The Signs of Death
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# HUMAN BRAIN, FUNCTIONAL ORGANISATION, ALTERED STATES OF CONSCIOUSNESS AND THE ASSESSMENT OF BRAIN DEATH*

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I appreciate very much the invitation to attend this interesting and important meeting but it was a somewhat challenging experience for me. Why, because 'signs of death' have not been a topic that my colleagues and I have specifically addressed in our research. At an evening meal preceding the conference those around the table including a delegation of bishops from Canada as well as conference participants, discussed the upcoming agenda. It was clear that most expected the topic would be restricted to brain death. As a result I became concerned that what I might have to offer would add little of substance to the deliberations of the meeting. Why was that so?

I am a neurologist and have spent most of my research career in the development and implementation of functional brain imaging techniques. These techniques emerged with the introduction of X-Ray computed tomography or CT in 1972, followed by positron emission tomography or PET in 1975. Magnetic resonance imaging or MRI had a somewhat more protracted germination period. The idea for MRI appeared in 1973 with the first anatomical images appearing in 1980 and the first functional images appearing in 1992. The latter work has become known as functional MRI or fMRI. These neuroimaging techniques have become a central element in cognitive neuroscience, a multidisciplinary research enterprise now being conducted world-wide to understand the relationship of brain and behaviour, especially in humans (for a more complete history of functional neuroimaging readers may wish to read Raichle, 2000).

It is critical to note, particularly in reference to this meeting that among these neuroimaging techniques PET is uniquely able to provide accurate, quantitative measurements of brain blood flow and metabolism. If cessa-

* The views expressed with absolute freedom in this paper should be understood as representing the views of the author and not necessarily those of the Pontifical Academy of Sciences. The views expressed in the discussion are those of the participants and not necessarily those of the Academy.

tion of blood flow and metabolism in the brain is a criterion for brain death then there is little doubt in my mind that PET could provide that information accurately and unequivocally.[1] However, I need not have journeyed to Rome in order to make such a declaration. Neuroscientists including most if not all of those present already know this.

But, as I thought about this a bit more deeply, it seemed to me that measurements of brain circulation and metabolism in an individual in whom the diagnosis of brain death was being considered could yield two possible outcomes. One, of course, would be that the circulation to the brain would be absent and no metabolic activity would be measured. This would certainly be consistent with the diagnosis of brain death. But suppose measurable circulation and metabolism were present. How should such information be interpreted? In considering this question I thought it useful to examine what functional neuroimaging has to offer. What follows is brief overview of functional brain imaging and how it might contribute to our assessment of brain death and altered states of consciousness. Many important scientific details are dealt with only briefly. Readers interested in a more detailed treatment may wish to consult (Raichle and Mintun, 2006).

It is of interest to note that an important scientific element of functional neuroimaging was discovered in Italy by the distinguished Italian physiologist Angelo Mosso. He was an enormously talented 19th century scientist who studied many different things among which was the relationship of brain blood flow to brain function. His book (*Uber den Kreislauf des Blutes im Menschlichen Gehirn*, Mosso, 1881), describes a gentleman by the name of Bertino who had a permanent defect in his skull (covered of course by the soft tissue of the scalp) from a neurosurgical intervention. What interested many prominent scientists in those days including Mosso were the brain's pulsations and what they might mean. Through the use clever devices of his own design Mosso was able to measure simultaneously the blood pressure in the forearm and the pulsations of the brain through the defect in Bertino's skull (one can liken the pulsations that Mosso was studying to those observed by every parent who notices the pulsations in the soft spot [fontanelle] of their newborn infant's skull). As Mosso was recording Bertino's brain pulsations the church bells rang. It was noon. Mosso noted immediately that the pulsations over the brain went up briefly prompting

[1] It is fair to say that future developments in MRI likely will make quantitative measurements of brain blood flow a reality with this technique as well.

him to ask the Bertino if he should you have said a prayer? Surprisingly, the brain pulsations again went up briefly. What Mosso did next was clearly the mark of a great scientist. He seized the opportunity to ask Bertino to multiply 8 by 12. When asked to do this Bertino's brain pulsations once again went up briefly and again moments later when he provided his answer to the question. Throughout there was no change in Bertino's blood pressure. Mosso concluded that Bertino's mental activity had changed blood flow to the brain. The validity of Mosso's conclusion has been reaffirmed literally thousands of times in the 125 years since it was presented and now resides at the heart of our understanding of the functional neuroimaging signals (Figure 1, see page 424).

While the measurement of blood flow itself was critical to functional neuroimaging with PET, it took an unexpected finding on the relationship of blood flow to brain oxygen consumption to pave the way for fMRI. As researchers began to explore in more depth the nature of the blood flow and metabolism changes occurring in the brain as function varied it was discovered that blood flow changed much more than did brain oxygen consumption (Fox and Raichle, 1986; Fox, Raichle *et al.*, 1988) (Figure 1, see page 424). This discovery was at variance with the standard view that blood flow varies to keep pace with the need for oxygen. This novel observation, as discussed in detail elsewhere (Raichle and Mintun, 2006), became the key to fMRI, a technique that has been responsible for the vast majority of functional brain images appearing in scientific journals and the lay press for the past 15 years. A full discussion of the physics behind fMRI is beyond the scope of this presentation. Suffice to say the MRI signal is quite sensitive to the amount of oxygen in circulating blood. As this changes regionally within the brain so does the intensity of the MRI signal. This has come to be known as the blood oxygen level dependent or BOLD signal of fMRI after the work of Ogawa and colleagues (Ogawa, Lee *et al.*, 1990).

In the past 15 years literally thousands of functional neuroimaging studies have been performed with fMRI. Among these many studies one stands out in terms of its relevance to the concerns of this conference. This report (Owen, Coleman *et al.*, 2006) presented fMRI studies of a patient in a vegetate state following severe head trauma. A vegetative state has come to be recognized in the neurological community as a condition in which a patient appears to be awake but exhibits no awareness of his or her environment. Surprisingly, despite fulfilling the criteria for the diagnosis of vegetative state, this patient exhibited changes in brain activity measured with fMRI that appeared remarkably similar to a group of normal control subjects when she was asked to imagine entering her house and walking from room to room.[2] While it remains to be determined whether these findings will generalize across patients currently receiving the diagnosis of vegetative state it is highly likely that such measurements will become increasingly important in the clinical management of these tragic patients. Future studies of this type will challenge scientists, theologians, ethicists and lay persons alike to understand more fully the relationship between brain function and behaviour and how this is being revealed by modern functional neuroimaging techniques.

With the exponentially increasing number of functional neuroimaging studies present in the scientific literature and often widely discussed in the lay press it is difficult to maintain a sense of perspective on just how much this information is telling us about how the brain works. Why is this so? It relates to the fact that the brain activity changes observed with functional neuroimaging represent very small changes in the overall activity of the brain (Raichle and Mintun, 2006). How do we know this?

Let us begin with a few simple facts about the human brain. It represents approximately 2% of the body's weight and yet it accounts for at least 20% of the body's energy consumption. This is 10 times the energy consumption predicted on the basis of its weight alone. Even more importantly between 60 and 80% of this energy consumption is related to the function of the brain. Yet, the changes reported in functional neuroimaging studies may be as little as 1% (see Raichle and Mintun, 2006 for a recent detailed summary of this literature).

Focusing in this manner on how the brain allocates its considerable energy resources for the functions it performs introduces a debate about the nature of brain function that has existed since the 18th century and possibly longer. This debate concerns two perspectives (Llinas, 2001).[3] One posits that the brain is primarily driven by external inputs; the other holds that the brain operates on its own, intrinsically, with sensory information interacting with rather than determining its operation. While today neither view is dominant, the former clearly has motivated the majority of research at all levels of neuroscience including almost all functional neuroimaging. This is not entirely surprising given the enormous success of experiments

[2] She also exhibited findings similar to normal controls when asked to imagine playing a game of tennis.

[3] Rodolfo Llinas provides a wonderful introduction to this interesting history in the first chapter of his book *I of the Vortex*.

measuring brain responses to controlled stimuli. From an energy, cost-based perspective, however, intrinsic activity may be far more significant than evoked activity in terms of overall brain function.

It is natural to inquire as to the nature of these costly intrinsic functions. In some ways it is similar to the questions surrounding 'dark energy' in astronomical terms (Raichle, 2006). The challenge we face is how to evaluate an aspect of brain functionality that is not directly related to the performance of an observable task. Fortunately, there are some important clues about how to proceed that will likely be relevant to discussions of altered states of consciousness in the future.

The first clue about the organization of the brain's intrinsic activity comes from the observation that when we engage in a task we observe not only task-relevant increases in brain activity but also highly organised activity decreases (Shulman, Fiez *et al.*, 1997; Raichle, MacLeod *et al.*, 2001) (Figure 2A, see page 425). The discovery of these activity decreases provided, we believe, the first glimpse of the nature of the brain's intrinsic activity and have increasingly suggested that this intrinsic activity exists in a highly organized manner at all times (Gusnard and Raichle, 2001; Raichle and Gusnard, 2005). This view has been reinforced by studies of what was initially viewed as 'noise' in the fMRI BOLD signal.

When conducting an fMRI functional neuroimaging study it has been customary to repeat studies many times in subjects in order to enhance signals of interest and suppress noise. This was standard operating procedure until it was discovered that the 'noise' in the fMRI BOLD signal (Figure 2B, see page 425) contained much valuable information on the organization of the brain's intrinsic activity. As demonstrated in Figure 2C (see page 425) large scale brain systems are revealed through patterns of spontaneous coherent activity emanating from the apparent 'noise' in the fMRI BOLD signal. While the images in Figure 2 (see page 425) depict one such system, and one likely important in the context of altered states of consciousness (Laureys, 2005), many other systems have been detected in the same manner (readers will find examples of interest in (Fox, Snyder *et al.*, 2005; Vincent, Snyder *et al.*, 2006) as well as reviews of this rapidly expanding literature).

What is important to note about the network of areas depicted in Figure 2 is that not only do these areas exhibit as a group activity decreases during the performance of a variety of tasks (Figure 2A) but at rest the areas within this network exhibit continuous, activity fluctuations (Figure 2B) that are coherent within the network (Figure 2C). This is also true of networks that exhibit task-relevant increases in activity (for example see (Fox, Corbetta *et al.*, 2006; Vincent, Snyder *et al.*, 2006). They too can be found to exhibit continuous activity fluctuations that are coherent within the network. In an interesting way this ongoing, dynamic organization of the brain, exhibited here as spontaneous fluctuations of the fMRI BOLD signal, appears to anticipate relationships among areas used in the performance of a wide range of tasks.

What is this intrinsic activity? One possibility is that it simply represents unconstrained, spontaneous cognition – our daydreams or, more technically, stimulus-independent thoughts. But our daydreams are highly unlikely to account for more than that elicited by responding to controlled stimuli, which accounts for a very small fraction of total brain activity (Raichle and Mintun, 2006).

Another possibility is that the brain's enormous intrinsic functional activity facilitates responses to stimuli. Neurons continuously receive both excitatory and inhibitory inputs. The 'balance' of these stimuli determines the responsiveness (or gain) of neurons to correlated inputs and, in so doing, potentially sculpts communication pathways in the brain (Haider, Duque *et al.*, 2006). Balance also manifests at a large systems level. For example, neurologists know that strokes damaging cortical centers controlling eye movements lead to deviation of the eyes toward the side of the lesion implying the pre-existing presence of 'balance'. It may be that in the normal brain, a balance of opposing forces enhances the precision of a wide range of processes. Thus, 'balance' might be viewed as a necessary enabling, but costly, element of brain function.

A more expanded view is that intrinsic activity instantiates the maintenance of information for interpreting, responding to and even predicting environmental demands. In this regard, a useful conceptual framework from theoretical neuroscience posits that the brain operates as a Bayesian inference engine designed to generate predictions about the future (Olshausen, 2003). Beginning with a set of 'advance' predictions at birth, the brain is then sculpted by worldly experience to represent intrinsically a 'best guess' ('priors' in Bayesian parlance) about the environment and, in the case of humans at least, to make predictions about the future (Ingvar, 1985). William James, in his *Principles of Psychology* (1890) captured this perspective in another way when he said: 'Enough has now been said to prove the general law of perception, which is this, that *whilst part of what we perceive comes through our senses from he object before us, another part* (and it may be the larger part) *always comes … out of our* *own head*'. Finally, it has long been thought that the ability to reflect on the past or contemplate the future has facilitated the development of unique human attributes such as imagination and creativity (Hawkins and Blakeslee, 2004; Gilbert, 2006).

How might such information be useful in the evaluation of individuals with altered states of consciousness? Following a long tradition in neurology, clinical assessments of prognosis and decisions about treatment continue to be made on the basis of clinical examinations by competent physicians. However, that assessment has been increasingly augmented by sophisticated tests of every conceivable sort the most sophisticated being those that assess directly the integrity and function of the brain. In this category functional neuroimaging is rapidly taking its place. The recent report by Owens and colleagues (Owen, Coleman *et al.*, 2006) mentioned earlier is the latest and certainly the most provocative to date. Other studies of this sort are sure to follow and fuel discussions about the relationship of brain function to behaviour in patients with altered states of consciousness.

In addition to this more traditional use of functional neuroimaging (i.e., examining the brain's response to momentary demands of the environment); e.g., (Owen, Coleman *et al.*, 2006) there is now before us the prospect of obtaining an even deeper understanding of the functional organization of the brain based on its intrinsic activity which we presently posit to underlie our ability to maintain information for interpreting, responding to, and even predicting environmental demands. Because this type of information can be obtained with functional neuroimaging without the need for any response on the part of the subject it is particularly suitable for the evaluation of patients with altered states of consciousness. However, our use of such information must be based on a thorough understanding of the basic neurobiology as well as the prognostic value of such information. Coming to this understanding will be one of the great challenges for researchers and clinicians in the coming years.

As we seek an ever deeper understanding of brain function and its relationship to behaviour it is of paramount importance to keep in mind that the brain is not just another organ with *a* function. Rather, it is a modular *system* of immense complexity which must function as an integrated whole for there to emerge the behaviours we associate with sentient human beings. Critical to our assessment of prognosis in cases with severe brain damage will be information on the integrity of brain systems as a functioning whole. Information from functional neuroimaging will likely be of considerable utility in this regard.

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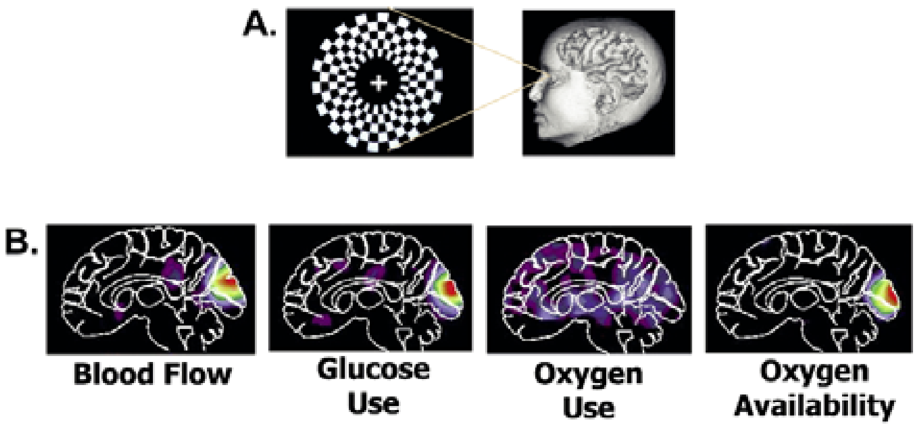


Figure 1. Stimulation of the human visual cortex with a reversing annular checkerboard when compared to a simple fixation crosshair (A) produces dramatic increases in blood flow and glucose use in the visual cortex that are unaccompanied by similar increases in oxygen use (B). The result is an increase in the local oxygen availability (B, right) because the increased supply of oxygen by flowing blood exceeds the increased local demand for oxygen. Functional neuroimaging with positron emission tomography (PET) has largely focused on the changes in blood flow (B, left) whereas functional magnetic resonance imaging (fMRI) has taken advantage of its sensitivity to the changes in oxygen availability (B, right). These data were adapted from our earlier published work (Fox, Raichle *et al.* 1988; Raichle and Mintun 2006).

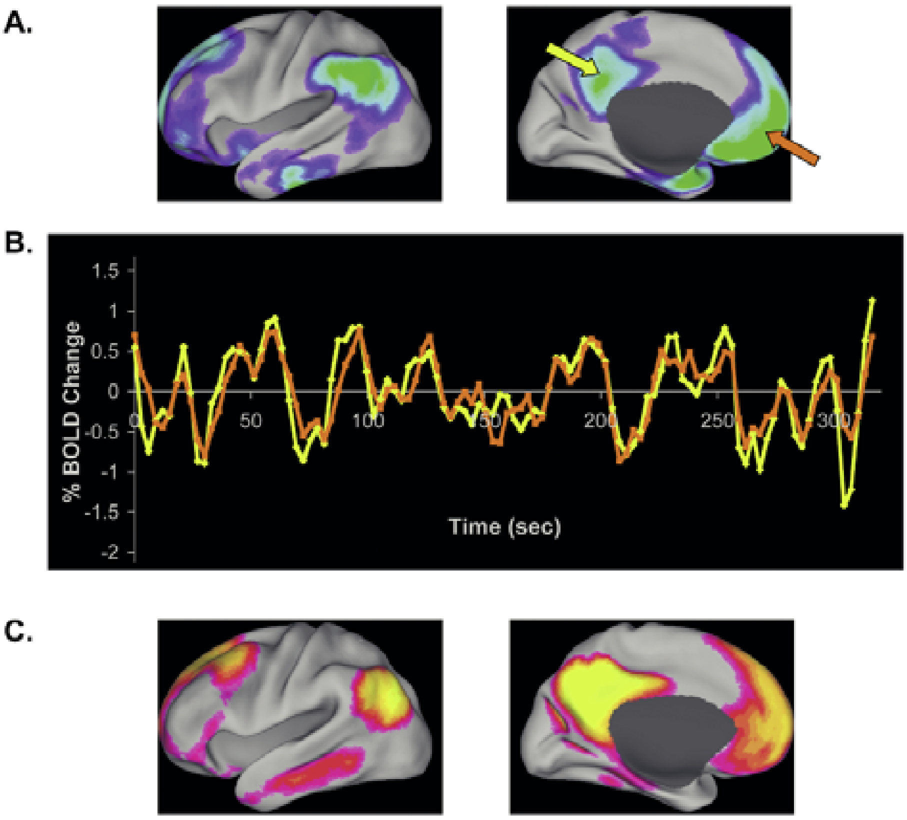


Figure 2. Performance of a wide variety of tasks has called attention to a group of brain areas (A) that decrease their activity during task performance in contrast to those areas in the brain that increase their activity as expected. What has been striking is the consistency with which these particular areas (A) behave in this manner. If one records the spontaneous fMRI BOLD signal activity in these areas in the resting state (arrows, A) what emerges is a remarkable similarity in the behaviour of the signals between areas (B). Using these fluctuations to analyze the network as a whole (Fox, Snyder *et al.* 2005; Vincent, Snyder *et al.* 2006) reveals a level of functional organization (C) that parallels that seen in the task related activity decreases. These data provide a dramatic demonstration of the ongoing organization of the human brain likely provides a critical context for all human behaviours. These data were adapted from our earlier published work (Shulman, Fiez *et al.* 1997; Gusnard and Raichle 2001; Raichle, MacLeod *et al*. 2001; Fox, Snyder *et al*. 2005).