network

Language is not a lonely occupation. Infants use language to communicate with others and are rapidly engaged in mutual exchange with caregivers. A mere exposure to speech is not sufficient to acquire a particular language as it has been elegantly confirmed by Kuhl *et coll.* (2003). These authors reported that English-speaking 9-month-old infants keep the capacity to discriminate a foreign (Cantonese) phonetic contrast only when they are playing with a Chinese speaker but not when they are just exposed to the video or audio recordings of the speaker. A passive exposure is thus not sufficient to maintain the discriminative value of a phonetic contrast without an active participation of the child in the communicative act. Indeed, our studies reveal that the linguistic network is in tied connections with other systems that might boost its efficiency. For example, awake infants display an increased activity in the right dorso-lateral frontal region when listening to their native language (see Figure 6, p. 259). This can be related either to an increase in vigilance stimulated by the recognition of a known stimulus or to a more specific linguistic memory recognition process in relation with the parietal storing of the intonative contour of the native language.

A second example is the wide activation induced by the mother's voice (see Figure 7, p. 259). Just after birth, behavioural studies indicate that infants already recognize their mother's voice (DeCasper & Fifer, 1980; Mehler, Bertoncini, & Barriere, 1978). Using fMRI, we observed several differences in the activations measured when infants are listening to their mother's voice and to the mother of the previous baby in the study. First, the mother's voice elicits higher activation in the left posterior part of the temporal lobe (see Figure 2, p. 256). This region, part of the dorsal linguistic pathway, is involved in phonological representations in adults (Caplan, Gow, & Makris, 1995) and is thought to be a plausible cortical source of phonetic mismatch responses that can be recorded with scalp event-related potentials in infants (Bristow *et al.*, 2009; Dehaene-Lambertz & Baillet, 1998). These results suggest that phonetic processing in infants is sensitive to talker characteristics and can be improved by listening to a highly familiar voice such as the mother's voice. This result is congruent with a behavioral study showing that, in the presence of distracting background speech, infants are better at learning words when they are spoken by the mother rather by an unfamiliar speaker (Barker & Newman, 2004). Our finding can also explain why the clarity of the mother's speech has a strong impact on infants' phoneme discrimination capacities (Liu, Kuhl, & Tsao, 2003). This also confirms our dynamic model presented above that phono-

logical representations are reinforced through active interactions with the care-givers thanks to top-down influences of frontal on temporal areas through the dorsal pathway.

Second, the mother's voice elicits significant negative bold response in several regions involved in emotional processing in adults such as the orbito frontal cortex, the putamen and the amygdala. This points to a potentially interesting linkage of linguistic and emotional network in infants that might play an important role in learning. Finally, there is a balance between the anterior prefrontal cortex activated by the mother's voice and the orbito-frontal cortex activated by the unknown voice (Figure 7, p. 259). This reminds the spatial separation observed in adults' frontal area between activity elicited when thinking about the self and familiar other versus unknown others (Amodio & Frith, 2006), or when focusing toward external world vs internal state (Wicker, Ruby, Royet, & Fonlupt, 2003). Once again, the organization of the infant brain appears very close to what is described in adults. Anterior frontal activations have also been reported in four-month-old infants perceiving communication cues (Grossmann *et al.*, 2008) and in one-year-old infants looking at their smiling mother relative to an unknown face (Minagawa-Kawai *et al.*, 2009). Thus, this area may be important for mother-infant contact and emotional attachment.

To conclude, neuroimaging researches offer a new view on infant development. Contrary to constructivism assumptions, a structured organization is present from the first days on, even in very preterm infants (Smyser *et al.*, 2010). This particular organization offers to infants a Swiss army knife of computational tools to process the external world. We have seen here through the example of language that several particularities of the adult brain, such as asymmetries, pre-exist to the mature stage and that some of the already functional pathway (i.e. dorsal linguistic pathway) can explain how infants can easily learn their native language. This emphasis on neural structure is not a denial of the importance of environment. On the contrary, we have seen that the linguistic network is intrinsically connected with the emotional and attentional networks, emphasizing the fact that infants are engaged in both learning to talk and learning to talk to another human fellow. This initial architecture has been selected through human evolution as the most efficient to help infants to pick the correct cues in the environment in order to build the rich and large social groups seen in humans. Thanks to the development of brain imaging, we are at the beginning of a new approach of development in which a better understanding of the structural and functional properties of the developmental brain should help to better define the neuronal algorithms that sustain human thoughts.



## References

- Amodio, D.M., & Frith, C.D. (2006). Meeting of minds: the medial frontal cortex and social cognition. *Nat Rev Neurosci*, 7(4), 268–277.
- Anwander, A., Tittgemeyer, M., von Cramon, D.Y., Friederici, A.D., & Knosche, T.R. (2007). Connectivity-Based Parcelation of Broca's Area. *Cereb Cortex*, 17(4), 816–825.
- Barker, B.A., & Newman, R.S. (2004). Listen to your mother! The role of talker familiarity in infant streaming. *Cognition*, 94(2), B45–53.
- Barkovich, A.J. (2000). Concepts of myelin and myelination in neuroradiology. *AJNR Am J Neuroradiol*, 21(6), 1099–1109.
- Binder, J.R., Frost, J.A., Hammeke, T.A., Bellgowan, P.S., Springer, J.A., Kaufman, J.N., et al. (2000). Human temporal lobe activation by speech and non-speech sounds. *Cerebral Cortex*, 10(5), 512–528.
- Boemio, A., Fromm, S., Braun, A., & Poeppel, D. (2005). Hierarchical and asymmetric temporal sensitivity in human auditory cortices. *Nat Neurosci*, 8(3), 389–395.
- Bristow, D., Dehaene-Lambertz, G., Matout, J., Soares, C., Gliga, T., Baillet, S., et al. (2009). Hearing faces: how the infant brain matches the face it sees with the speech it hears. *J Cogn Neurosci*, 21(5), 905–921.
- Cantalupo, C., & Hopkins, W.D. (2001). Asymmetric Broca's area in great apes. *Nature*, 414(6863), 505.
- Cantalupo, C., Pilcher, D.L., & Hopkins, W.D. (2003). Are planum temporale and sylvian fissure asymmetries directly related? A MRI study in great apes. *Neuropsychologia*, 41(14), 1975–1981.
- Caplan, D., Gow, D., & Makris, N. (1995). Analysis of lesions by MRI in stroke patients with acoustic-phonetic processing deficits. *Neurology*, 45(2), 293–298.
- Chen, Z.J., He, Y., Rosa-Neto, P., Germann, J., & Evans, A.C. (2008). Revealing modular architecture of human brain structural networks by using cortical thickness from MRI. *Cereb Cortex*, 18(10), 2374–2381.
- Chi, J.G., Dooling, E.C., & Gilles, F.H. (1977). Gyral development of the human brain. *Annals of Neurology*, 1, 86–93.
- Cunningham, D.J. (1892). *Contribution to the surface anatomy of the cerebral hemispheres*. Dublin: Royal Irish Academy.
- DeCasper, A.J., & Fifer, W.P. (1980). Of human bonding: Newborns prefer their mother's voices. *Science*, 208, 1174–1176.
- Dehaene-Lambertz, G., & Baillet, S. (1998). A phonological representation in the infant brain. *NeuroReport*, 9, 1885–1888.
- Dehaene-Lambertz, G., Dehaene, S., Anton, J.L., Campagne, A., Ciuciu, P., Dehaene, G.P., et al. (2006a). Functional segregation of cortical language areas by sentence repetition. *Hum Brain Mapp*, 27(5), 360–371.
- Dehaene-Lambertz, G., Dehaene, S., & Hertz-Pannier, L. (2002). Functional neuroimaging of speech perception in infants. *Science*, 298(5600), 2013–2015.
- Dehaene-Lambertz, G., Hertz-Pannier, L., Dubois, J., Meriaux, S., Roche, A., Sigman, M., et al. (2006b). Functional organization of perisylvian activation during presentation of sentences in preverbal infants. *Proc Natl Acad Sci U S A*, 103(38), 14240–14245.
- Dehaene-Lambertz, G., & Houston, D. (1998). Faster orientation latencies toward native language in two-month-old infants. *Language and Speech*, 41, 21–43.
- Dehaene-Lambertz, G., Montavont, A., Jobert, A., Alliol, L., Dubois, J., Hertz-Pannier, L., et al. (2010). Language or music, mother or Mozart? Structural and environmental influences on infants' language networks. *Brain and Language*, 114(2), 53–65.
- Dehaene, S., & Cohen, L. (2007). Cultural recycling of cortical maps. *Neuron*, 56(2), 384–398.



- Dubois, J., Benders, M., Cachia, A., Lazeyras, F., Ha-Vinh Leuchter, R., Sizonenko, S.V., *et al.* (2008). Mapping the early cortical folding process in the preterm newborn brain. *Cerebral Cortex*, 18(6), 1444–1454.
- Emmorey, K., Allen, J.S., Bruss, J., Schenker, N., & Damasio, H. (2003). A morphometric analysis of auditory brain regions in congenitally deaf adults. *Proc Natl Acad Sci U S A*, 100(17), 10049–10054.
- Fransson, P., Skiold, B., Engstrom, M., Hallberg, B., Mosskin, M., Aden, U., *et al.* (2009). Spontaneous brain activity in the newborn brain during natural sleep – an fMRI study in infants born at full term. *Pediatr Res*, 66(3), 301–305.
- Fransson, P., Skiold, B., Horsch, S., Nordell, A., Blennow, M., Lagercrantz, H., *et al.* (2007). Resting-state networks in the infant brain. *Proc Natl Acad Sci U S A*, 104(39), 15531–15536.
- Frey, S., Campbell, J.S., Pike, G.B., & Petrides, M. (2008). Dissociating the human language pathways with high angular resolution diffusion fiber tractography. *J Neurosci*, 28(45), 11435–11444.
- Fukunaga, M., Li, T.Q., van Gelderen, P., de Zwart, J.A., Shmueli, K., Yao, B., *et al.* (2010). Layer-specific variation of iron content in cerebral cortex as a source of MRI contrast. *Proc Natl Acad Sci U S A*, 107(8), 3834–3839.
- Gandour, J., Wong, D., Lowe, M., Dziedzic, M., Sathannuwong, N., Tong, Y., *et al.* (2002). A cross-linguistic fMRI study of spectral and temporal cues underlying phonological processing. *J Cogn Neurosci*, 14(7), 1076–1087.
- Gannon, P.J., Holloway, R.L., Broadfield, D.C., & Braun, A.R. (1998). Asymmetry of Chimpanzee Planum Temporale: Humanlike Pattern of Wernicke's Brain Language Area Homolog. *Science*, 279(9 January), 220–222.
- Geschwind, N., & Levitsky, W. (1968). Human brain: Left-Right Asymmetries in Temporal Speech Region. *Science*, 161, 186–187.
- Gilissen, E. (2001). Structural symmetries and asymmetries in human and chimpanzee brains. In D. Falk & K.R. Gibson (eds.), *Evolutionary anatomy of the primate cerebral cortex* (pp. 187–215). Cambridge: Cambridge University Press.
- Giraud, A.L., Kleinschmidt, A., Poeppel, D., Lund, T.E., Frackowiak, R.S., & Laufs, H. (2007). Endogenous cortical rhythms determine cerebral specialization for speech perception and production. *Neuron*, 56(6), 1127–1134.
- Glasel, H., Leroy, F., Dubois, J., Hertz-Pannier, L., Mangin, J., & Dehaene-Lambertz, G. (submitted). A robust cerebral asymmetry in the infant language network: the rightward superior temporal sulcus.
- Grossmann, T., Johnson, M.H., Lloyd-Fox, S., Blasi, A., Deligianni, F., Elwell, C., *et al.* (2008). Early cortical specialization for face-to-face communication in human infants. *Proc Biol Sci*, 275(1653), 2803–2811.
- Hein, G., & Knight, R.T. (2008). Superior temporal sulcus – It's my area: or is it? *J Cogn Neurosci*, 20(12), 2125–2136.
- Hill, J., Dierker, D., Neil, J., Inder, T., Knutsen, A., Harwell, J., *et al.* (2010). A surface-based analysis of hemispheric asymmetries and folding of cerebral cortex in term-born human infants. *J Neurosci*, 30(6), 2268–2276.
- Homae, F., Watanabe, H., Nakano, T., Asakawa, K., & Taga, G. (2006). The right hemisphere of sleeping infant perceives sentential prosody. *Neurosci Res*, 54(4), 276–280.
- Hopkins, W.D., Taglialetela, J.P., Meguerditchian, A., Nir, T., Schenker, N.M., & Sherwood, C.C. (2008). Gray matter asymmetries in chimpanzees as revealed by voxel-based morphometry. *Neuroimage*, 42(2), 491–497.
- Imada, T., Zhang, Y., Cheour, M., Taulu, S., Ahonen, A., & Kuhl, P.K. (2006). Infant

- speech perception activates Broca's area: a developmental magnetoencephalography study. *Neuroreport*, 17(10), 957-962.
- James, W. (1892). Psychology. Briefer Course. In *Writings* (1878-1899) (pp. 18-34). New-York: Holt (published again in Library of America, 1212 p. 1992).
- Johnson, M.B., Kawasawa, Y.I., Mason, C.E., Krsnik, Z., Coppola, G., Bogdanovic, D., et al. (2009). Functional and evolutionary insights into human brain development through global transcriptome analysis. *Neuron*, 62(4), 494-509.
- Johnson, M.H. (2001). Functional brain development in humans. *Nature Reviews Neuroscience*, 2(7), 475-483.
- Jusczyk, P.W., Kennedy, L.J., & Jusczyk, A.M. (1995). Young infants' retention of information about syllables. *Infant Behavior and Development*, 18, 27-41.
- Kaas, J.H., & Hackett, T.A. (2000). Subdivisions of auditory cortex and processing streams in primates. *Proc Natl Acad Sci U S A*, 97(22), 11793-11799.
- Kohler, E., Keysers, C., Umiltà, M.A., Fogassi, L., Gallese, V., & Rizzolatti, G. (2002). Hearing sounds, understanding actions: action representation in mirror neurons. *Science*, 297(5582), 846-848.
- Kostovic, I., & Judas, M. The development of the subplate and thalamocortical connections in the human foetal brain. *Acta Paediatr*, 99(8), 1119-1127.
- Kriegstein, A., Noctor, S., & Martinez-Cerdeno, V. (2006). Patterns of neural stem and progenitor cell division may underlie evolutionary cortical expansion. *Nat Rev Neurosci*, 7(11), 883-890.
- Kuhl, P.K., & Meltzoff, A.N. (1996). Infant vocalizations in response to speech: vocal imitation and developmental change. *J Acoust Soc Am*, 100(4 Pt 1), 2425-2438.
- Kuhl, P.K., Tsao, F.M., & Liu, H.M. (2003). Foreign-language experience in infancy: Effects of short-term exposure and social interaction on phonetic learning. *Proc Natl Acad Sci U S A*.
- LeMay, M. (1984). Radiological Developmental and fossil asymmetries. In N. Geschwind & A. M. Galaburda (eds.), *Cerebral dominance* (pp. 26-42). Harvard University Press: Cambridge.
- Lenneberg, E. (1967). *Biological foundations of language*. New York: Wiley.
- Lerch, J.P., Worsley, K., Shaw, W.P., Greenstein, D.K., Lenroot, R.K., Giedd, J., et al. (2006). Mapping anatomical correlations across cerebral cortex (MACACC) using cortical thickness from MRI. *Neuroimage*, 31(3), 993-1003.
- Leroy, F., Glasel, H., Dubois, J., Hertz-Pannier, L., Thirion, B., Mangin, J.F., et al. (2011). Early Maturation of the Linguistic Dorsal Pathway in Human Infants. *J Neurosci*, 31(4), 1500-1506.
- Liu, H.-M., Kuhl, P.K., & Tsao, F.-M. (2003). An association between mother's speech clarity and infants' speech discrimination skills. *Developmental Science*, 6, F1-F10.
- Mechelli, A., Crinion, J.T., Noppeney, U., O'Doherty, J., Ashburner, J., Frackowiak, R.S., et al. (2004). Neurolinguistics: structural plasticity in the bilingual brain. *Nature*, 431(7010), 757.
- Mehler, J., Bertoncini, J., & Barriere, M. (1978). Infant recognition of mother's voice. *Perception*, 7(5), 491-497.
- Minagawa-Kawai, Y., Matsuoka, S., Dan, I., Naoi, N., Nakamura, K., & Kojima, S. (2009). Prefrontal Activation Associated with Social Attachment: Facial-Emotion Recognition in Mothers and Infants. *Cereb Cortex*, 19, 284-292.
- Ochiai, T., Grimault, S., Scavarda, D., Roch, G., Hori, T., Riviere, D., et al. (2004). Sulcal pattern and morphology of the superior temporal sulcus. *Neuroimage*, 22(2), 706-719.
- Pandya, D.N., & Yeterian, E.H. (1990). Architecture and connections of cerebral cortex: implications for brain evolution and function. In A.B. Scheibel & A.F. Wechsler (eds.), *Neurobiology of higher cognitive function* (pp. 53-83). New York: Guilford Press.

- Paus, T., Zijdenbos, A., Worsley, K., Collins, D.L., Blumenthal, J., Giedd, J.N., *et al.* (1999). Structural maturation of neural pathways in children and adolescents: in vivo study. *Science*, 283(5409), 1908-1911.
- Pena, M., Maki, A., Kovacic, D., Dehaene-Lambertz, G., Koizumi, H., Bouquet, F., *et al.* (2003). Sounds and silence: An optical topography study of language recognition at birth. *Proc Natl Acad Sci U S A*, 100(20), 11702-11705.
- Perani, D., Saccuman, M. C., Scifo, P., Spada, D., Andreolli, G., Rovelli, R., *et al.* Functional specializations for music processing in the human newborn brain. *Proc Natl Acad Sci U S A*, 107(10), 4758-4763.
- Perrot, X., Rylvlin, P., Isnard, J., Guenot, M., Catenoix, H., Fischer, C., *et al.* (2006). Evidence for corticofugal modulation of peripheral auditory activity in humans. *Cereb Cortex*, 16(7), 941-948.
- Petrides, M., & Pandya, D.N. (2006). Efferent association pathways originating in the caudal prefrontal cortex in the macaque monkey. *J Comp Neurol*, 498(2), 227-251.
- Rilling, J.K., Glasser, M.F., Preuss, T.M., Ma, X., Zhao, T., Hu, X., *et al.* (2008). The evolution of the arcuate fasciculus revealed with comparative DTI. *Nat Neurosci*, 11(4), 426-428.
- Rizzolatti, G., & Craighero, L. (2004). The mirror-neuron system. *Annu Rev Neurosci*, 27, 169-192.
- Scott, S.K., McGettigan, C., & Eisner, F. (2009). A little more conversation, a little less action – candidate roles for the motor cortex in speech perception. *Nat Rev Neurosci*, 10(4), 295-302.
- Sininger, Y.S., & Cone-Wesson, B. (2004). Asymmetric cochlear processing mimics hemispheric specialization. *Science*, 305(5690), 1581.
- Smyser, C.D., Inder, T.E., Shimony, J.S., Hill, J.E., Degnan, A.J., Snyder, A.Z., *et al.* (2010). Longitudinal analysis of neural network development in preterm infants. *Cereb Cortex*, 20(12), 2852-2862.
- Sowell, E.R., Peterson, B.S., Thompson, P.M., Welcome, S.E., Henkenius, A.L., & Toga, A.W. (2003). Mapping cortical change across the human life span. *Nat Neurosci*, 6(3), 309-315.
- Sowell, E.R., Thompson, P.M., Rex, D., Kornsand, D., Tessner, K.D., Jernigan, T.L., *et al.* (2002). Mapping sulcal pattern asymmetry and local cortical surface gray matter distribution in vivo: maturation in perisylvian cortices. *Cerebral Cortex*, 12(1), 17-26.
- Sun, T., Patoine, C., Abu-Khalil, A., Visvader, J., Sum, E., Cherry, T.J., *et al.* (2005). Early asymmetry of gene transcription in embryonic human left and right cerebral cortex. *Science*, 308(5729), 1794-1798.
- Telkemeyer, S., Rossi, S., Koch, S.P., Nierhaus, T., Steinbrink, J., Poeppel, D., *et al.* (2009). Sensitivity of newborn auditory cortex to the temporal structure of sounds. *J Neurosci*, 29(47), 14726-14733.
- Toga, A.W., & Thompson, P.M. (2003). Mapping brain asymmetry. *Nat Rev Neurosci*, 4(1), 37-48.
- Van Essen, D.C. (2005). A Population-Average, Landmark- and Surface-based (PALS) atlas of human cerebral cortex. *Neuroimage*, 28(3), 635-662.
- Wada, J.A., Clarke, R., & Hamm, A. (1975). Cerebral hemispheric asymmetry in humans. Cortical speech zones in 100 adults and 100 infant brains. *Archives of Neurology*, 32(4), 239-246.
- Wicker, B., Ruby, P., Royet, J.P., & Fonlupt, P. (2003). A relation between rest and the self in the brain? *Brain Res Brain Res Rev*, 43(2), 224-230.
- Witelson, S.F., & Pallie, W. (1973). Left hemisphere specialization for language in the newborn: Neuroanatomical evidence for asymmetry. *Brain*, 96, 641-646.
- Yakovlev, P.I. (1962). *Morphological criteria of growth and maturation of the nervous system in man*. Research Publications – Association for Research in Nervous and Mental Disease (Baltimore, MD), 32, 3-46.

- Yeni-Komshian, G.H., & Benson, D.A. (1976). Anatomical study of cerebral asymmetry in the temporal lobe of humans, chimpanzees, and rhesus monkeys. *Science*, 192(4237), 387-389.
- Zatorre, R.J., & Belin, P. (2001). Spectral and temporal processing in human auditory cortex. *Cerebral Cortex*, 11(10), 946-953.

# SOCIAL COGNITION AND THE SEEDS OF EDUCATION

■ ANDREW N. MELTZOFF

## Social cognition and the seeds of education

*He who thus considers things in their first growth and origin, whether a state or anything else, will obtain the clearest view of them. – Aristotle*

Education, neuroplasticity, and developmental psychology have much in common: All are concerned with the original nature of humans and how it is transformed by experience.

In the modern world, the educator, neuroscientist, and developmental psychologist occupy separate disciplines, use different techniques, and publish in different venues for different audiences. But before this specialization, the three perspectives were intertwined as philosophers pondered questions about the roots of civilization and what distinguished humans from other animals. In the *Republic*, Plato considered the design of a just society, and immediately raised two issues about children, ‘What will their education be?’ and ‘You know, don’t you, the beginning of any process is the most important, especially for anything young and tender? It’s at that time that it is most malleable and takes on any pattern one wishes to impress on it’ (Book II).

In *Émile*, Rousseau contemplated education and espoused a revolutionary idea about childrearing: ‘Why should not his education begin before he can speak’ and ‘As I said before, man’s education begins at birth; before he can speak or understand he is learning. Experience precedes instruction’ (Book I).

These thinkers, of course, knew little about the brain and did not anticipate many of the empirical discoveries about child development, but they shared the conviction that education is the wet-nurse to civilization and childhood is a ‘sacred’ (Rousseau) and ‘most important’ (Plato) time.

Modern scientists have produced empirical data about the importance of childhood and have discovered physiological mechanisms conforming to some of the philosophers’ key intuitions. Neuroscientists introduced the concept of ‘neuroplasticity’ which echoes Plato’s musings about early malleability; and a Nobel Prize was awarded to D. Hubel and T. Wiesel for research on the ‘critical period’ which is akin to Plato’s imprinting on the young and tender. Modern educators seek to expand primary and secondary instruction, arguing that children deserve ‘P-12’ education (P = pre-school) and that parents are

a baby's first and best teacher – echoing Rousseau's previously revolutionary cry that education should begin at birth.

We can discern a coalescing of ancient and modern ideas, but there is not universal agreement about the best path forward. The contemporary scholar, John Bruer, wrote a provocative paper in 1997 entitled 'Education and the brain: A bridge too far'. He argued that there is a yawning chasm between brain science and the practice of education.

There may be a way of reconciling the dreams of Plato and Rousseau with the sobering reality of Bruer's arguments. Enter the third, sometimes forgotten discipline mentioned in the opening paragraph of this essay – child development. Even if we accept Bruer's metaphor of two landmasses (brain science and education) that are too far apart to be bridged, we should not ignore another landmass jutting out between them (child development). Perhaps we can build smaller connecting bridges. How the child's brain changes with experience (neuroscience) can be linked to the study of the child's developing thoughts, emotions, intentions, and actions (child psychology), which in turn can be connected to the study of designed learning environments made to facilitate learning and help all children achieve their full potential (education). The gaps are smaller if we bridge from neuroscience to child psychology to education than if we try to span from the first to the third directly.

The scientific study of child development is a relatively new discipline. Perhaps the first systematic investigation of child development was Darwin's (1877) 'A biographical sketch of an infant'. It was a meticulous record of the mental growth of his own child, Doddy, and published in the philosophical journal, *Mind*. Next came Jean Piaget who provided data that surpassed Darwin's observations. When Piaget wanted to know if infants believed in the reality of things they could not see, he did not simply wait and observe infants, he hid their favorite object under an occluder to test whether they would search for it. In an interesting historical twist, Piaget became the director of the Institut Jean-Jacques Rousseau in Rousseau's birthplace, Geneva, in 1921. Piaget transformed the field by moving beyond baby observational techniques, but he did not utilize the most valuable tools of experimental science – random assignment and control groups. The field of experimental infant psychology was born in the late 1950s and early 60s, and the first meeting of the International Conference on Infant Studies took place in 1978.

In this essay I focus on scientific advances in childhood social cognition – what children know about themselves and other people. I do so for two reasons. First, the empirical discoveries about early social cognition are surprising. Piaget's (1954) theory held that infants are born 'solipsists' with no

initial connections to other people. The new work shows that newborns are anything but, and completely revises our views. Empirical evidence shows that young infants recognize the equivalence between self and other right from birth, and we are beginning to understand the psychological and neuroscience basis of these self-other mappings. Second, human education fundamentally depends on social cognition. Good teachers, like good parents, take the perspective of the learner and adjust their teaching so that it can be best absorbed; reciprocally, attentive learners are constantly trying to discern the tutor's intentions (Bruner, 1996). Both teacher and learner are engaged in acts of social cognition.

I explore the origins and early development of social cognition, but do not provide a full literature review. The essay offers a selective examination of studies from my laboratory illustrating the philosophy that education 'begins at birth'. I trace key changes in social cognition that occur from infancy to early childhood. The specific topics include: (i) learning through social imitation, (ii) children's dawning understanding of others as sentient beings like the self, and (iii) how the identity and academic interests of primary-school children are sculpted by the cultural context in which they grow up.

### **Childhood imitation**

A distinctive characteristic of human beings is the capacity to learn from watching the actions of others and imitating them. I see another act, and I can immediately use this as a model for my own acts. I can duplicate other people's successes, avoid their failures, and learn about myself by watching them. Although many other animals learn from experience, they do not readily learn from watching *others'* experiences.

Imitation underlies human culture. It supplements biological evolution as a mechanism for transferring ingenious inventions and practices from one generation to the next. Without imitative learning the knowledge of how to build a fire, use a lever, or tie a knot would have had to be re-invented in each generation. Such skills are not innate; nor are they learned through trial and error or via explicit instruction. Rather, a child watches an expert in the culture and the child 'absorbs' the conduct. In cultures lacking formal schoolhouses, apprenticeship and imitation is a prominent form of 'education', and it has been so for millennia. Aristotle said it well: 'Imitation is natural to man from childhood, one of his advantages over the lower animals being this, that he is the most imitative creature in the world, and learns at first by imitation' (*Poetics*).

Aristotle is right so far as he goes, but that does not end the matter for the scientist who is interested in the mechanisms underlying imitation and its de-



velopment with age. The empirical work has revealed two surprising facts about childhood imitation: (i) its origins and (ii) how it is regulated by emotion.

### *The original state*

*Conceptual problem.* If we are seeking origins, the imitation of facial expressions is a good place to start. Infants have the motor skills to move their faces, so copying others is not ruled out. There is a conceptual problem, however. Infants can see another person's face but they cannot see their own face. If they are young enough, they will never have seen their face in a mirror. Facial imitation poses a formidable challenge, because the infant must match a gesture he sees a person perform with a gesture of his own that is invisible to him and accessible only through tactile-proprioceptive feelings. Facial imitation can be thought of as posing the philosophical problem of Other Minds in action. The child knows himself from the inside and the other from the outside. How can he bring the two together?

In traditional developmental theory facial imitation was regarded as a landmark cognitive milestone. Piaget (1962) thought that young infants could not perform such 'invisible imitation', because they had no way to connect self and other. Infants were born 'solipsistic' (Piaget, 1954), or so he argued.

*Empirical findings and inferences.* My colleagues and I tested newborn infants in a hospital setting. The oldest infant was 36 hours old and the youngest was just 42 *minutes* old at the time of test. The newborns were shown simple facial gestures: poking out the tongue and opening and closing the mouth. In other studies neonates saw hand movements, lip pursing, and head movements. To the surprise of many, the empirical data revealed that young infants imitated all these acts (Meltzoff & Moore, 1977, 1997). This is remarkable because they are imitating actions they see other people perform with actions of their own that they cannot see themselves do. There is a basic human connection between self and other that is present at birth. Imitation is a congenital aspect of social behavior (see Figure 1).

The interpretive framework I put forward is that there is a basic body scheme that allows infants, even newborns, to see the acts of others as 'like me'. Imitation is a matching-to-target process. The goal or behavioral target is specified visually. Infants' self-produced movements provide proprioceptive feedback that can be compared to the visually specified target. According to the framework, the comparison is possible because human acts are represented within a common code, which we refer to as a 'supramodal' representation that transcends single modalities such as vision or touch and unites them in a common language (Meltzoff & Moore, 1997). We also proposed that infants' prenatal movements may prepare them for imitation.



**Figure 1.** Photographs of human neonates under 1-month-old imitating adult facial expressions. (From Meltzoff & Moore, *Science*, 1977).

Films of infants in the womb document that they make hand, facial, and limb movements. This prenatal motor experience provides them with a proprioceptive memory about how the parts of the body move. The tongue is felt to move in very different ways than hinged joints. When infants see these movements postnatally they assimilate them to the felt motor patterns experienced prenatally (Meltzoff & Moore, 1997).

The essential point is that infants are born into a social world and can connect with others from their very first encounters with them. They perceive the acts of self and other as equivalent. In their very first encounters with mother, this is not an alien object, but someone who moves ‘like me’. This has far-reaching implications for theories of social cognition, and the neural correlates are being explored using infant brain measures such as electroencephalography (EEG) (Marshall & Meltzoff, 2011).

### ***Regulating imitation: emotion and the roots of conscience***

*Conceptual problem.* Human imitation extends beyond the duplication of simple movements and mannerisms in three ways. First, humans also learn how to use tools and manipulate culturally specific objects by watching how others do so. Second, humans do not only learn in one-to-one interaction, but also learn indirectly by eavesdropping on the interactions of others. Third, humans begin to assimilate ‘good’ or ‘bad’ from watching how

others respond. A child need not act and be scolded, but can learn from monitoring how the parent responds to the actions of a sibling. If it is a forbidden act, the child will regulate his natural tendency to imitate. We investigated these issues empirically.

*Empirical findings and inferences.* In these studies infants watched an adult perform novel actions on objects. For example, the adult (Model) brought out a black box and used a stick as a tool to push a button that activated the object. When infants are presented with the same box, they immediately imitate the act. Next, we tested whether emotion regulates imitation. We had 18-month-old infants watch the Model perform novel actions on objects but had a second adult (Emoter) react with an angry negative emotion, as if the Model was performing a forbidden act. Then the child was presented with the object. We found that the children regulated their conduct; they did not imitate the forbidden act (Repacholi, Meltzoff, & Olsen, 2008).

This is not ‘emotional contagion’, because the child’s motor acts were gated by whether the Emoter was or wasn’t looking at the child. If the Model and Emoter went through the same script, and the Emoter left the room, the baby performed the forbidden action. If the Emoter turned her back or closed her eyes, the child performed the forbidden act. The critical feature was whether the Emoter was visually monitoring the baby – in cases that the Emoter was watching the infant, the infant did not imitate.

The study establishes that even preverbal babies are not slavish imitators. Moreover, babies learn from second-hand experience. The child himself was not scolded – the child simply observed someone else being scolded, and that was sufficient to inhibit imitation.

There were individual differences. Some children were excellent self-regulators and some were not. We are interested in whether there are inborn differences in inhibitory control, and how such is cultivated through mother-infant interaction before children enter our laboratory at 18 months of age. We also want to assess whether our preverbal measure is predictive of children’s capacity to delay gratification and regulate their behavior when they are in primary school.

What about a sense of conscience? The preverbal babies refrain from replicating the forbidden acts only if they are watched. At older ages children refrain in a wider set of circumstances. Inasmuch as the origins of conscience can be investigated empirically, this research paradigm may offer a good start. Certainly, the change from regulating behavior when watched (infants) to regulating behavior based on internalized rules (older children and adults) is a momentous shift. This developmental change is of interest to scientists, philosophers, and religious leaders alike.

## Recognizing other people as sentient beings

Human beings have mental states – thoughts, feelings, and perceptions – that we strive to understand by paying close attention to our fellow humans. One important contributor to ‘reading’ others’ internal states is paying attention to their eyes – the eyes are called a ‘window of the soul’.

If a person talking to you turns to look at something you tend to follow their gaze. Gaze following is a key component of learning and education inside and outside the classroom. Gaze following establishes common ground and indicates a shared topic. As children try to understand the meaning of words, they take into account the direction of parental gaze. Although words can refer to absent objects, parts of things, and hypotheticals (Quine, 1960), parents spend a lot of time labeling here-and-now whole objects for infants (Markman, 1989; Tomasello & Farrar, 1986). St. Augustine noted that children are assisted in language acquisition by paying attention to the gaze of adults: ‘I watched and remembered that they used that sound when they wanted to indicate that thing. Their intention was clear, for they used bodily gestures, those natural words which are common to all races, such as facial expressions or glances of the eyes...’ (Book I).

Scientists seek to uncover the mechanisms by which infants come to understand the meaning of another’s gaze. When the child sees an adult turn to face an object do they process this simply a physical movement or do they ascribe mental states to the act?

### *Infant gaze following*

*Conceptual problem.* Common observation reveals that babies look where another is looking, but observation alone does not reveal the mechanism. One theory attributes very little to the child: The head is a large moving orb infants visually track as it rotates, and they accidentally catch sight of the target object in the periphery. What looks like gaze following is nothing more than tracking a physical motion – physics not psychology. A richer interpretation is that infants desire to see what another is seeing. Infants attribute psychological contact or mental experience to the one who gazes. Experiments are needed to discover the mechanisms underlying gaze following.

*Empirical findings and inferences.* In one study an adult turned to look at distal objects on a random schedule (see Figure 2). The trick was that in some cases the adult turned with eyes open and in other cases with eyes closed. The head movements were identical in both cases. If infants are simply tracking the head movements, they should perform equally. The results show that 1-year-olds are significantly more likely to follow the adult who turned with eyes open, suggesting that they know something about visual contact (Brooks

& Meltzoff, 2002). However, another study reveals that this knowledge is limited. If the adult has her vision blocked by a blindfold, 1-year-olds mistakenly follow her 'gaze'. It seems that 1-year-olds know that eye closure blocks the adult's vision but not that an inanimate occluder does so. Why?

One idea is that infants are using their own self-experience to give special meaning to the eye closures of others. Infants have agency over opening and closing their eyes. When they do not want to see something they close their eyes. They have complete control and a lot of practice with closing their eyes to make the world go black. I believe that they use this to interpret the eye closures of other people. We sought to test this idea.



**Figure 2.** A 12-month-old boy follows the gaze of an adult. Infants learn about people and things by looking where other people look. (From Meltzoff *et al.*, *Science*, 2009).

### *Others 'like me': using self-experience to understand others*

*Conceptual problem.* Infants understand biological occluders (eye closures) before they understand inanimate occluders (blindfolds). My idea is that they are using their own phenomenological experience gained by performing bodily acts (eye closing/opening) to give meaning to the matching acts of others. If this is true, then providing infants self-experience with blindfolds should allow them to understand, for the first time, what it is like for another person who is wearing a blindfold.

*Empirical findings and inferences.* Meltzoff and Brooks (2008) did the relevant experiment. Infants sat at a table, which had an interesting object on it. When they turned to look at the object, the experimenter gently raised a blindfold to block their vision. The blindfold was subsequently lowered and infants were allowed to play with it. Then another interesting object was put on the table, the infants looked, and the adult again raised the blindfold to block their line of regard. This was repeated for almost ten minutes. The training was restricted to infants' own vision rather than anyone else wearing blindfolds. Then, for the first time, the adult wore the blindfold and the standard gaze-following test was administered.

The experience completely changed infants' interpretation of the adult. Now they did not follow the blindfolded adult's 'gaze' to the object (Meltzoff & Brooks, 2008). They generalized from their own experience to that of another person. Since they could not see (self-experience) when a blindfold was in front of their eyes, they inferred that the other could not see when in a similar situation. Control conditions gave infants equal amounts of time to familiarize themselves with the black cloth while it lay on the table and did not have this effect.

Infants imbue the actions of others with felt meaning based on their own experience. This opens up a new way of thinking about infant's understanding other mental states, beyond visual perception. Consider intention. Meltzoff (1995) showed that 18-month-olds can infer the simple intentions of other people. An adult tried to pull apart a barbell-shaped toy, but his hands slipped off, and the goal was not achieved. He tried again in a new way and was also not successful. The infant only saw the efforts but not the successful act. Nonetheless, when infants were given the object they carefully wrapped their hands around the ends of the object and firmly pulled it apart. Preverbal infants understand our goals and re-enact what we intend to do, not what we did do.

The gaze following work provides theoretical leverage for understanding infants' attribution of goals and intentions to others. One reason infants can make sense of the purposeful behavioral of others is that they have intentions themselves. They have tried unsuccessfully to pull apart objects. I believe infants use their own self-experiences to understand the similar behaviors in others. Others who act 'like me' have similar mental states like me. I infuse the behavior of others with my own phenomenological experience. Doing so provides a first step toward perspective taking.

### **Cultural stereotypes and school**

The adult social world is complex, and the human mind tries to simplify and predict what to expect when we meet a stranger or interact with a friend. One strategy is to use stereotypes – simplified concepts about social groups that are applied to individuals to characterize them and anticipate their behavior. If I inform you that you will be meeting a librarian in one room and a professional athlete in the other, you immediately conjure up a stereotype to prepare for these social encounters (probably you imagine a smaller, meeker person in the first room and a larger, boisterous person in the second). It does not occur to you at first, without deeper reflection, that a professional jockey might be smaller and milder than a librarian.

Many stereotypes are harmless, but some are pernicious. Rousseau was concerned with the pernicious stereotypes and prejudices that Émile would

be exposed to in public education, and outlined a scheme to shield the boy. He proposed a well-trained, private tutor and no public schooling with groups of children. Whatever one thinks about this, it is not practical for society to educate children through one-on-one tutors for each child 'to guide him from birth to manhood'. Rousseau, of course, acknowledged this impracticality. So what is to be done?

One step is to examine the stereotypes that confront children as they enter formal schooling and the influence they have on children's education and self-development. A further step would be to design interventions to change things. This discussion focuses only on the former.

A collection of pernicious academic stereotypes concerns race and gender. This is particularly salient for mathematics and reading. One pervasive stereotype is that science, technology, engineering and mathematics (STEM disciplines) 'go with' males and that reading and poetry 'go with' females (Nosek, Banaji, & Greenwald, 2002; Nosek *et al.*, 2009; National Academy of Sciences Report, 2011). Our concern here is when these cultural stereotypes are absorbed by the child and begin to influence their sense of identity and schooling.

There is new evidence that as early as primary school, American girls have assimilated the cultural stereotype that girls are not associated with mathematics and have extended this belief to themselves (Cvencek, Meltzoff, & Greenwald, 2011). Academic stereotypes about other children who are perceived as 'like me' influence children's own self-concepts and can constrict their academic interests and aspirations.

### ***Math-gender stereotypes in young children***

*Conceptual problem.* American adolescents take a standardized test measuring mathematics and reading called the Scholastic Aptitude Test (SAT). Every year for the past 20 years, boys have significantly outscored girls on the SAT-Mathematics portion of the test. This has led to some to speculate that boys have a higher 'innate aptitude' for mathematics, others to suggest differences in upbringing, and still others to dispute the validity of the test or suggest other factors (Ceci & Williams, 2007; Spelke, 2005). We cannot solve this dispute in any simple way, but my colleagues and I decided to assess young children's thoughts about cultural stereotypes for mathematics and their own dawning feelings of interest and identification with the discipline (Cvencek, Meltzoff, & Greenwald, 2011).

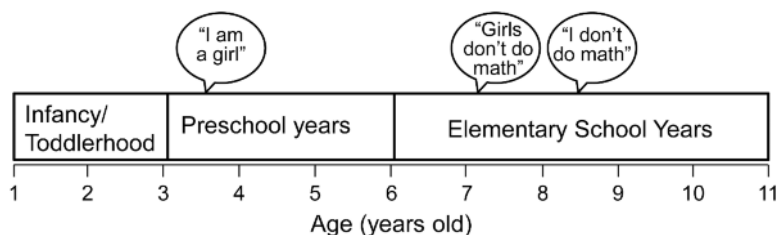
We made conceptual distinctions among three ideas that are often conflated in the literature on educational and developmental psychology (and more clearly separated in social psychology with adults). First, we said that a child's *gender identity* refers to children's association between themselves



and a particular gender (male or female). Second, *math-gender stereotypes* refer to the association of mathematics with male or female. Third, *math self-concept* refers to the association between oneself and mathematics. These conceptual distinctions allowed us to separate children's recognition of cultural stereotypes about groups (math-gender stereotypes) versus their own felt self-identification with mathematics. In principle, one could be raised in a culture that holds stereotypes about one's gender without subscribing to them oneself; the stereotype refers to the social group to which one belongs, whereas the self-concept refers to you as an individual. What is the developmental pattern connecting these three concepts?

*Empirical findings and inferences.* We tested a large number of children in the schools, with equal number of boys and girls at each grade between 1<sup>st</sup> and 5<sup>th</sup> grade. We used both explicit (self-report) and implicit (child Implicit Association Test) measures (see Cvencek, Meltzoff, & Greenwald, 2011 for details). Our results confirmed previous work showing that girls and boys identified with their own gender in 1<sup>st</sup> grade (gender identity). The new finding was that children as early as 2<sup>nd</sup> grade have already assimilated the pervasive American stereotype that math is for boys (math-gender stereotypes). A little later in development, sex differences emerged in self-concepts, such that boys tended to self-identify with math (math self-concept) and girls with reading. A schematic of the results are shown in Figure 3.

The striking finding is that boys and girls both believe that math is for boys as early as 2<sup>nd</sup> grade. This is *before* they have learned their multiplication tables (a 3<sup>rd</sup> grade topic in American schools). It is widely known that inasmuch as there are any grades given for mathematics or pre-mathematics in kindergarten through 2<sup>nd</sup> grade, girls receive higher grades than the boys. We do not think, therefore, that children are using their own personal experience with mathematics to build these early stereotypes or academic self-concepts. What is going on?



**Figure 3.** Schematic child development timeline based on research on gender identity, math-gender stereotypes, and math self-concepts in young children. (See Cvencek, Meltzoff, & Greenwald, *Child Development*, 2011).

We think that even the youngest girls and boys are profoundly influenced by pervasive cultural stereotypes. They intermix cultural stereotypes with their own knowledge of themselves to draw implications. Children unconsciously complete an Aristotelian syllogism in a way that is *psychologically* compelling: I am a girl, girls don't go with math, and therefore math is not for me (Cvencek, Meltzoff, & Greenwald, 2011).

From a developmental viewpoint, children have followed others 'like me' since infancy. They engage in action imitation, duplicating the behavior of others when they are preverbal babies. They imitate more abstract rules by the time they are 3 years old (Williamson, Jaswal, & Meltzoff, 2010). I propose that this drive to imitate serves children well in the early phases of identification with people, but also begins to exert pressure on children to adopt attributes of the social group to which they belong. By school age, if not before, they begin to 'imitate' and take on the academic characteristics of others 'like me'. If girls are not associated with mathematics, according to a cultural stereotype, then young girls in that culture will tend to think mathematics is 'not for me', which can influence their self-concepts, interests, and future aspirations.

We are pursuing several questions: (i) What is the relative contribution of parents, teachers, peers and media in creating these stereotypes? (ii) What are the mechanisms by which individuals can overcome cultural stereotypes? They may have personal relationships that outweigh the dominant stereotype (e.g., a mother who is a mathematics teacher or a similar role model). (iii) Are there differences across cultures? In some countries girls systematically do better than boys on standardized mathematics tests, and Cvencek and I will initiate a cross-cultural study investigating the development of math stereotypes, self-concepts in Singaporean primary school children, starting in the autumn of 2011.

## Reflections

Certain questions about human nature are too puzzling and foundational to remain the province of any one discipline. Such is the case with social cognition. We know ourselves from the inside; we know others from the outside. How can we connect?

Modern science offers an approach to the problem. We examine the social mind of infants. Babies do not speak or understand verbal language. Yet, they interact with their mothers, they emote, and they seem to be more than mere automata. They think without language. The hard question is what they think about *us*. The (relatively new) field of developmental social cognition is probing this issue, and the empirical results seem promising.

## *Theory*

Starting from the beginning, we now know that newborns are not only visually attracted to faces, but that they can imitate them. When infants see a person act, they can map this onto their own corresponding body parts and duplicate it. This is puzzling because newborns have never seen their own faces – there are no mirrors in the womb. Yet they connect.

I argue that this recognition of the equivalence between self and other at the level of action is the bedrock of human social cognition. From the moment that newborns first see another face, they recognize it as ‘like me’. This felt kinship with other fellow humans is the start of social understanding, not its culmination; it undergirds and supports enculturation and does not spring from it in the first instance.

This ‘like me’ bond also provides an avenue for psychological change. It fosters change in two directions. Going from others to self, infants watch others and learn more about the causal consequences of human actions without having to produce them. This amplifies learning opportunities beyond trial and error learning and independent invention. Infants can profit from the successes (and failures) of others, because others’ endeavors are proxies for the infant’s own acts. This is adaptive for human infants who cannot move around much to perform their own experiments on the physical world.

Going from self to other, infants expand their understanding of other people based on their own felt experiences. Others are attributed the experiences infants have when they perform similar actions. Infants themselves have felt joy and produced smiles; this gives them leverage for ascribing positive emotion to others who are acting in this same way. At a certain age infants may try to manipulate objects and fail to achieve their goals. This gives them a way of interpreting the unsuccessful attempts of others. They know from first-hand experience that a certain pattern of try-and-try-again behavior is a concomitant of purposeful striving and effortful attempts toward a goal. They can recognize that another is matching their action pattern. Their unconscious inference is that others who act ‘like me’ have internal states and feelings like I do when I behave this way. As children’s self-experience broadens, it broadens their appreciation of others.

A similar argument applies to the pattern of gaze adults exhibit in every day life. Infants interpret the looking behavior of others in a ‘like me’ fashion. They know that when they close their eyes or have a barrier in front of them, they cannot see distal objects. This allows them to make inferences about the perceptual experiences of others. They can discern when another is or is not in psychological contact with the external world. This is the beginning of

appreciating someone else's the viewpoint – the dawn of perspective-taking and recognizing the similarities (and differences) in how others see the world (see Moll & Meltzoff, 2011, for more detailed argument).

Admittedly, these developments are only the first steps toward understanding the minds and hearts of other people. It is a useful start, however, because a chief stumbling block in other historical theories has been removed. We do not need to account for how a 'solipsistic' newborn emerges from his or her shell, because that is not the original state; nor are we compelled to think of newborns as having an adult-like understanding, because there is an inkling of how an initial state could be transformed through a combination of first-hand experiences and observations of other people.

While infants focus on their relationship with individuals (mom, dad, siblings), older children increasingly become concerned with groups. I think that the 'like me' mechanism available to infants also exerts force in older children and impels them to categorize people based on self-relevant attributes. New experiments are beginning to show that 'in-groups' are readily formed by preschool children based on gender (Cvencek, Greenwald, & Meltzoff, 2011) and based on other more arbitrary attributes in older children (Dunham, Baron, & Carey, 2011). In this essay we considered the implications for education and children's sense of identification with academic disciplines. We found that primary-school children had assimilated the cultural stereotype that boys are associated with mathematics. By primary school, children not only behave like others (action imitation) but also begin to take on attributes that are culturally assigned to the groups of which they are a member. The 'like me' mechanisms that connect young babies to individuals now functions to connect older children to groups and their associated attributes.

### *From theory to practice*

Plato was concerned about the impressions adults make on our children and Rousseau despaired at the 'prejudices' of society to such a degree that he espoused private tutors rather than public education. Our children, however, cannot be shielded from our culture.

What can we do? We can educate ordinary citizens and policymakers alike about the new findings in child development. The science shows that our own children are watching us, which compels self-reflection on the models we provide. We now understand that education begins 'at birth' and we are teachers of our 'young and tender'. Society depends on the education of our children, and Plato's question is for all of us: 'What will their education be?'

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## References

- Aristotle. (2001). *The basic works of Aristotle*. R. McKeon (Ed.). New York: Modern Library.
- Augustine, St. (1997). *The Confessions* (M. Boulding, Trans.). New York: Vintage Books.
- Brooks, R., & Meltzoff, A.N. (2002). The importance of eyes: How infants interpret adult looking behavior. *Developmental Psychology*, 38, 958-966.
- Bruer, J.T. (1997). Education and the brain: A bridge too far. *Educational Researcher*, 26, 4-16.
- Bruner, J. (1996). *The culture of education*. Cambridge, MA: Harvard University Press.
- Ceci, S.J., & Williams, W. (2007). *Why aren't more women in science? Top researchers debate the evidence*. Washington, DC: American Psychological Association Press.
- Cvencek, D., Greenwald, A.G., & Meltzoff, A.N. (2011). Measuring implicit attitudes of 4-year-olds: The preschool implicit association test. *Journal of Experimental Child Psychology*, 109, 187-200.
- Cvencek, D., Meltzoff, A.N., & Greenwald, A. G. (2011). Math-gender stereotypes in elementary school children. *Child Development*, 82, 739-1033.
- Darwin, C. (1877). A biographical sketch of an infant. *Mind*, 2, 285-294.
- Dunham, Y., Baron, A.S., Carey, S. (2011). Consequences of 'minimal' group affiliations in children. *Child Development*, 82, 793-811.
- Markman, E.M. (1989). *Categorization and naming in children: Problems of induction*. Cambridge, MA: MIT Press.
- Marshall, P.J., & Meltzoff, A.N. (2011). Neural mirroring systems: Exploring the EEG mu rhythm in infancy. *Developmental Cognitive Neuroscience*, 1, 110-123.
- Meltzoff, A.N. (1995). Understanding the intentions of others: Re-enactment of intended acts by 18-month-old children. *Developmental Psychology*, 31, 838-850.
- Meltzoff, A.N., & Brooks, R. (2008). Self-experience as a mechanism for learning about others: A training study in social cognition. *Developmental Psychology*, 44, 1257-1265.
- Meltzoff, A.N., Kuhl, P.K., Movellan, J. & Sejnowski, T.J. (2009). Foundations for a new science of learning. *Science*, 325, 284-288.
- Meltzoff, A.N., & Moore, M.K. (1977). Imitation of facial and manual gestures by human neonates. *Science*, 198, 75-78.
- Meltzoff, A.N., & Moore, M.K. (1997). Explaining facial imitation: A theoretical model. *Early Development and Parenting*, 6, 179-192.
- Moll, H., & Meltzoff, A.N. (2011). How does it look? Level 2 perspective-taking at 36 months of age. *Child Development*, 82, 661-673.
- National Academy of Sciences (2010). *Rising above the gathering storm, revisited: Rapidly approaching category 5*. National Academy of Sciences Press: Washington, DC.

- Nosek, B.A., Banaji, M.R., & Greenwald, A.G. (2002). Math = male, me = female, therefore math  $\neq$  me. *Journal of Personality and Social Psychology*, 83, 44-59.
- Nosek, B.A., Smyth, F.L., Sriram, N., Lindner, N.M., Devos, T., Ayala, A., ... Greenwald, A.G. (2009). National differences in gender-science stereotypes predict national sex differences in science and math achievement. *Proceedings of the National Academy of Sciences*, 106, 10593-10597.
- Piaget, J. (1954). *The construction of reality in the child* (M. Cook, Trans.). New York: Basic Books.
- Piaget, J. (1962). *Play, dreams and imitation in childhood* (C. Attegnio & F.M. Hodgson, Trans.). New York: Norton.
- Plato. (1997). *Plato: Complete works*. J.M. Cooper (ed.). Indianapolis, IN: Hackett Books.
- Quine, W.V.O. (1960). *Word and object*. Cambridge, MA: MIT Press.
- Repacholi, B.M., Meltzoff, A.N., & Olsen, B. (2008). Infants' understanding of the link between visual perception and emotion: 'If she can't see me doing it, she won't get angry'. *Developmental Psychology*, 44, 561-574.
- Rousseau, J.-J. (1972). *Émile* (B. Foxley, Trans.). London: J.M. Dent & Sons Ltd. (Original work published 1762).
- Spelk, E.S. (2005). Sex differences in intrinsic aptitude for mathematics and science? *American Psychologist*, 60, 950-958.
- Tomasello, M., & Farrar, M.J. (1986). Joint attention and early language. *Child Development*, 57, 1454-1463.

# DEVELOPMENTAL CHANGES IN NEURONAL OSCILLATIONS AND SYNCHRONY: EVIDENCE FOR A LATE CRITICAL PERIOD

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## The role of synchronized oscillations

Synchronised neural oscillations in low- (delta, theta and alpha) and high- (beta and gamma) frequency bands are a fundamental mechanism for enabling coordinated activity during normal brain functioning [Buzsaki & Draguhn, 2004; Fries, 2009]. A large body of evidence from invasive electrophysiology in non-human primates and electro- and magnetoencephalographic- (EEG/MEG) recordings in humans that have tested the amplitude and synchrony of neural oscillations have demonstrated close relations between synchronous oscillatory activity and a variety of cognitive and perceptual functions. An important link between oscillations and cortical computations was the discovery of the role of oscillatory rhythms in the beta/gamma range (20–80 Hz) in establishing precise synchronization of distributed neural responses. Gray and colleagues [Gray *et al.*, 1989] showed that action potentials generated by cortical cells align with the oscillatory rhythm in the beta and gamma range, which has the consequence that neurons participating in the same oscillatory rhythm synchronize their discharges with high precision. Thus, it is a central role of cortical oscillations in the beta/gamma range to enable neuronal synchronization and by virtue of establishing systematic phase lags, to define precise temporal relations between the discharges of distributed neurons [Womelsdorf *et al.*, 2007].

Self-generated oscillations and synchronization are highly dynamic phenomena and depend on numerous conditions, such as central states [Herculano *et al.*, 1999], stimulus configuration [Gray and Singer, 1989; Gray *et al.*, 1989] or attention [Fries *et al.*, 2001]. The strength of synchrony is closely correlated

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with perceptual processes such as feature binding, subsystem integration, brightness perception and interocular rivalry [for a recent review see Uhlhaas *et al.*, 2009a]. In addition, the strength of synchronization predicts whether an animal will give a correct response in an upcoming trial of a perceptual decision task, [Kreiter and Singer, 1996] suggesting its important functional role.

In addition to the high frequency oscillations in the beta- and gamma-band, oscillatory rhythms in the theta- and alpha-band also play an important role in cortical computations. Alpha activity (8–12 Hz) has been associated with inhibitory functions [Klimesch *et al.*, 2007] but also with the long-distance coordination of gamma-oscillations [Palva and Palva, 2007] and theta activity has been proposed to support large-scale integration of subsystems serving the formation and recall of memories [Buzsaki, 2005]. In general, there is a correlation between the distance over which synchronization is observed and the frequency of the synchronized oscillations. Short distance synchronization tends to preferentially occur at higher frequencies (gamma-band) than long-distance synchronization, which often manifests itself in the beta- but also in the theta- (4–8 Hz) and alpha- (8–12 Hz) frequency range [Kopell *et al.*, 2000; von Stein *et al.*, 2000].

While the relationship between neural synchrony and cognitive and perceptual processes has received widespread attention, a less explored aspect is the possible role of neural synchrony in the development of cortical networks. Oscillations and the generation of synchronized neuronal activity play a crucial role in the activity dependent self-organisation of developing networks [Ben-Ari, 2001; Hebb, 1949; Khazipov and Luhmann, 2006; Singer, 1995] (Figure 1, p. 260). The development and maturation of cortical networks critically depends on neuronal activity, whereby synchronized oscillations play an important role in the stabilization and pruning of connections [Hebb, 1949]. For example, in spike-timing dependent plasticity, pre- and post-synaptic spiking within a critical window of tens of milliseconds has profound functional implications [Markram *et al.*, 1997]. Stimulation at the depolarizing peak of the theta cycle in the hippocampus favours long-term potentiation (LTP), whereas stimulation in the trough causes depotentiation (LTD) [Huerta and Lisman, 1993]. The same relationship holds for oscillations in the beta- and gamma-frequency range [Wespataat *et al.*, 2004], indicating that oscillations provide a temporal time structure that allows for precise alignment of the amplitude and temporal relations of presynaptic and postsynaptic activation that determine the polarity (strengthening or weakening) of synaptic changes. Accordingly, the extensive modifications of synaptic connections during the development of cortical networks are critically dependent upon precise timing of neural activity.

Conversely, synchronisation of oscillatory activity is an important index of the maturity of cortical networks. Neural oscillations depend on anatomical and physiological parameters that undergo significant changes during development [Buzsaki and Draguhn, 2004]. Thus, synchronisation of oscillatory activity in the beta- and gamma-frequency range is dependent upon cortico-cortical connections that reciprocally link cells within the same cortical area, across different areas or even across the two hemispheres [Engel *et al.*, 1991; Löwel and Singer, 1992]. Furthermore, GABAergic interneurons play a pivotal role in establishing neural synchrony in local circuits, as indicated by the fact that a single GABAergic neuron may be sufficient to synchronise the firing of a large population of pyramidal neurons [Cobb *et al.*, 1995] and that the duration of the inhibitory post-synaptic potential (IPSP) can determine the dominant frequency of oscillations within a network [Wang and Buzsaki, 1996].

Postnatally, changes occur in both GABAergic neurotransmission [Doischer *et al.*, 2008; Hashimoto *et al.*, 2009] and the myelination of long axonal tracts [Ashtari *et al.*, 2007; Perrin *et al.*, 2009]. Thus, changes can be expected in the frequency and synchronisation (amplitude) of oscillation as well as in the precision with which rhythmic activity can be synchronised over longer distances at different developmental stages.

In the following we will provide evidence for important changes in parameters of neural synchrony during childhood and adolescence. While high-frequency activity emerges during early development, we will show that cortical networks fully sustain precise synchrony only during the transition from adolescence to adulthood, which is compatible with concurrent changes in anatomy and physiology.

### Resting-state oscillations

Developmental changes in the frequency spectrum of the EEG were first described by Berger and subsequent studies have confirmed pronounced changes in the amplitude and distribution of oscillations in different frequency bands [for a review see Niedermeyer, 2005]. In adults, resting-state activity is characterised by prominent alpha-oscillations over occipital electrodes while low (delta, theta) and high (beta, gamma) frequencies are attenuated. During childhood and adolescence, however, there is a reduction in the amplitude of oscillations over a wide frequency range that is particularly pronounced for delta- and theta-activity [Whitford *et al.*, 2007]. These development changes occur more rapidly in posterior than in frontal regions [Niedermeyer, 2005] and follow a linear trajectory until age 30 [Whitford *et al.*, 2007]. When the relative magnitude is taken into ac-

count, oscillations in the alpha- and beta-range increase whereas activity in lower frequency bands decreases with age.

Changes in resting-state activity during adolescence can also be observed during sleep. Campbell and Feinberg [2009] analysed delta- and theta-activity during non-rapid eye movement sleep (non-REM) in a cohort of 9- and 12-year-old children twice yearly over a 5-year period and observed profound changes in slow-frequency oscillations. The power of delta-oscillations did not change between 9-11 years but then showed a reduction by over 60% until 16.5 years. Similar results were obtained for oscillations in the theta-band. According to the authors, the decrease in the power of low-frequency oscillations reflects synaptic pruning and is independent of pubertal stages.

In contrast to the reduction of slow-wave activity, resting-state gamma-band oscillations increase during development. They can be detected around 16 months and continue to increase in amplitude until age 5 [Takano and Ogawa, 1998]. Correlations between the amplitude over frontal electrodes and the development of language and cognitive skills suggest a functional role of early gamma-band activity in the maturation of cognitive functions [Benasich *et al.*, 2008].

Changes in the amplitude of oscillations are accompanied by developmental trends in the synchrony of oscillations. Thatcher *et al.* [2008] tested the hypothesis that white matter maturation involves the differential development of short- and long-range fibre connections and is reflected in changes in the coherence of beta-oscillations. EEG coherence between 2 months and 16 years of age was characterised by an increase in coherence at shorter distances ( $< 6$  cm) while long-range coherence ( $> 24$  cm) did not vary with age. Pronounced increases in long-range coherence in the alpha-band were reported by Srinivasan *et al.* [1999]. The authors tested EEG-coherence in 20 children (6-11 years) and 23 adults (18-23 years). Reduced power over anterior electrodes in children was accompanied by reduced coherence between anterior and posterior electrodes. These findings suggest that in addition to an increase in fast rhythmic activity, the maturation of oscillations during childhood and adolescence is accompanied by an increase in precision with which oscillations are synchronised suggesting a continued maturation in the spatial and functional organisation of cortical networks.

### **Maturation of steady-state responses**

Steady-State Responses (SSR) represent a basic neural response to a temporally modulated stimulus to which it is synchronized in frequency

and phase. Thus, steady-state paradigms are ideally suited to probe the ability of neuronal networks to generate and maintain oscillatory activity in different frequency bands. Previous research had shown that the power of the auditory SSR is largest in the 40 Hz range [Galambos *et al.*, 1981], suggesting a natural resonance frequency of cortical networks.

Developmental studies have so far focused on the auditory SSR (ASSR). Rojas *et al.* [2006] examined the 40 Hz ASSR in MEG data in 69 participants in the age range from 5–52 years. Regression analyses showed a significant effect for age indicating that the amplitude of the 40 Hz ASSR between 200–500 ms increased significantly during development. Specifically, a marked increase in 40 Hz power was observed during childhood and adolescence and appeared to reach a plateau during early adulthood.

The protracted maturation of the auditory SSR was confirmed in a recent study by Poulsen *et al.* [2009]. Sixty-five participants aged 10 were tested with EEG in a longitudinal study that involved a follow up after 18 months. Comparison with an adult group revealed a marked reduction of the 40 Hz ASSR in children relative to adult participants. In addition to an overall reduction of the amplitude of the ASSR, adults were also characterised by a reduced variability and higher peak frequencies than children. Similar differences were also found between 10 and 11.5 year old children. Analyses of developmental changes of the source waveforms indicated that adults had significantly higher source power in the left temporal cortex whereas no difference was found for activity in the right temporal source nor in the brainstem.

### **Development of task-related oscillations**

Csibra *et al.* [2000] measured gamma-band responses in EEG data in 6- and 8-month-old infants during the perception of Kanisza squares that require the binding of contour elements into a coherent object representation. Based on prior behavioural studies that showed that infants up to 6 months of age are unable to perceive Kanisza figures, the authors hypothesized that perceptual binding in 8-month-old infants is related to the emergence of gamma-band oscillations. This was supported by an induced oscillatory response between 240–320 ms over frontal electrodes that was not present in the younger group, suggesting that the emergence of gamma-band oscillations during infancy is correlated with the maturation of perceptual functions.

Further studies have demonstrated continued maturation of neural synchrony during visual processing until adulthood. Werkle-Bergner *et al.* [2009] tested the amplitude and phase-stability of evoked gamma-band os-

cillations during the perception of squares and circles in children (10–12 years), young adults (20–26 years) and older adults (70–76 years). Evoked oscillations in children were significantly reduced between 30–148 Hz over occipital electrodes relative to adults. In addition, gamma-band activity in children was not modulated by the size of the stimulus as in adult and older participants. Participants in the 70–76 years age range, while displaying a similar degree of phase-locking, were characterised by reduced amplitudes of gamma-band oscillations relative to younger adults during the perception of large stimuli.

The development of induced oscillations and their synchronisation was examined in a study by Uhlhaas *et al.* [2009b] who investigated children, adolescent participants and young adults during the perception of Mooney faces (see Figure 1, p. 260). In adult participants, perceptual organisation of upright Mooney faces was associated with prominent gamma-band oscillations over parietal electrodes as well as long-range synchronisation in the theta- and beta-band. During development, profound changes in these parameters occurred that correlated with improved detection rates and reaction times. In particular, neural synchrony in the beta- and gamma-band increased until early adolescence (12–14 years) that was followed by a *reduction* in phase-synchronisation and amplitude of high-frequency oscillations during late adolescence (15–17 years). In 18–21 year olds, high-frequency oscillations showed a significant increase relative to late adolescent participants that was accompanied by a reorganisation in the topography of phase-synchrony patterns in the beta-band as well as by an increase in theta phase-synchrony between frontal and parietal electrodes. Accordingly, the development of induced oscillations and their synchronisation from late adolescence to early adulthood reflect a critical developmental period that is associated with a rearrangement of functional networks and with an increase of the temporal precision and spatial focusing of neuronal interactions.

Changes in neural synchrony have also been demonstrated in auditory processing during development. Müller *et al.* [2009] assessed differences in oscillatory activity between 0–12 Hz in young children (age: 9–11 years), older children (age: 11–13 years), young adults (age: 18–25 years) and older adults (age: 64–75 years) during an auditory oddball task. Differences in the synchronisation and amplitude of oscillations in EEG-data were most prominent for comparisons between children and young adults and for the processing of attended and deviant stimuli. Children were characterised by reduced synchronisation in local circuits over fronto-central electrodes at delta- and theta-frequencies as well as by reduced long-range synchronisation. Reduced local and long-range synchronisation was accompanied,

however, by a relative increase in the power of evoked and induced oscillations in children in the same frequencies, suggesting that, as development progresses, low-frequency activity is characterised by a shift to more precisely synchronised oscillations during adolescence. Similar results were reported by Yordanova *et al.* in the alpha-band [1996].

Changes in neural synchrony during development are also present in the motor system in which beta-band oscillations are associated with the preparation and execution of motor commands [Kilner *et al.*, 2000]. Synchrony of spinal inputs to motoneurons can be investigated by measuring the covariation of signals from electromyographic (EMG) recordings over abductor muscles. Farmer *et al.* [2007] analysed the coherence of EMG-signals in the 1–45 Hz frequency range during development in a sample of 50 participants (age range: 4–59 years). Pronounced developmental changes in beta-band coherence were found between 7–9 and 12–14 years, with adolescent participants showing elevated levels of beta-band coherence relative to children.

### Relations to anatomical and physiological changes

Following the emergence of gamma-band oscillations during infancy [Benasich *et al.*, 2008; Takano and Ogawa, 1998] oscillations shift to higher frequencies and synchronisation becomes more precise [James *et al.*, 2008; Müller *et al.*, 2009; Poulsen *et al.*, 2009; Rojas *et al.*, 2006; Uhlhaas *et al.*, 2009b]. This development is not complete until early adulthood and neural synchrony continues to mature throughout the adolescent period, which represents a critical phase of brain maturation.

The maturation of neural synchrony during adolescence is compatible with the development of cognitive functions during this period that depend on neural synchrony, such as working memory and executive processes [Luna *et al.*, 2004] as well as with concurrent changes in anatomy and physiology [Toga *et al.*, 2006]. Specifically, late development of gamma-band oscillations is compatible with recent data suggesting important changes in GABAergic neurotransmission during adolescence. Hashimoto *et al.* [2009] showed a predominance of GABA  $\alpha_2$  subunits in the monkey dorsolateral prefrontal cortex (DLPFC) during early development, whereas in adult animals  $\alpha_1$  subunits are more expressed. This switch was accompanied by marked changes in the kinetics of GABA transmission, including a significant reduction in the duration of miniature IPSPs in pyramidal neurons. The shift in  $\alpha$  subunit expression could provide a direct correlate of the observed increase in both amplitude and frequency of gamma-band oscillations during adolescence as  $\alpha_1$  subunits predominate at synapses of parvalbumin (PV)-positive basket cells

(BCs) [Klausberger *et al.*, 2002] that are crucially involved in the generation of gamma-band oscillations [Sohal *et al.*, 2009].

The decrease in the slow-wave oscillations (delta, theta) has been related to synaptic pruning [Feinberg and Campbell, 2010]. According to this view, the higher number of synapses during childhood could explain the excess of delta- and theta-oscillations as well as the initially high metabolic rate that becomes reduced during adolescence leading to reduced slow-wave activity and decreased energy consumption.

In addition to the changes in the amplitude of oscillations, changes in the precision of synchrony have been observed that can be related to anatomical changes. The development of white matter that continues until early adulthood [Ashtari *et al.*, 2007; Salami *et al.*, 2003] probably contributes to the maturation of long-range synchronisation between cortical regions by increasing the precision and frequency with which neural oscillations can be propagated. This is supported by several studies showing that the myelination of long axonal fibres increases during adolescence and results in enhanced long-range connectivity.

The data on the development of high-frequency oscillations and their synchronisation during adolescence are furthermore consistent with and extend findings on age-related changes in fMRI-activity patterns in a variety of cognitive tasks [Casey *et al.*, 2008] and during the resting-state [Supekar *et al.*, 2009]. These studies revealed a developmental pattern whereby brain areas critical for task performance become increasingly activated [Durston *et al.*, 2006]. Activation of frontal and parietal regions was found to be more prominent and focused in adult participants than in children and adolescents during tasks involving working memory, executive controls and visual processing [Crone *et al.*, 2006; Golarai *et al.*, 2007; Rubia *et al.*, 2007]. As the amplitude of the BOLD-signal is closely and positively correlated with the entrainment of neurons into synchronized gamma-band oscillations [Niessing *et al.*, 2005], the fMRI data are fully compatible with the notion that the ability of cortical networks to engage in precisely synchronized high-frequency oscillations increases during development and is a hallmark of maturity.

### **Implications for psychopathology and education**

In addition to the role of neural synchrony during normal brain maturation, the reviewed data have also important implications for the understanding of neuropsychiatric disorders, such as Autism Spectrum Disorders (ASDs) and Schizophrenia, which are associated with abnormal neural synchrony and aberrant neurodevelopment [Uhlhaas and Singer, 2010, 2007].



Considering the important role of neural synchrony in the shaping of cortical circuits at different developmental periods, we hypothesize that in ASDs abnormal brain maturation during early pre-natal and post-natal periods results in cortical circuits which are unable to support the expression of high-frequency oscillations during infancy. These impaired oscillations may in turn reduce the temporal precision of coordinated firing patterns and thereby disturb activity dependent circuit selection during further development. In schizophrenia, on the other hand, clinical symptoms typically manifest themselves during the transition from late adolescence to adulthood. As high-frequency oscillations and their synchronisation increase strongly during late adolescence and are associated with a reorganisation of cortical networks, we propose that in schizophrenia cortical circuits are unable to support the neural coding regime that emerges during late adolescence and relies on temporally more precise and spatially more focused synchronisation patterns.

With respect to educational considerations the data recording a marked reorganisation of cortical networks during late adolescence may be of particular relevance. They suggest a transition from a more diffuse protonetwork towards more focused, presumably more specialized subnetworks, and a late but substantial increase in the temporal precision of phase locking across cortical areas. These changes suggest the existence of a critical period of brain development during late adolescence. The neuronal underpinnings of this developmental phase are less well studied than those underlying the critical periods in early life, during which brain architectures are subject to extensive epigenetic shaping by experience dependent processes. The reason is that, until recently, postpubertal brain development was mainly considered as a consolidation process associated with the final stage of myelination and not with major reorganisation of functional networks. In the light of the new evidence it appears necessary to explore in greater depth not only the neurobiological changes underlying this late reorganisation but also the possible windows of opportunity that this developmental phase may provide for epigenetic, in particular educational influences. If the mechanisms supporting these late developmental changes share features with those acting during the early critical periods, one should expect enhanced susceptibility to use dependent modifications, i.e. to epigenetic shaping. This may shed new light on Freud's view that late adolescence provides a 'second chance'.

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## References

- Ashtari, M., *et al.* (2007) White matter development during late adolescence in healthy males: A cross-sectional diffusion tensor imaging study. *Neuroimage* 35, 501–510.
- Ben-Ari, Y. (2001) Developing networks play a similar melody. *Trends Neurosci.* 24, 353–360.
- Benasich, A.A., *et al.* (2008) Early cognitive and language skills are linked to resting frontal gamma power across the first 3 years. *Behav. Brain Res.* 195, 215–222.
- Buzsaki, G. (2005) Theta rhythm of navigation: link between path integration and landmark navigation, episodic and semantic memory. *Hippocampus* 15, 827–840.
- Buzsaki, G., and Draguhn, A. (2004) Neuronal oscillations in cortical networks. *Science* 304, 1926–1929.
- Campbell, I.G., and Feinberg, I. (2009) Longitudinal trajectories of non-rapid eye movement delta and theta EEG as indicators of adolescent brain maturation. *Proc. Natl. Acad. Sci. USA* 106, 5177–5180.
- Casey, B.J., Jones, R.M., Hare, A.T. (2008) The adolescent brain. *Ann. N.Y. Acad. Sci.* 1124, 111–126.
- Cobb, S.R., *et al.* (1995) Synchronization of neuronal activity in hippocampus by individual GABAergic interneurons. *Nature* 378, 75–78.
- Crone, E.A., *et al.* (2006) Neurocognitive development of the ability to manipulate information in working memory. *Proc. Natl. Acad. Sci. USA* 103, 9315–9320.
- Csibra, G., *et al.* (2000) Gamma oscillations and object processing in the infant brain. *Science* 290, 1582–1585.
- Doischer, D., *et al.* (2008) Postnatal differentiation of basket cells from slow to fast signaling devices. *J. Neurosci.* 28, 12956–12968.
- Durston, S., *et al.* (2006) A shift from diffuse to focal cortical activity with development. *Dev. Sci.* 9, 1–8.
- Engel, A.K., *et al.* (1991) Interhemispheric synchronization of oscillatory neuronal responses in cat visual cortex. *Science* 252, 1177–1179.
- Farmer, S.F., *et al.* (2007) Changes in EMG coherence between long and short thumb abductor muscles during human development. *J. Physiol.* 579, 389–402.
- Feinberg, I., and Campbell, I.G. (2010) Sleep EEG changes during adolescence: An index of a fundamental brain reorganization. *Brain Cogn.* 72, 56–65.
- Fries, P. (2009) Neuronal gamma-band synchronization as a fundamental process in cortical computation. *Annu. Rev. Neurosci.* 32, 209–24.
- Fries, P., *et al.* (2001) Modulation of oscillatory neuronal synchronization by selective visual attention. *Science* 291, 1560–1563.
- Galambos, R., *et al.* (1981) A 40-Hz auditory potential recorded from the human scalp. *Proc. Natl. Acad. Sci. USA* 78, 2643–2647.
- Golarai, G., *et al.* (2007) Differential development of high-level visual cortex

- correlates with category-specific recognition memory. *Nat. Neurosci.* 10, 512-522.
- Gray, C.M., and Singer, W. (1989) Stimulus-specific neuronal oscillations in orientation columns of cat visual cortex. *Proc. Natl. Acad. Sci. USA* 86, 1698-1702.
- Gray, C.M., et al. (1989) Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. *Nature* 338, 334-337.
- Hashimoto, T., et al. (2009) Protracted developmental trajectories of GABA(A) receptor alpha1 and alpha2 Subunit expression in primate prefrontal cortex. *Biol. Psychiatry* 65, 1015-1023.
- Hebb, D.O. (1949) *The organization of behavior: A neuropsychological theory*. Wiley
- Herculano-Houzel, S., et al. (1999) Precisely synchronized oscillatory firing patterns require electroencephalographic activation. *J. Neurosci.* 19, 3992-4010.
- Huerta, P.T., and Lisman, J.E. (1993) Heightened synaptic plasticity of hippocampal CA1 neurons during a cholinergically induced rhythmic state. *Nature* 364, 723-725.
- James, L.M., et al. (2008) On the development of human corticospinal oscillations: age-related changes in EEG-EMG coherence and cumulant. *Eur. J. Neurosci.* 27, 3369-3379.
- Khazipov, R., and Luhmann, H.J. (2006) Early patterns of electrical activity in the developing cerebral cortex of humans and rodents. *Trends Neurosci.* 29, 414-418
- Kilner, J.M., et al. (2000) Human cortical muscle coherence is directly related to specific motor parameters. *J. Neurosci.* 20, 8838-8845.
- Klausberger, T., et al. (2002) Cell type- and input-specific differences in the number and subtypes of synaptic GABA(A) receptors in the hippocampus. *J. Neurosci.* 22, 2513-2521.
- Klimesch, W., et al. (2007) EEG alpha oscillations: the inhibition-timing hypothesis. *Brain Res. Rev.* 53, 63-88.
- Kopell, N., et al. (2000) Gamma rhythms and beta rhythms have different synchronization properties. *Proc. Natl. Acad. Sci. USA* 97, 1867-1872.
- Kreiter, A.K., and Singer, W. (1996) Stimulus-dependent synchronization of neuronal responses in the visual cortex of the awake macaque monkey. *J. Neurosci.* 16, 2381-2396.
- Löwel, S., and Singer, W. (1992) Selection of intrinsic horizontal connections in the visual cortex by correlated neuronal activity. *Science* 255, 209-212.
- Luna, B., et al. (2004) Maturation of cognitive processes from late childhood to adulthood. *Child Dev.* 75, 1357-1372.
- Markram, H., et al. (1997) Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. *Science* 275, 213-215.
- Müller, V., et al. (2009) Lifespan differences in cortical dynamics of auditory perception. *Dev. Sci.* 12, 839-853.
- Niedermeyer, E. (2005) Maturation of the EEG: Development of Waking and Sleep Patterns. In: Niedermeyer, E., Da Silva, F.L., (Eds.). *Electroencephalography: Basic Principles, Clinical Applications, and Related Fields*. Lippincott Williams & Wilkins, Philadelphia, 209-234.
- Niessing, J., et al. (2005) Hemodynamic signals correlate tightly with synchronized gamma oscillations. *Science* 309, 948-951.
- Palva, S., and Palva, J.M. (2007) New vistas for alpha-frequency band oscillations. *Trends Neurosci.* 30, 150-158.
- Perrin, J.S., et al. (2009) Sex differences in the growth of white matter during adolescence. *Neuroimage* 45, 1055-1066.
- Poulsen, C., et al. (2009) Age-related changes in transient and oscillatory brain responses to auditory stimulation during early adolescence. *Dev. Sci.* 12, 220-235.
- Rojas, D.C., et al. (2006) Development of the 40Hz steady state auditory evoked

- magnetic field from ages 5 to 52. *Clin. Neurophysiol.* 117, 110–117.
- Rubia, K., *et al.* (2007) Linear age-correlated functional development of right inferior fronto-striato-cerebellar networks during response inhibition and anterior cingulate during error-related processes. *Hum. Brain Mapp.* 28, 1163–1177.
- Salami, M., *et al.* (2003) Change of conduction velocity by regional myelination yields constant latency irrespective of distance between thalamus and cortex. *Proc. Natl. Acad. Sci. USA* 100, 6174–6179.
- Singer, W. (1995) Development and plasticity of cortical processing architectures. *Science* 270, 758–764.
- Sohal, V.S., *et al.* (2009) Parvalbumin neurons and gamma rhythms enhance cortical circuit performance. *Nature* 459, 698–702.
- Srinivasan, R. (1999) Spatial structure of the human alpha rhythm: global correlation in adults and local correlation in children. *Clin. Neurophysiol.* 110, 1351–1362.
- Supekar, K., *et al.* (2009) Development of large-scale functional brain networks in children. *PLoS Biol.* 7, e1000157.
- Takano, T., and Ogawa, T. (1998) Characterization of developmental changes in EEG-gamma band activity during childhood using the autoregressive model. *Acta Paediatr. Jpn.* 40, 446–452.
- Thatcher, R.W., *et al.* (2008) Development of cortical connections as measured by EEG coherence and phase delays. *Hum. Brain Mapp.* 12, 1400–1415.
- Toga, A.W., *et al.* (2006) Mapping brain maturation. *Trends Neurosci.* 29, 148–159.
- Uhlhaas, P.J., and Singer, W. (2010) Abnormal oscillations and synchrony in schizophrenia. *Nat. Rev. Neurosci.* 11, 100–113.
- Uhlhaas, P.J., and Singer, W. (2007) What do disturbances in neural synchrony tell us about autism. *Biol. Psychiatry* 62, 190–191.
- Uhlhaas, P.J., *et al.* (2009a) Neural synchrony in cortical networks: history, concept and current status. *Frontiers Integr. Neurosci.* 3, 17.
- Uhlhaas, P.J., *et al.* (2009b) The development of neural synchrony reflects late maturation and restructuring functional networks in humans. *Proc. Natl. Acad. Sci. USA* 106, 9866–9871.
- von Stein, A., *et al.* (2000) Top-down processing mediated by interareal synchronization. *Proc. Natl. Acad. Sci. USA* 97, 14748–14753.
- Wang, X.J., and Buzsaki, G. (1996) Gamma oscillation by synaptic inhibition in a hippocampal interneuronal network model. *J. Neurosci.* 16, 6402–6413.
- Werkle-Bergner, M., *et al.* (2009) EEG gamma-band synchronization in visual coding from childhood to old age: Evidence from evoked power and inter-trial phase locking. *Clin. Neurophysiol.* 120, 1291–1302.
- Wespstat, V., *et al.* (2004) Phase sensitivity of synaptic modifications in oscillating cells of rat visual cortex. *J. Neurosci.* 24, 9067–9075.
- Whitford, T.J., *et al.* (2007) Brain maturation in adolescence: concurrent changes in neuroanatomy and neurophysiology. *Hum. Brain Mapp.* 28, 228–237.
- Womelsdorf, T., *et al.* (2007) Modulation of neuronal interactions through neuronal synchronization. *Science* 316, 1609–1612.
- Yordanova, J.Y., *et al.* (1996) Developmental changes in the alpha response system. *Electroencephalogr. Clin. Neurophysiol.* 99, 527–538.

## STATEMENT

# HUMAN NEUROPLASTICITY AND EDUCATION

## FINAL STATEMENT

■ ANTONIO M. BATTRO, STANISLAS DEHAENE, WOLF J. SINGER,  
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The methods of brain and cognitive sciences have reached a stage such that we can now objectively monitor the developmental trajectory of the child's brain and document how this trajectory is being shaped by parenting, education and other environmental influences.

Non-invasive brain imaging methods can now be used, together with behavioral measurements, to examine the development of infant cerebral and mental organization and its growth. The results reveal both a highly structured early organization of brain networks for language, with hemispheric specialization, and its very fast maturation in the first months of life, which can now be indexed by objective measurement.

Brain maturation continues in adolescence and early adulthood, with remarkable changes in the dynamic interactions of distributed brain regions. The initially rather diffuse networks become more segregated and focused. The genetically determined layout of the connection architecture provides a universal neural platform, shared by all humans, but which will be later shaped by specific cultural experiences.

Schooling, in particular, is a major event in children's lives. Brain imaging results reveal the great impact caused by early education to domains such as language, literacy, arithmetic and reasoning. For instance, the brain of illiterate adults differs in several clearly identifiable features from the brain of alphabetized adults. The brain changes induced by education are made possible by the remarkable adaptivity that characterizes the developing brain. It results from the fact that brain development is associated with a continuous formation and removal of neuronal connections, whereby experience determines which connections get consolidated. This extensive neuroplasticity is revealed in a particularly salient way by extreme cases such as hemispherectomized children. Another example comes from studies of blind children, where the intact but deprived visual cortex begins to respond intensely to touch, including Braille reading. Even in the normally developing brain, similar processes of 'cortical recycling' are occurring also during normal development, as the novel acquisitions of reading and mathematics invade evolutionarily older cortical regions and reorient their operation towards the specific processing of new human inventions such as numbers or the alphabet.

Plasticity is massive in the child's brain, but continues to exist in many if not all brain pathways throughout life – brain-imaging shows, for instance, that adult alphabetization courses lead to brain changes that are similar to those seen in schooled children who learned to read during childhood. Recent evidence indicates that neural pathways, dendritic trees, synaptic pruning and even gene expression are being modified in millions of neurons as a function of learning experience.

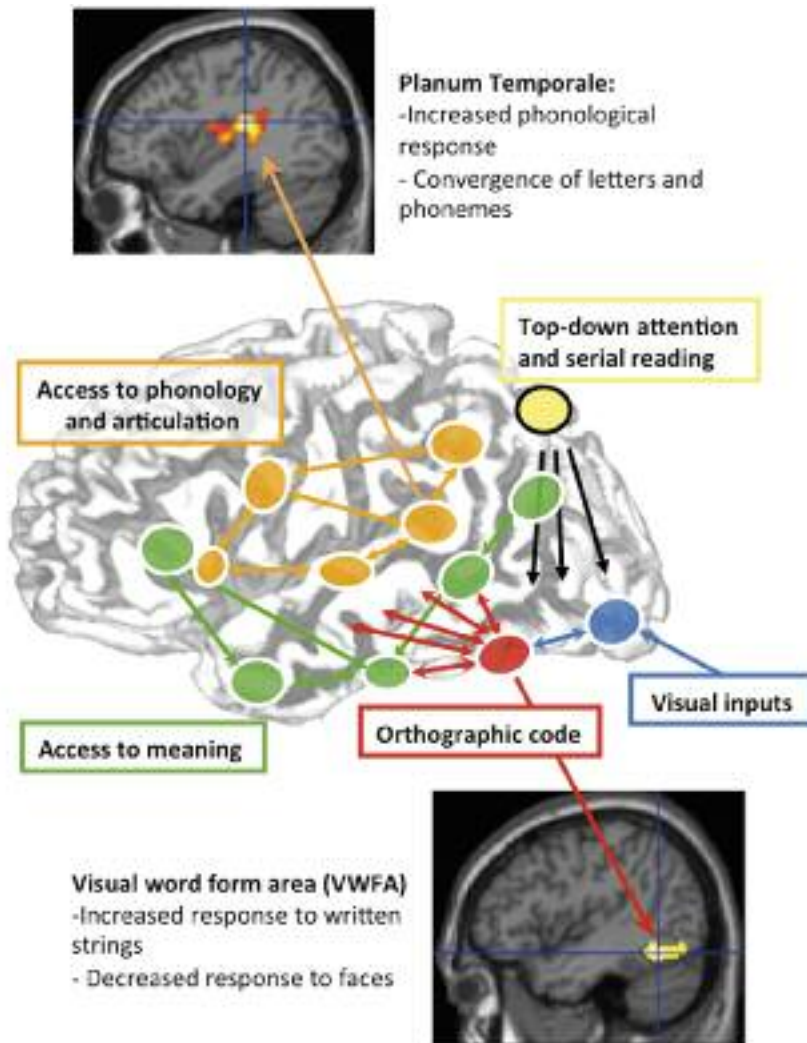
The conditions under which learning occurs in young children are being clarified. Experiments in second-language learning demonstrate that passive exposure to language is ineffective – social interaction with an active tutor is essential. These experiments emphasize the importance of teachers and families as providing a social environment optimally conducive to learning. Early intervention programs that teach both children and parents the principles of attention focusing can be highly effective. These early interventions seem to be particularly effective for socially and economically deprived children and therefore have a potential to bring greater equity and justice to the education system.

Synaptic and genetic mechanisms of mental retardation are being elucidated in specific genetic disease such as fragile X, to such an extent that the tools of molecular medicine begin to open new strategies for possible intervention. Neuroplasticity begins at the point when the brain is beginning to be formed, before birth, and genetic variations or mutations, as well as early environmental influences, can lead to brain changes that may explain why some children develop learning disabilities. The cognitive science of education is leading to novel tools for assessing the progress of individual children and for detecting possible difficulties, hidden disabilities as well as individual differences. This can lead to new interventions specifically tailored to a given child. The use of adaptive computer software and online tutoring, carefully adjusted in difficulty, can play a special role here.

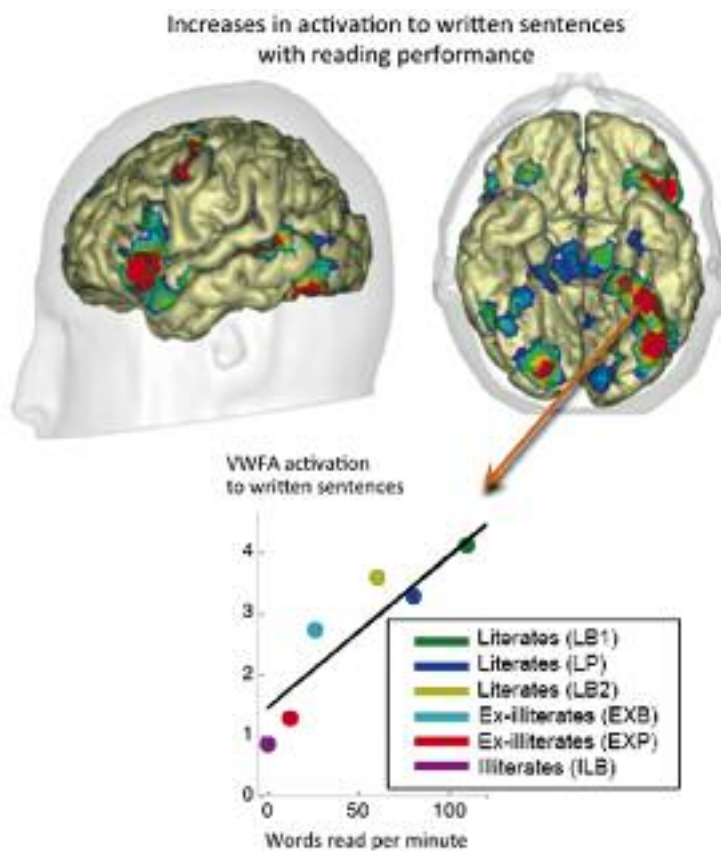
In summary, the bridges between brain science and education are numerous and quickly developing. Neuroplasticity is the key bridging process, and its molecular, neuronal and brain-wide mechanisms should be better investigated in the future. However, the state of scientific knowledge is already sufficient to conclude that investment in early education can have a profound impact on brain organization throughout life and therefore on health, economy, and social justice. While these insights concern mainly the development and acquisition of instrumental abilities, little is known to date about the mechanisms through which moral values, rules of social conduct and dispositions for ethical behavior are installed by education. Since these properties and abilities are also of utmost importance for the future of mankind, intensification of research in this domain is considered an important desideratum.



## Tables


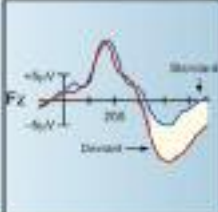

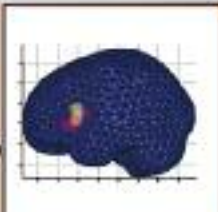






**Figure 1.** Overview of the brain systems for reading, showing two major sites of change induced by literacy. The central diagram, taken from (Dehaene, 2009), illustrates the major left-hemisphere regions involved in expert reading. During reading, the written word projected onto the retina first reaches the occipital visual cortex. From there, it is channeled to the left-hemisphere visual word form area (VWFA), which encodes the visual orthography of the string: the sequence of letters and their relations. Most words are identified quickly and effortlessly, in parallel, but for long or hard-to-read words, a left-to-right serial orientation of attention to the sequence, arising from dorsal parietal cortex, may be needed. The identified visual string is then transmitted to distinct areas involved in meaning and in pronunciation (auditory phonology and articulatory). The insets show two brain regions where activation is dramatically increased in literate relative to illiterate adults (redrawn from data in Dehaene, Pegado, *et al.*, 2010): the visual word form area (bottom) and the planum temporale (top). These regions contribute to a grapheme-to-phoneme conversion route. Developing this pathway is an essential goal of reading acquisition.

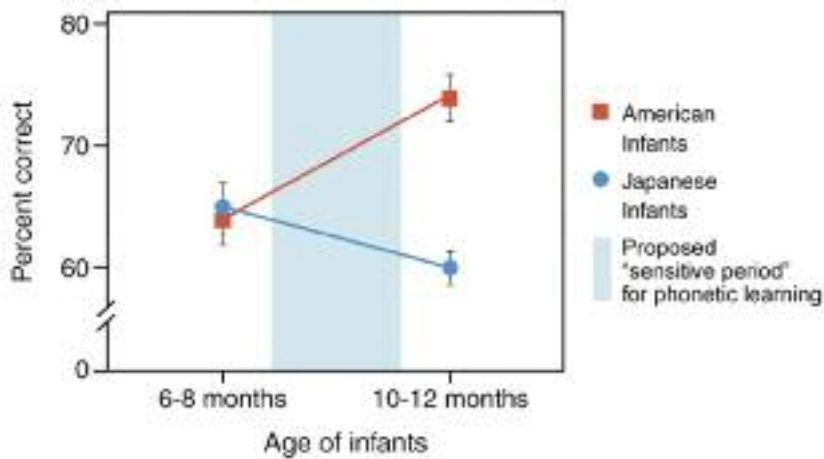


**Figure 2.** Overview of changes induced by learning to read in adults. The image shows all the regions where activation increased with reading performance, in response to the visual presentation of written sentences (redrawn from data in Dehaene, Pegado, *et al.*, 2010). Literacy increases activation in the visual word form area (VWFA, inset graph), even in unschooled ex-illiterate adults who learned to read during adulthood. Literacy also allows the entire left-hemisphere network of language areas to be activated through the visual modality.

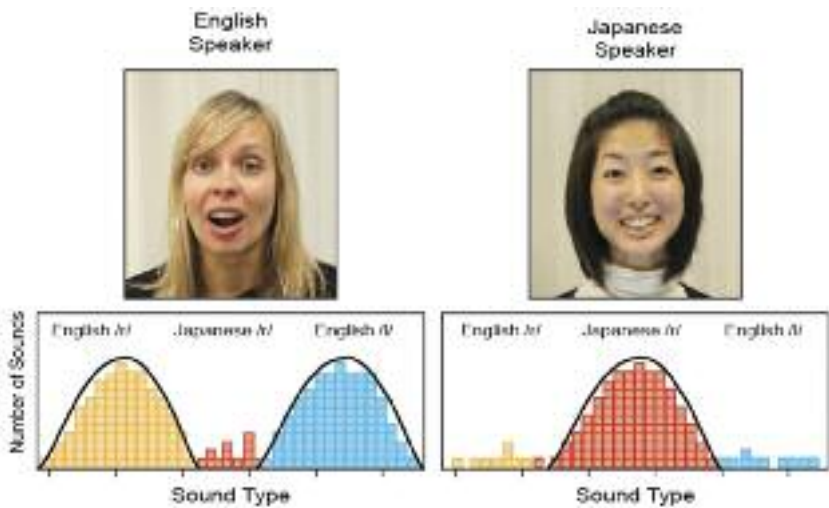
## NEUROSCIENCE TECHNIQUES USED WITH INFANTS

Inexpensive		<p>EEG/ERP: Electrical field changes</p> <p>Excellent temporal resolution</p> <p>Studies cover the lifespan</p> <p>Sensitive to movement</p> <p>Noiseless</p>	
Expensive		<p>MEG: Magnetic field changes</p> <p>Excellent temporal &amp; spatial resolution</p> <p>Studies on adults and young children</p> <p>Head tracking for movement calibration</p> <p>Noiseless</p>	
Expensive		<p>fMRI: Hemodynamic changes</p> <p>Excellent spatial resolution</p> <p>Studies on adults &amp; a few on infants</p> <p>Extremely sensitive to movement</p> <p>Noise protectors needed</p>	
Moderate		<p>NIRS: Hemodynamic changes</p> <p>Good spatial resolution</p> <p>Studies infants in the first 2 years</p> <p>Sensitive to movement</p> <p>Noiseless</p>	

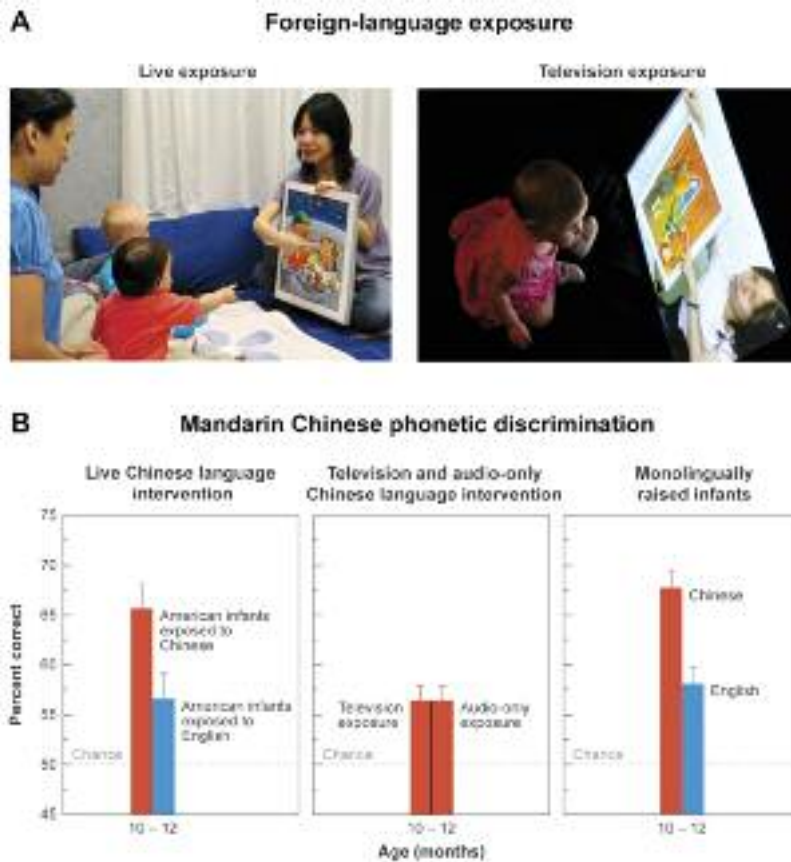
**Figure 1.** Four techniques now used extensively with infants and young children to examine their responses to linguistic signals (From Kuhl & Rivera-Gaxiola, 2008).



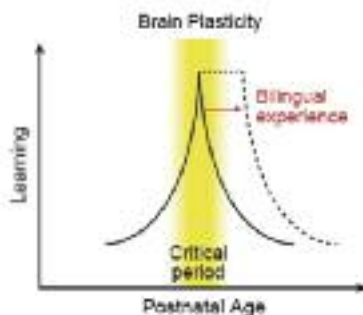
**Figure 3.** Effects of age on discrimination of the American English /ra-la/ phonetic contrast by American and Japanese infants at 6–8 and 10–12 months of age. Mean percent correct scores are shown with standard errors indicated (Kuhl et al., 2006).



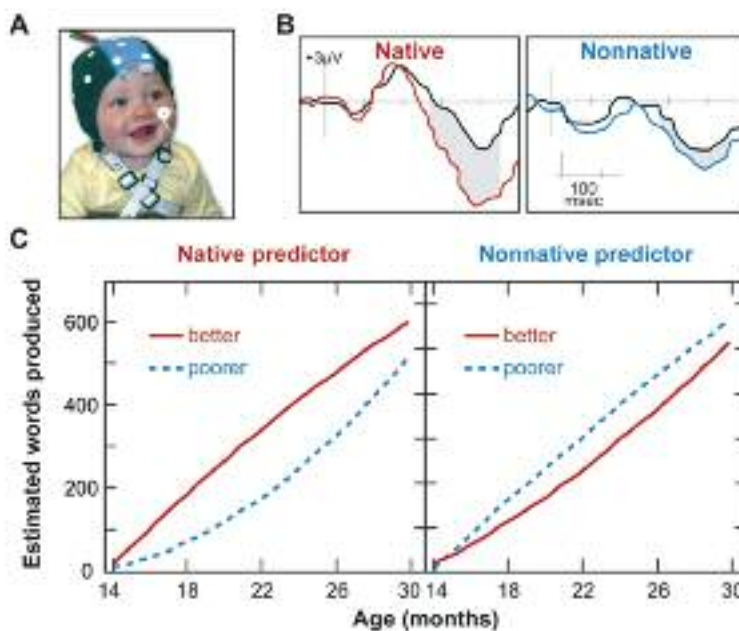
**Figure 4.** Idealized case of distributional learning is shown. Two women speak ‘motherese’, one in English and the other in Japanese. Distributions of English /r/ and /l/, as well as Japanese /r/, are shown. Infants’ sensitivity to these distributional cues has been shown with simple stimuli. (Adapted from Kuhl, 2010b).



**Figure 5.** The need for social interaction in language acquisition is shown by foreign-language learning experiments. Nine-month-old infants experienced 12 sessions of Mandarin Chinese through (A) natural interaction with a Chinese speaker (left) or the identical linguistic information delivered via television (right) or audiotape (not shown). (B) Natural interaction resulted in significant learning of Mandarin phonemes when compared with a control group who participated in interaction using English (left). No learning occurred from television or audiotaped presentations (middle). Data for age-matched Chinese and American infants learning their native languages are shown for comparison (right) (adapted from Kuhl et al., 2003).



**Figure 6.** On the NLM-e account, monolingual and bilingual children ‘open’ the critical period for phonetic learning at the same point in time. However, bilingual children remain ‘open’ to the effects of experience for a longer period of time, due the higher variability in speech input.



**Figure 7.** (A) A 7.5-month-old infant wearing an ERP electrocap. (B) Infant ERP waveforms at one sensor location (CZ) for one infant are shown in response to a native (English) and nonnative (Mandarin) phonetic contrast at 7.5 months. The mismatch negativity (MMN) is obtained by subtracting the standard waveform (black) from the deviant waveform (English = red; Mandarin = blue). This infant’s response suggests that native-language learning has begun because the MMN negativity in response to the native English contrast is considerably stronger than that to the nonnative contrast. (C) Hierarchical linear growth modeling of vocabulary growth between 14 and 30 months for MMN values of +1SD and -1SD on the native contrast at 7.5 months (C, left) and vocabulary growth for MMN values of +1SD and -1SD on the nonnative contrast at 7.5 months (C, right) Kuhl, 2010a).



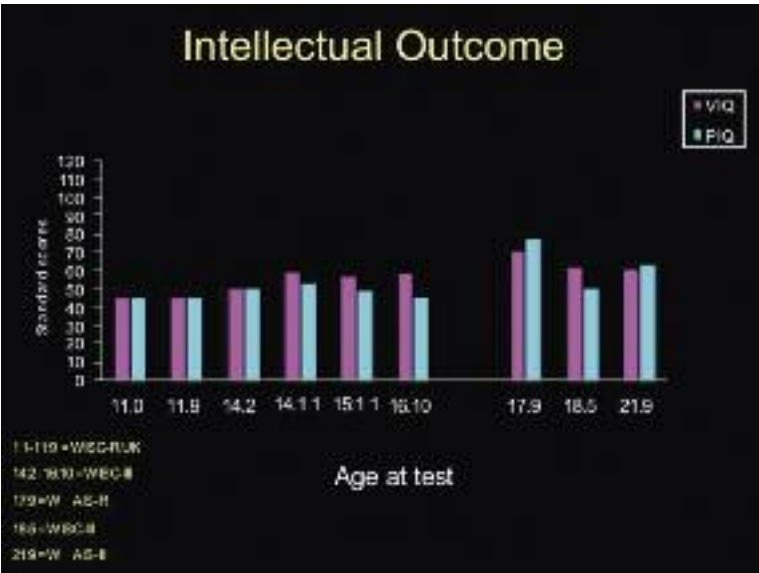


Figure 2. Alex’s standardized (mean = 100, SD, 15) intelligence quotients (pink: Verbal IQ; blue: Performance IQ) between the ages of 11:0 and 21:9 years. Range of the average population intelligence quotients (green) is from 80 to 109.

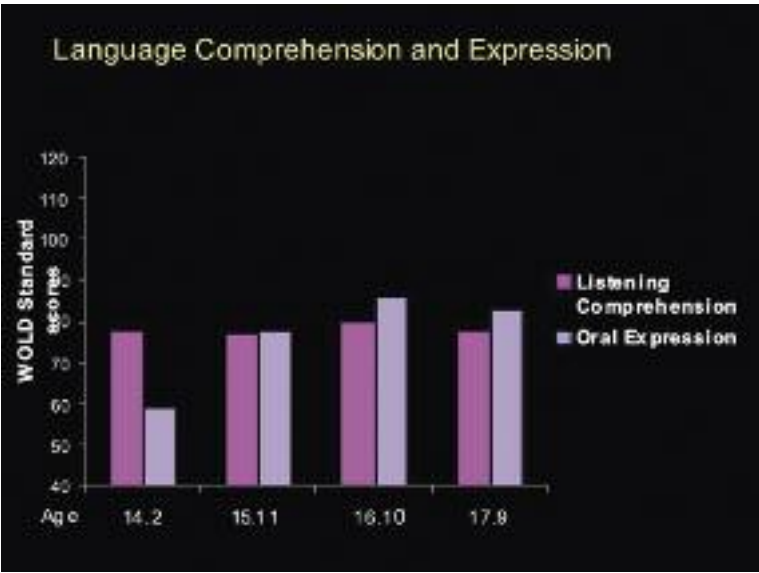
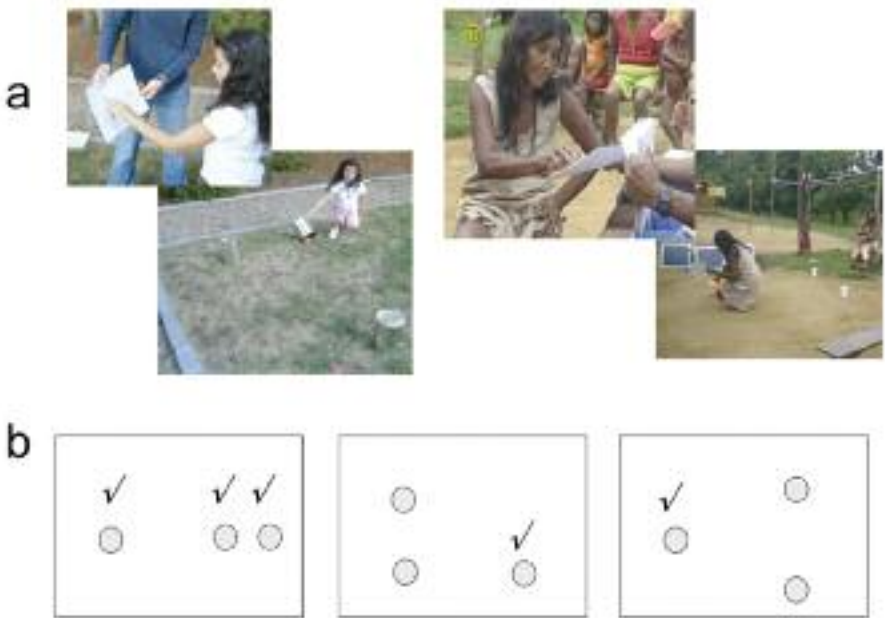


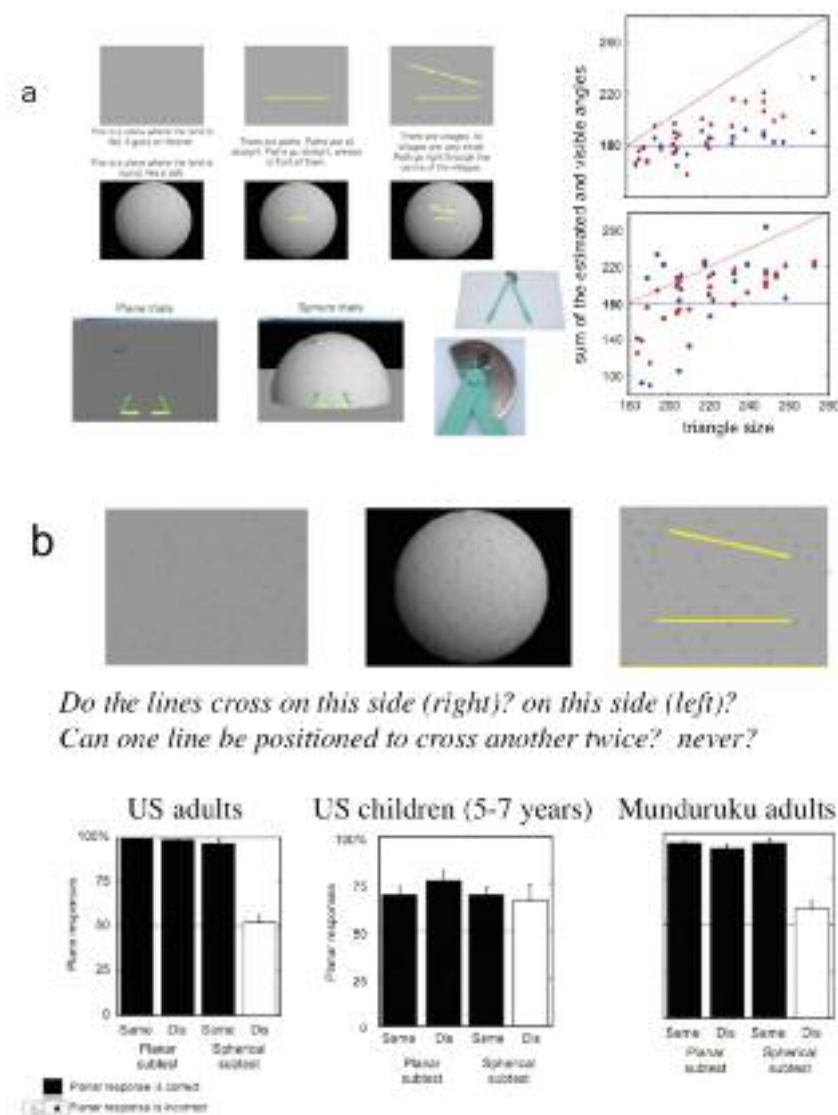
Figure 4. Everyday language comprehension and expression skills of Alex showing improvements in oro-vocal communication during adolescence.



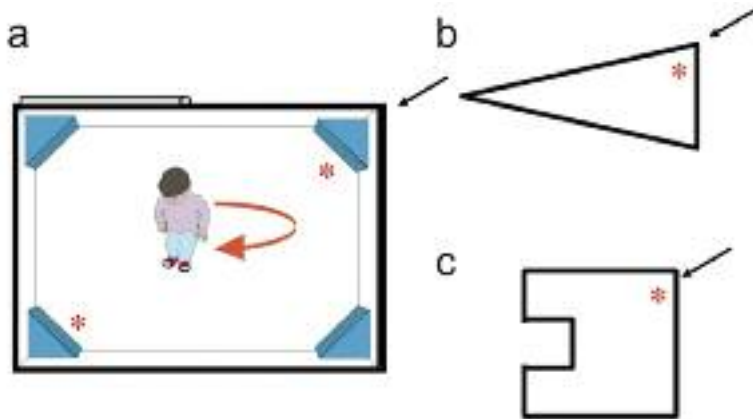
Figure 5. Development of literacy skills during adolescence.



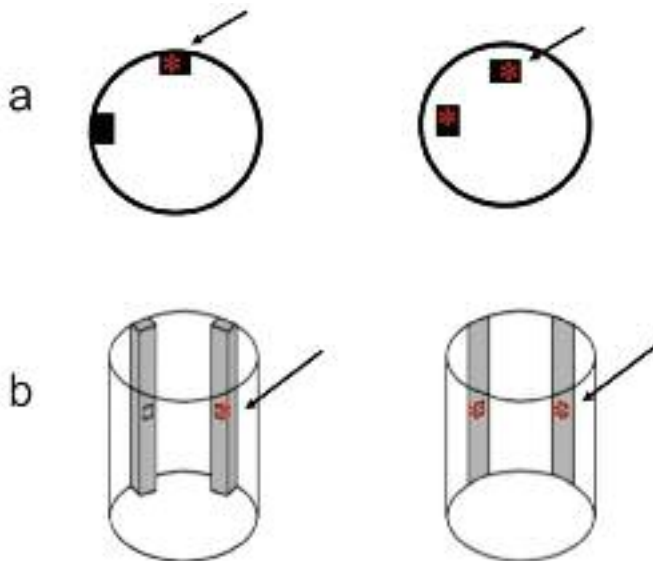
**Figure 1.** Displays and performance in a test of navigation by purely geometric maps in adults and children in two cultures. (a) The experimental settings and a sample task in the studies with U.S. children (left) and Amazonian adults (right). (b) The three map configurations used in the study with 4-year-old children; adults in the two cultures were tested with the triangular maps only. Arrows indicate the target locations at which 4-year-old children were successful; adults in both cultures performed above chance at all locations (after Shusterman *et al.*, 2008, and Dehaene *et al.*, 2006).



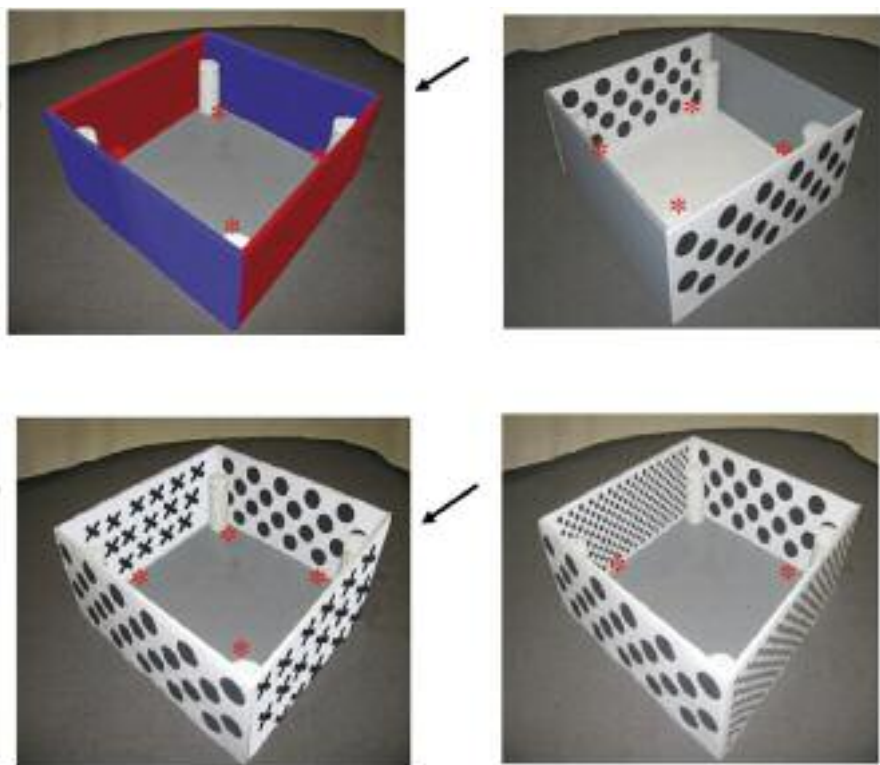
**Figure 2.** Displays for tests assessing abstract geometrical intuitions. (a) The displays and instructions for a study of triangle completion. Participants were introduced to a plane or sphere (top left) and then judged the position and angle at which the two lines met at the unseen apex of a triangle (below left). Scatterplots show the mean sums of angle estimates with the two visible angles on each trial, for U.S. adults (top right) and 6-year-old U.S. children (below right). Planar trials appear in blue and spherical trials in red; solid lines indicate correct responses. (b) Example displays and questions for a study of intuitions about points and lines. Participants gave verbal yes/no judgments to all questions. Percent planar responses are given separately for the plane and the sphere, and separately for judgments for which answers do and do not differ on the two surfaces (after Izard *et al.*, 2011a).



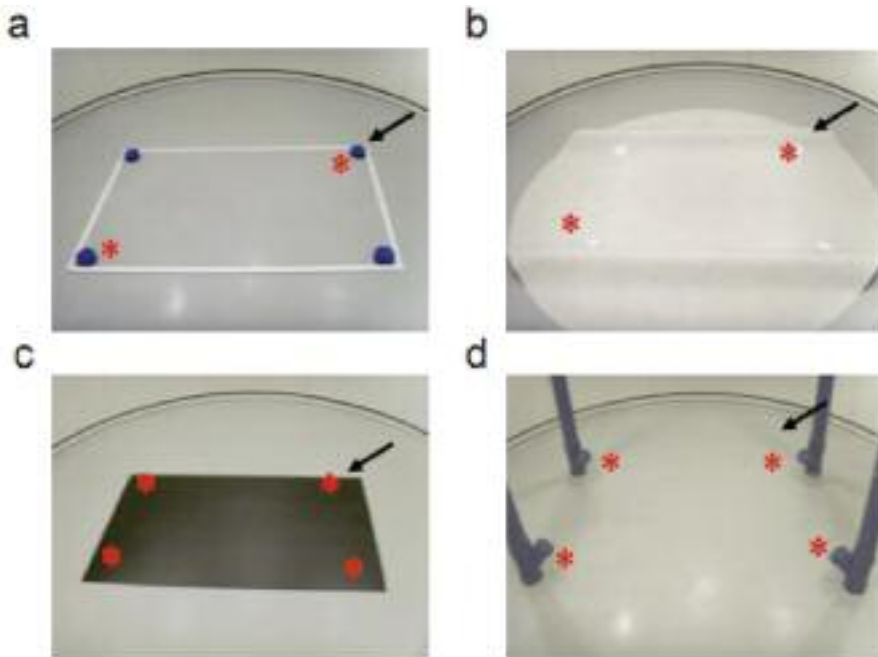
**Figure 3.** Overhead view of the arrays used in tests of children's reorientation in arenas with distinctive shapes. Arrows indicate the location of the hidden object (counterbalanced across children and rotated into alignment here to convey the findings); asterisks indicate the location(s) of children's search (a) in rectangular arenas (after Hermer & Spelke, 1996), (b) in isosceles arenas (after Lourenco & Huttenlocher, 2006), and (c) in a square arena with a symmetry-breaking bump in one wall (after Wang *et al.*, 1999).



**Figure 4.** Arrays used in tests of children's reorientation by geometric perturbations in the 3D extended surface layout, by geometrically similar configurations of freestanding objects, or by projectively similar configurations of 2D surface markings. Arrows indicate the location of the hidden object; asterisks indicate the location(s) of children's search. (a) Overhead view of arrays in which the same columns were flush against the boundary surface or freestanding. (b) Oblique view of arrays in which the columns were 3D projections or 2D patches (after Lee & Spelke, 2010).

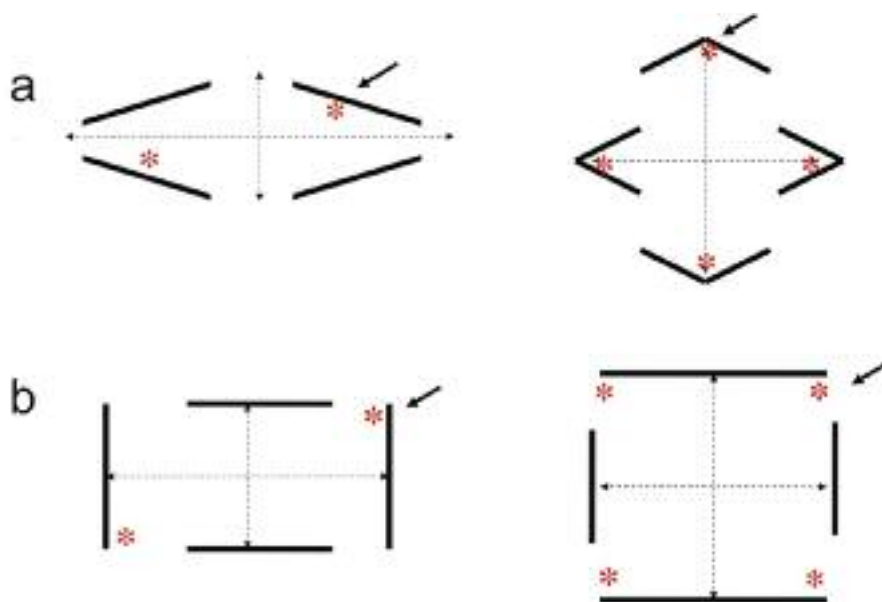


**Figure 5.** Arrays used in tests of children's reorientation in square arenas whose alternating walls differed in color, patterning, or relative size. Arrows indicate the location of the hidden object; asterisks indicate the locations of children's search (after Huttenlocher & Lourenco, 2007).

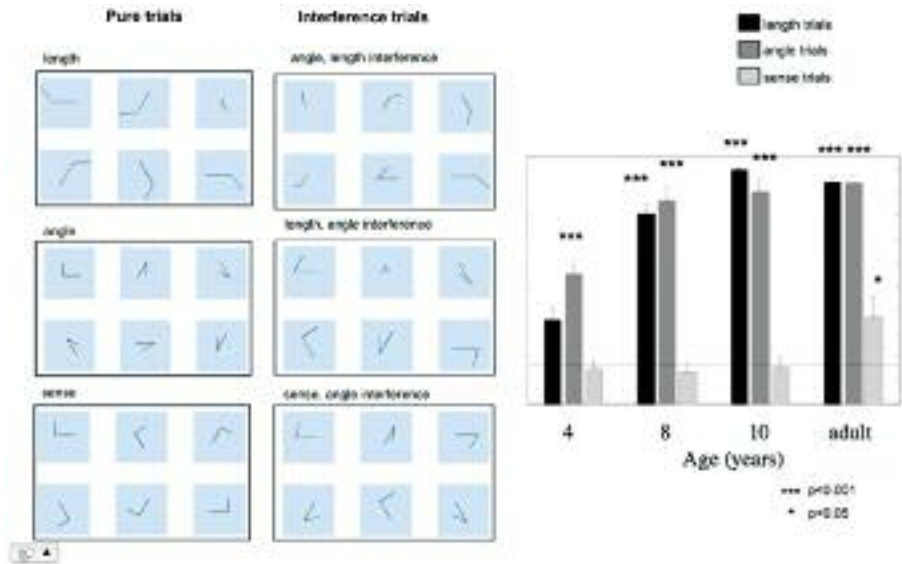


**Figure 6.** Arrays used in tests comparing children's reorientation by subtle perturbations in the 3D surface layout caused by (a) a 2-cm frame or (b) two gradual bumps, to their reorientation by prominent brightness edges in (c) 2D patterns or (d) freestanding objects. Arrows indicate the location of the hidden object; asterisks indicate the locations of children's search (after Lee & Spelke, 2011).

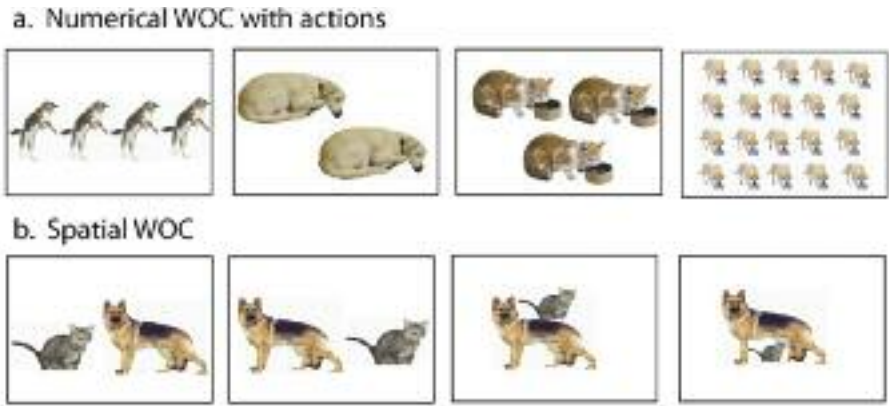




**Figure 7.** Arrays used in tests comparing children's abilities to reorient by angle and length to their abilities to reorient by surface distance. Dashed arrows indicate the distance relationships within the test spaces. Solid arrows indicate the location of the hidden object; asterisks indicate the locations of children's search in (a) fragmented rhomboid arrays and (b) fragmented rectangular arrays (after Lee *et al.*, in review).



**Figure 8.** Arrays used in tests assessing the sensitivity of children and adults to simple forms differing in length, angle, or sense. Arrays on the left present forms that are identical except for orientation and for the tested property; arrays in the center present forms that vary randomly in a second property. Performance of adults and children appears on the right (after Izard & Spelke, 2009, and Izard *et al.*, 2011b).



**Figure 10.** Arrays used to elicit numerical and spatial descriptions from IC, a deaf adolescent who communicated only by means of a non-conventional gestural system. (a) When IC viewed successive arrays presenting the same kinds of objects in different numbers, he spontaneously produced gestures for numbers to distinguish later arrays from earlier ones. (b) When IC viewed successive arrays of the same kinds of objects in different spatial arrangements, he never produced gestures for these relationships, even after repeated prompting and modeling of such gestures.

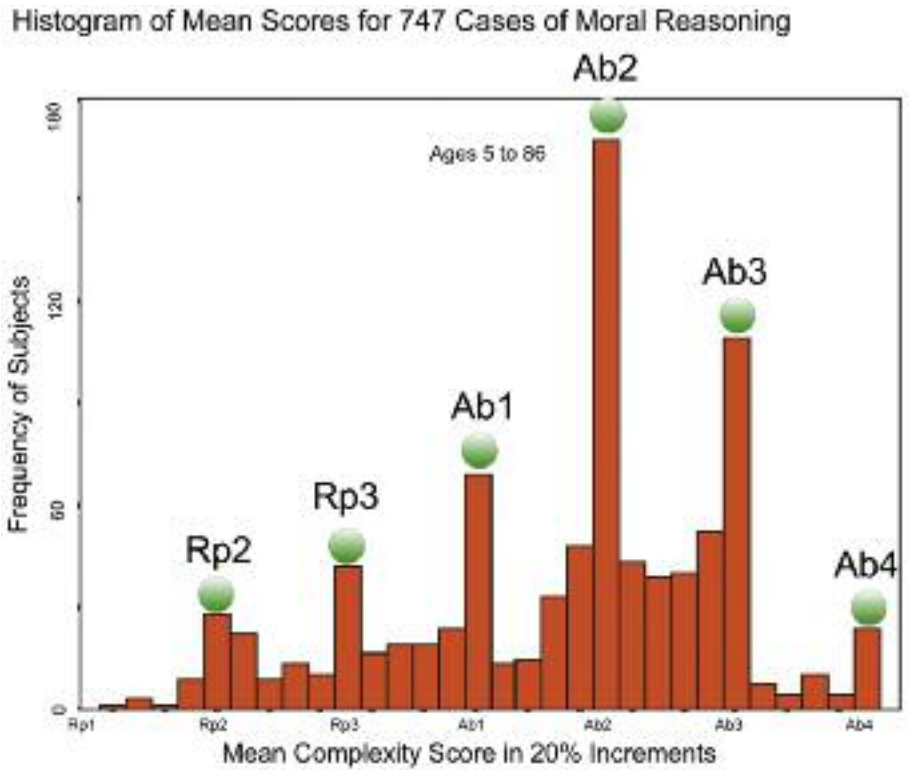
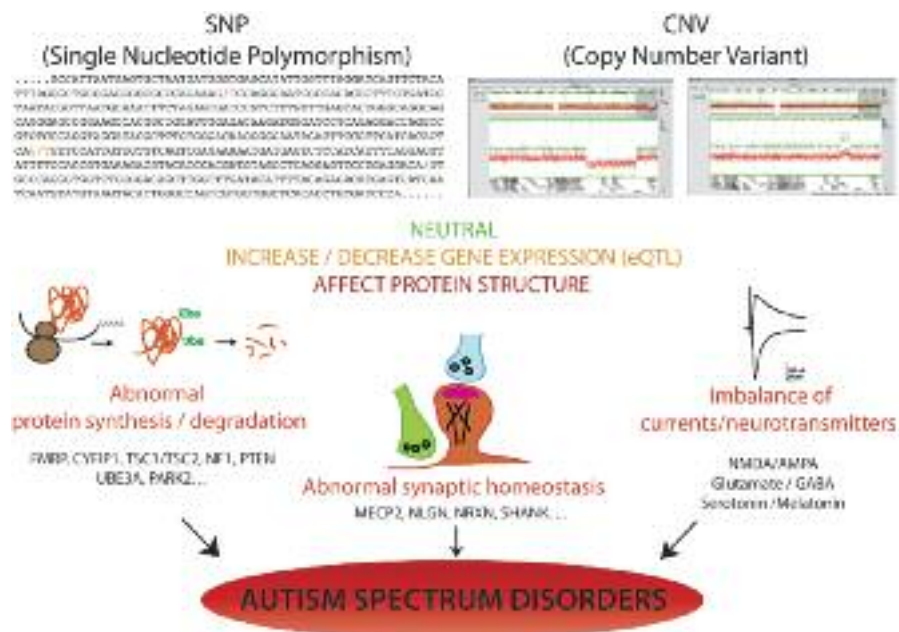
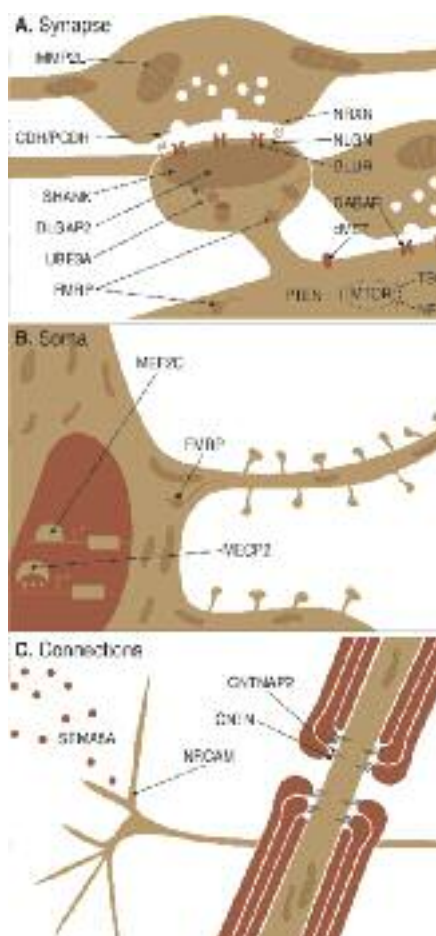


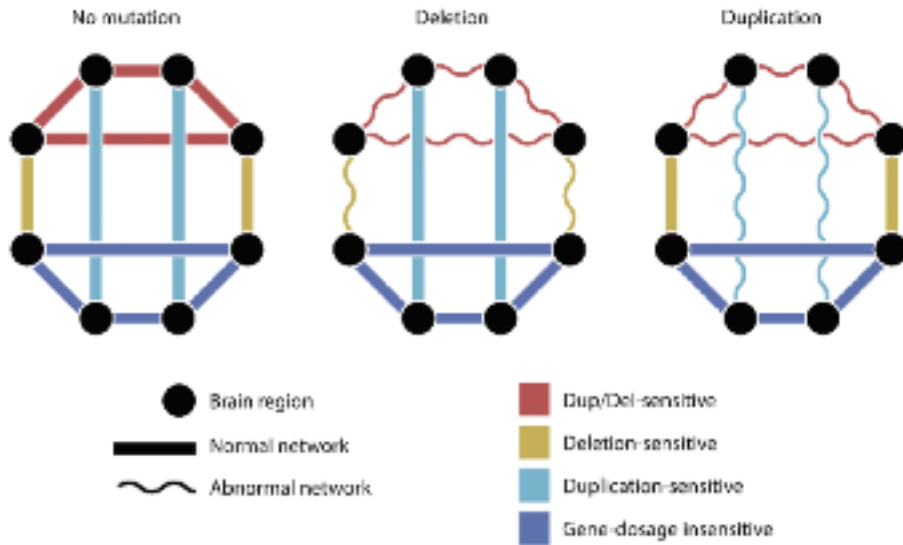
Figure 5. Distribution of levels of moral arguments based on Rasch analysis.



**Figure 1.** The human genome diversity and the biological processes associated with autism spectrum disorders. Genome diversity is made of single nucleotide polymorphisms (SNP) and of copy number variants (CNV). On the top left, SNPs are indicated by the possibility of two different nucleotides in the human genome sequence. On the top right, CNVs are loss or gain of genomic segment of >1000 kb. They can be detected *via* SNP arrays and visualized by the SnipPeep software. SNPs and CNVs can be neutral or modifying gene expression or protein structure. A subset of these variations can influence protein translation/degradation, synaptic homeostasis and the balance between synaptic currents. All these features are known to increase risk of having autism spectrum disorders.



**Figure 2** Cellular distribution of the proteins associated with ASD. The proteins associated with ASD appear to participate into three main biological processes. First (panel A), at the synapse cell adhesion proteins such as cadherins (CDH), protocadherins (PCDH), neuroligins (NLGN) and neuurexins (NRXN) are involved in synaptic recognition and assembly. Within the postsynaptic density, scaffold proteins such as SHANK3 and DLGAP2 assemble the synaptic components and provide a link between membrane proteins and the actin skeleton. FMRP transports mRNA at the dendrites and regulates local translation of synaptic proteins. In the cytoplasm, the mTOR pathway regulates translation and is influenced by proteins such as PTEN, NF1, TSC1/TS2 and c-MET. The E3 ligase UBE3A is involved in the targeting of synaptic proteins to the proteasome. Receptors for glutamate (GLUR) and GABA (GABAR) are playing a central role in producing excitatory and inhibitory currents, respectively. IMPP2L is a peptidase within the inner membrane of the mitochondria. Second (panel B), in the nucleus the methyl binding protein MECP2 and transcription factors such as MEF2C regulate the expression of neuronal genes involved in the formation of neuronal circuits and synaptic functions. The FMRP protein transports and regulates the translation of mRNA at the synapse. Finally (panel C), at the nodes of Ranvier proteins such as CNTN and CNTNAP2 organize the tight junctions between the axon and the myelinating glia. At the membrane or in the intercellular space, cell adhesion molecules and secreted proteins such as NRCAM or SEMA5A act as guidance cues for axonal outgrowth.



**Figure 3. Different resilience of brain networks to gene dosage.** Depending on their different resilience, the functional effects of abnormal gene-dosage could seem localized, even if the genetic abnormalities are widespread. Brain networks involved in evolutionary older biological processes might have developed more compensatory mechanisms than those supporting more recent cognitive functions. In the illustration we distinguish four possibilities, networks insensitive to gene-dosage (dark blue), networks only sensitive to duplications (light blue) or deletions (orange), and finally, those unable to compensate for gene-dosage abnormalities (red). Nodes represent brain regions, and edges between nodes represent their functional link. Wavy edges represent sub-optimal functional links.

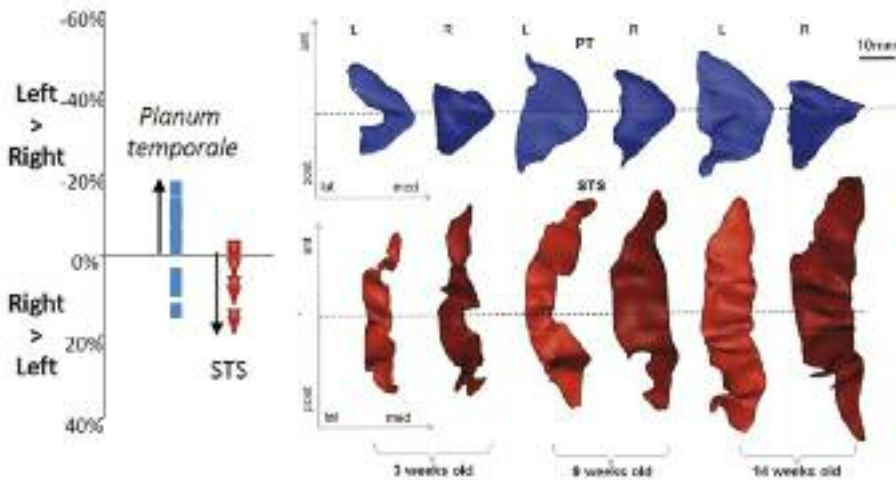


Figure 1. Structural asymmetries in human infants. A) Lateralization index (L-R/L+R) of the surface of the *planum temporale* and of the superior temporal sulcus (STS) in 14 infants. B) Individual examples showing the larger left *planum* and right STS in three infants spanning the time range considered (after Glasel *et al.*, submitted).

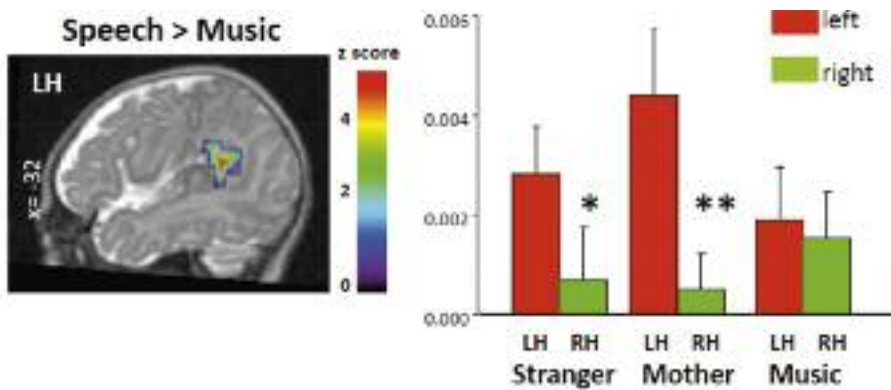
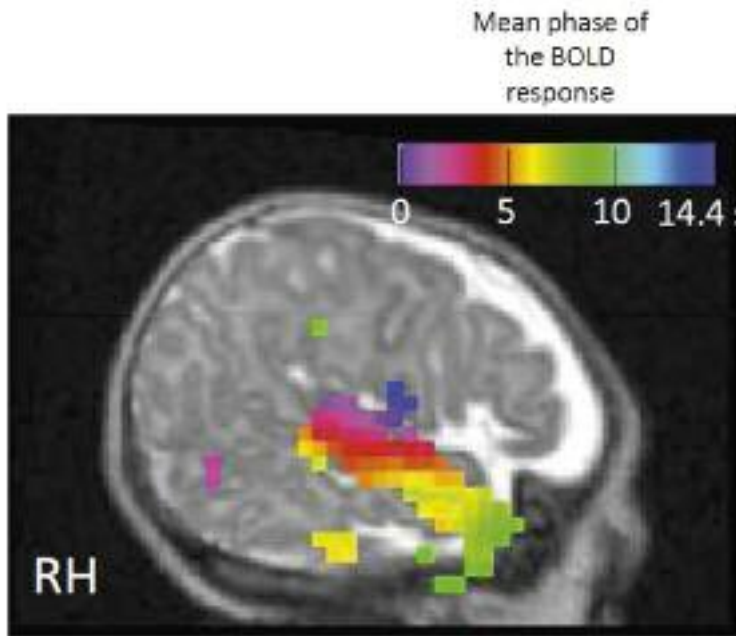
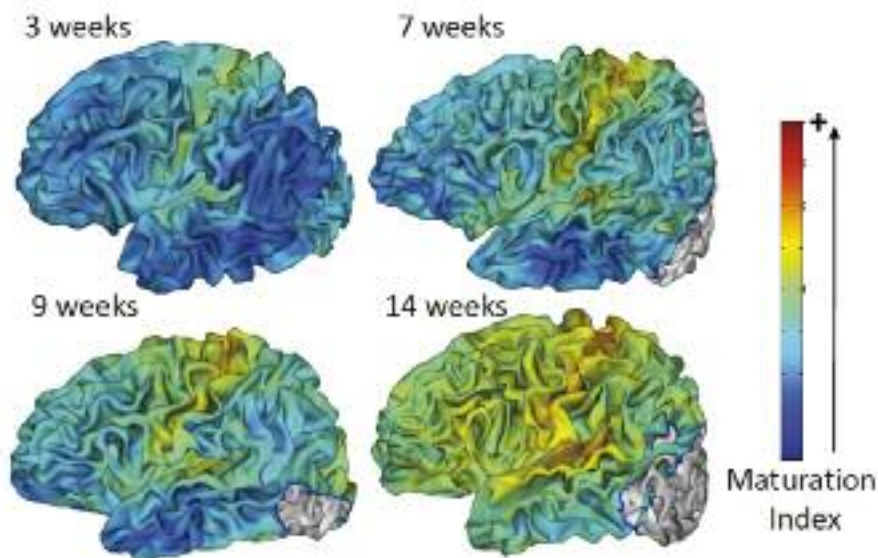


Figure 2. Hemispheric asymmetry for speech in the left *planum temporale*. (A) A comparison of the activations to speech and music in three-month-olds isolates a cluster in the left *planum temporale* (here projected on sagittal slices of a baby T2 anatomical image). (B) Boxplot of the individual activations averaged over the left and right *planum temporale* for three types of auditory stimulus: music, mother's voice and an unknown voice (arbitrary units). There is a significant left/right asymmetry for both speech conditions but not for music (\*\*  $p < .01$ , \*  $p < .05$ , after Dehaene-Lambertz *et al.*, 2010).

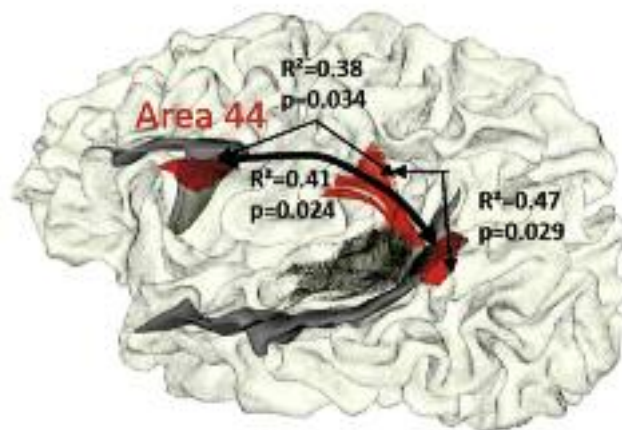




**Figure 3.** Phase measurement along the superior temporal region in three-month-old infants. The phase of the evoked fMRI responses to a single sentence was measured in 3-month-old infants (after Dehaene-Lambertz *et al.*, 2006b). A systematic gradient of response delays was found along both temporal regions, with fast on-line responses near Heschl gyrus (pink color), and increasingly slower responses as one moves either back into the *planum temporale* and Wernicke's area on the left side or forward along the STS toward the temporal pole and Broca's area (yellow-green color). A similar arrangement exists in adults (Dehaene-Lambertz *et al.*, 2006a), where it cannot be attributed purely to synaptic or hemodynamic delays, but may reflect integration and closure of speech segments of different lengths (phoneme, syllable, word, whole phrase). The presence of this gradient in very young infants, prior to any babbling, and its similarity to the hierarchical organization of anatomical projections in other primates (Kaas and Hackett, 2000; Pandya and Yeterian, 1990), suggests that it may constitute an innate bias that constrains language acquisition to a nested hierarchical structure.



**Figure 4.** Cortical maturation during the first months of life. An index based on the T2w signal and measured at each cortical point is projected on 3D meshes (left hemisphere) at 4 different ages. No data (grey region) is presented where absence of CSF in the T2w image prevents the computation of the index. The primary cortices are clearly more mature than the other cortices. By contrast, the maturation is delayed in the temporal region, in particular relative to frontal areas.



**Figure 5.** Correlations between white and gray matter maturation along the dorsal pathway. The STS, the precentral/inferior frontal sulci and the arcuate fasciculus of an individual infant are presented on his brain mesh. The arcuate fasciculus is limited to the parietal and temporal sections easily identifiable in infants. The regions significantly correlated at a group level are marked in red and correspond to the parietal part of the arcuate, the ventral part of the posterior STS and area 44 at the junction between the precentral and the inferior frontal sulcus (after Leroy *et al.*, 2011).

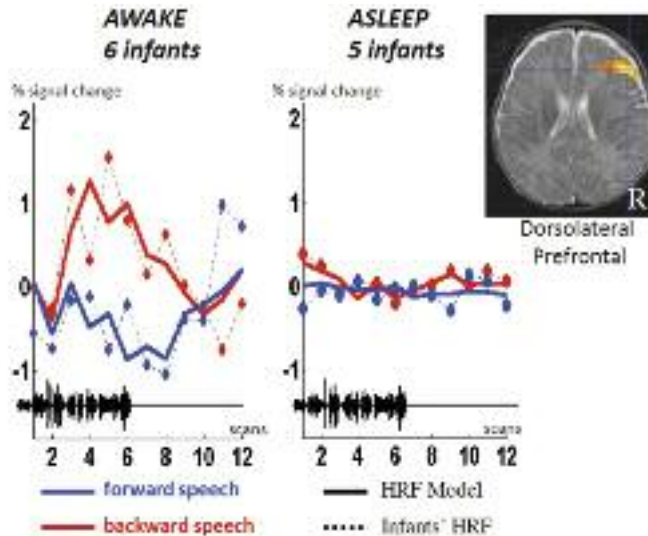


Figure 6. Responses to forward and backward speech in awake and asleep three-month-old infants. No response is seen in frontal regions in asleep infants although temporal areas are reacting to sound. In awake infants, there is a strong response to the native language (forward speech) which is not present for an impossible or unknown language (backward speech). These results underscore the participation of frontal regions in infants' cognition (after Dehaene-Lambertz *et al.*, 2002).

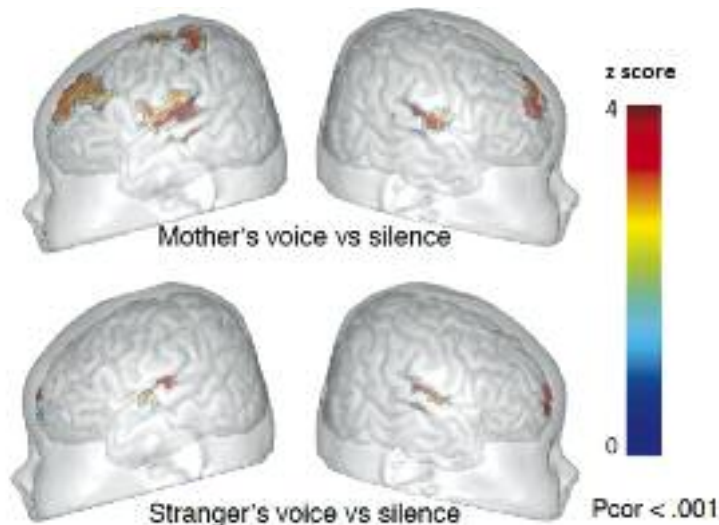
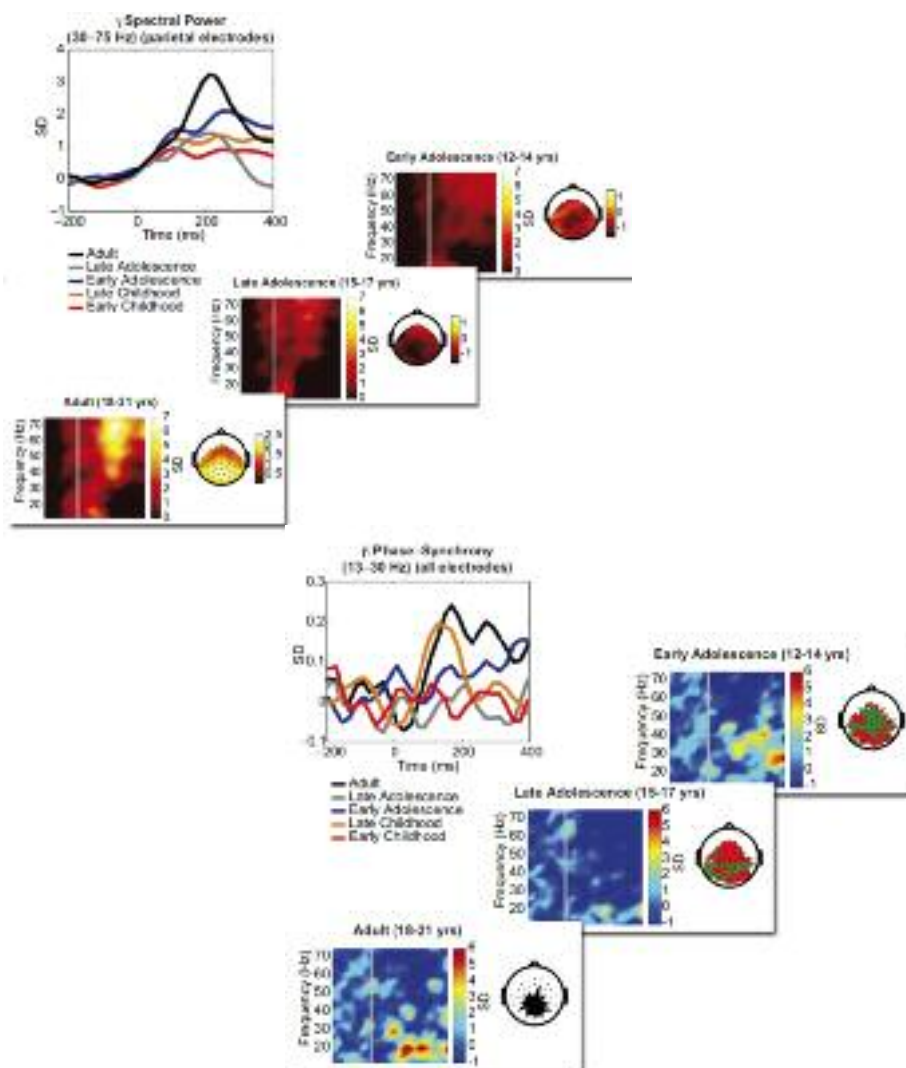


Figure 7. Activations in response to a known (the mother) and an unknown voice in two-month-old infants. The mother's voice elicits larger responses in the linguistic regions of the posterior temporal area, and also in the anterior prefrontal cortex and in the amygdala. The linguistic system is in tied connection with the attentional and emotional system (after Dehaene-Lambertz *et al.*, 2010).



**Figure 1. Development of task-related neural synchrony.** Left panel: Comparison of spectral power of oscillations in the 30-75 Hz range across all electrodes between 100-300 ms during the presentation of Mooney faces at different ages and time-frequency maps (x-axis: time; y-axis: normalised spectral power in standard deviations (SD)) for early adolescent, late adolescent and adult participants. The data show that gamma-oscillations increase significantly during the transition from adolescence to adulthood. Right panel: Comparison of phase-synchrony in the 13-30 Hz frequency range for all electrode pairs between 100-300 ms at different ages (top left panel) and phase synchrony charts of oscillations in the beta- and gamma-band averaged across all electrodes (x-axis: time; y-axis: normalised phase-synchrony in standard deviations (SD)) for early adolescent, late adolescent and adult participants. Note the drastic reduction in phase locking in the group of late adolescents [adapted from Uhlhaas *et al.*, 2009b].