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# Neurophysiology of functional imaging

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# Abstract

The successes of PET and fMRI in non-invasively localizing sensory functions had encouraged efforts to transform the subjective concepts of cognitive psychology into objective physical measures. The assumption was that mental functions could be decomposed into non-overlapping, contextindependent modules that are operated on by separable areas of a computer-like brain. The modularity concept and the computer theory of brain both have been challenged by neurophysiological measures of baseline and incremental functional energetics, and by the many reports of delocalized and negative BOLD signals. Combining fMRI and electrophysiological measures of brain function we have made connections between these neurophysiological results and observable properties of mental life (i.e., awareness). We illustrate this approach with a sensory stimulation experiment; the *degree* of localization found in BOLD signal was related to the energetic status of the brain which, when manipulated by anesthetics, affected the degree of awareness. The influence of brain energy upon functional imaging maps is changing the interpretations of neuroimaging experiments, from psychological concepts generating computer-like responses to empirical responses dominated by the high brain activity at rest. In our view "baseline" is an operational term, an adjective that defines a property of a state of the system before it is perturbed by a stimulus. Given the dependence of observable psychological properties upon the "baseline" energy, we believe that it is unnecessarily limiting to define a particular state as *the* baseline.

# Keywords

awake; conciousness; oxygen consumption; neuroimaging; neurotransmitter

# Introduction

Non-invasive brain imaging methods (i.e., PET and fMRI) have had tremendous success in localizing sensory functions. Using the simple differencing method, primary motor and sensory

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cortices can be reliably mapped with results matching those previously only found by invasive methods (Hubel and Wiesel, 1959; Wandell et al., 2007). For more complex mental functions, such as language, fMRI can show hemispheric dominance so reliably that it is now routinely used to guide surgical decisions in patients with refractory epilepsy (Medina et al., 2007). These successes have encouraged scientists to use neuroimaging to address psychological questions in an effort to transform the contingent, subjective concepts of psychology and everyday life into communicable understandings with the objectivity of physical science.

# Cognitive neuroimaging

In the earliest years of functional imaging, its main focus was on Neurophysiology so as to determine the regulation of cerebral metabolism and blood flow during brain function. The first SPECT and PET maps of brain activity in response to concepts of Cognitive Psychology were so beautiful that they raised hopes for this kind of objective psychology (Lassen et al., 1978; Reivich et al., 1983). As PET and fMRI developed the ability to map responses to mental stimuli, the techniques became more widely used for experiments investigating psychological processes. The original questions investigated in the emerging field of Cognitive Neuroimaging were derived from Cognitive Psychology (Neisser, 1967; Fodor, 1980, 2000) whose key assumption is that mental functions are composed of innate modules that have identifiable, specific cognitive content which are processed by the computer-like brain that operates on them to create the functions of Mind. In the early years of Cognitive Psychology the couplings of modules to brain activity had been measured by timing the subject's task performance as additional modular components were added to the task (Donders, 1868). However soon after fMRI and PET showed the ability to image brain responses, they became the preferred methods for locating brain regions in support of mental models. The components of psychological function, assumed to be distinct non-overlapping cognitive components (or modules), were further assumed by Cognitive Neuroscience to activate specific, reproducible brain regions. A particular cognitive module was assumed to always activate the same brain region whether presented in a verbal, visual, or mechanical context. The hierarchical sensory inputs, known to be separable into distinct responses (e.g., to color or motion, etc) and processed as separable and distinct regions, were the models for cognitive modules.

The tight link between brain regions and cognitive modules has been formalized as the "general linear model" (GLM) by the tensor relationships in Statistical Parameter Mapping (SPM) (Frackowiak et al., 2004). SPM is widely used for data analysis to transform the observed brain voxels into a linear set of cognitive modules. The requirements for modularity are very demanding, but if results describe a brain that acts rationally and objectively like a Turing computer in response to algorithms written by cognitive concepts, no subjective judgments would be needed (with GLM). In this event measured brain activity would provide objective representation of concept. The mutual gains to be found for both Cognitive Psychology and Neuroimaging are evident. The Cognitive modules of mental activity were incorporated into PET and fMRI experiments whose brain responses were expected to be focal and reproducible. While the analogy with the sensory pathways has guided expectations of cognitive functional imaging and whereas GLM has been built into data interpretation, still there has not been any definition of the degree of brain localization that would serve as a criterion for accepting or disproving this model. Neuroimaging provided Cognitive Psychology with goals of objective scientific understanding of psychological concepts that would thereby overcome the uncertain subjectivities of psychology. Cognitive Psychology proposed to resolve questions unanswered in previous psychologies by the assumption that cognitive concepts were modular and identifiable by localized brain responses, although the caveat about localization remains unresolved.

It would be difficult to overemphasize the revolutionary nature of Cognitive Psychology. The empirical tradition in neuroscience, physiology, and biochemistry is to derive understanding of higher order qualities of mental life from physical observations and mechanisms. The claims of Cognitive Psychology reversed this order by assuming that innate concepts combine to produce complex mental functions and behavior. However in the assumption that psychological concepts could be identified, were independent of context and that the location of brain operations performing the function could be inferred from the images of these concepts, Cognitive Neuroimaging was restoring the methodology of Deductive Science. The definition of the assumed cognitive concepts was not up for testing, only their cerebral localization.

### The modularity concept

The philosophical problem of defining concepts of mental function was a primary concern of Ludwig Wittgenstein, who showed that only mathematical or logical terms can be unequivocally defined, whereas even simple terms like "chair" defy explanations that would identify all objects we regard as chairs and exclude all that we do not (Wittgenstein, 1953). Once we recognize that common objects cannot be defined with the rigor of logic, we realize how revolutionary it would be if words like "working memory" or "attention" could be defined logically and objectively. While the limits of everyday language are obvious, the informative images generated by PET and fMRI suggested that the brain could possibly overcome these limits and provide explicit physical regions representing strict verbal definitions. The empirical question posed from this perspective for functional imaging became where these preconceived concepts were localized on the assumption that it was possible to find unique and specific brain responses to mental concepts regardless of their context. Once identified, the brain responses would validate the existence of the proposed concepts.

The most important requirement of cognitive modules is that they must be independent of context. This principle came under pressure when it became apparent that the concepts of Cognitive Psychology, such as working memory or attention, provoked brain activations that invariably depend on context. Meta-analyses have shown that no matter how working memory tasks were broken down into conceptual components such as storage, rehearsal, or recall of information, still no mental components could be identified that consistently stimulated the same brain region independent of context (Wager and Smith, 2003; Jonides et al., 2008). Similarly other meta-analyses showed the same lack of a unique localization for other concepts of Cognitive Psychology, such as different forms of memory or attention (Cabeza and Nyberg, 2000). Hence it became evident, although the full strength of this conclusion is still not widely acknowledged, that PET and fMRI experiments gave valuable experimental information about the brain, but did not support the assumptions of modular concepts being defined objectively by localized responses of a computer-like brain. Jerry Fodor, in abandoning Cognitive Psychology (Fodor, 2000) showed that "massive modularity" is required by the theory but this term has not been translated into specific brain responses. In the absence of a disprovable theory as to how the brain operates on modules, could the imaging results disprove the model? Accordingly the expectations of objective, brain responses to mental modules have been neither fulfilled nor rigorously disproven and the field remains empirical.

#### **Delocalized activity**

Besides the difficulties besetting the modularity concept, an additional problem arose from a wide range of fMRI experiments. It became apparent that cortical activations in response to cognitive activity were widespread, being found in many regions, instead of being reproducibly localized as were the primary responses to sensory inputs. This dealt a blow to the hope that even though cognitive concepts might not strictly define modules of brain functions; still brain localization would make concepts more transparent. Regional brain activations might not be independent of context, but they still might be somewhat localized around concepts. In pursuit

of these hopes of identifying brain regions processing conceptual modules, Cognitive Neuroimaging has always been inclined towards a localizationalist view of brain function. In establishing the field, Fodor (1983) wrote that Franz Joseph Gall (1758–1828) the advocate of phrenology "appears to have had an unfairly rotten press" (in pp. 14). Without, at that time, requiring a strict localization of concept, Fodor did represent the yearning for localized responses, although later his requirement of "massive modularity" brought brain localization to a central position. The localization of specific brain functions seemed the logical way of viewing the organization of the brain for many neuroimagers. In this hope the concept might remain vague but the general location would be clear.

The question to what extent brain function is localized remains unsettled after generations of neuroscientific study. Delocalizationalist views have been brought forward, for instance, by Karl Lashley (1890–1958), who showed with careful dissections that the efficiency of a complex mental function is proportional to the extent of a brain injury within a larger area (Lashley, 1951). The famous Russian neuroscientist Alexander Luria (1902–1977) described how a given area of the brain can be involved in relatively few or many different behaviors depending on brain injury and training (Luria, 1966). The contemporary neurophysiologist Roy John has pointed out that more delocalized concepts of brain function, despite substantial empirical scientific support, have faded from the front page of neuroscience and have been replaced by the localizing powers of Cognitive Neuroimaging (John, 2005).

The absence of strong support for cognitive modularity and a very localized phrenology are generally, but not universally, accepted. However in their place, and usually not distinguished from the original revolutionary hopes of clarification, experimental results are being interpreted in terms of flexible definitions of both cognitive concepts and the degree of localization. The way in which a "localized" brain region is defined so as to support conceptual expectations by expanding the definition of "localized", was illustrated by early PET (Frith et al., 1991) and fMRI (Phelps et al., 1996; Hyder et al., 1997) embodying "willed action". During verbal or sensorimotor stimulations, the experiments contrasted novel and routine tasks. The novel verbal task was verbal fluency, to generate words beginning with a specific letter, while the control task was to repeat a word. Analogously, the novel sensorimotor task was to move either of two fingers when one was touched, while the routine task required that the finger touched be moved. The differences between the tasks were taken to reflect internal willed action vs. external response determination. The difference maps between the novel and routine for both modalities found activations in the prefrontal cortex and provided detailed coordinates for the centers of activation. In the verbal task, the differences located the activation in the left prefrontal cortex and the anterior cingulate, whereas the sensorimotor coordinates were bilaterally located in the prefrontal cortex and in the anterior cingulate. Frith et al. (1991) described a common volume of activation in the dorsolateral prefrontal cortex (DLPFC) which they assigned to the common "willed action" component in the different tasks. They concluded "Thus an association between response generation (willed action) and activity in DLPFC has been consistently observed in different PET studies."

However, while the later fMRI data confirmed that both verbal and motor difference images showed activation in the DLPFC, they showed unambiguously that the two modalities activate different regions of the DLPFC. The fMRI motor and verbal localizations are separated by 21 millimeters – a clear separation of responses to the two modalities. Furthermore, a careful examination of the PET results showed an identical separation. In both experiments the strong left hemisphere response to the verbal tasks contrasted with the bilateral response to motor tasks, which clearly distinguished the two modalities! So the fMRI and PET results were identical but the two reports came to different conclusions about the two kinds of tasks.

The PET authors, with a theoretical predisposition to accept modularity of both the psychological concept and of the brain response, concluded that broadly defined "DLPFC" was activated by both modalities. The later fMRI conclusion, however, distinguished between the localization of verbal and motor activations, although both are in the DLPFC. This use of

the localization of verbal and motor activations, although both are in the DLPFC. This use of an alternative description of a brain region that includes both localizations, i.e. DLPFC, instead of using the different locations actually measured, is a common procedure in functional imaging studies which has misleading consequences. First, by lumping specific activations into the large volume of DLPFC it suggested that the concept of "willed action" had been identified independent of the context, i.e. verbal or sensory, in which it had been incorporated. Second it illustrated how the expectations of cognitive psychology were determining how brain regions should be identified. Instead of the location of activations being defined as measured, their definition was enlarged as necessary so as to fit the psychological theory. The above is not an isolated example, but rather is a common description of present interpretations of functional imaging results, in which large brain areas (e.g., the prefrontal cortex or the amygdyla) are assigned to the subjective concepts (of executive function or emotion respectively). In this way brain voxels are another approximate description of mental activities, similar to words, but not with the rigor offered by the measurement.

#### **Negative BOLD**

Cognitive Neuroscience in addition to assuming psychological modules had also postulated that the modules were operated on by a computer-like brain although the details of such processing had no consensus. The assumption of a computer-like brain was confounded by results showing that imaging signals observed in certain brain regions were rather consistently negative during stimulation (Shulman et al., 1997). By the time that negative BOLD signals became noteworthy, the role of cerebral energetics and metabolism in brain function had been well developed (Rothman et al., 1999). The coalescence of magnetic resonance studies with electrophysiology had been advancing knowledge in these areas rapidly. Combined <sup>13</sup>C MRS, electrophysiology, and fMRI results (as discussed in the next section) provided an easy resolution to the paradoxical finding of negative BOLD. These studies showed that the incremental energy consumption in a typical cognitive task, obtained from the calibrated fMRI signal (Ogawa et al., 1993), was at most a few percent of the total energy consumption, obtained from interpretation of <sup>13</sup>C MRS data (Shulman and Rothman, 1998). Furthermore both incremental and total energies were used to support functional processes triggered by neuronal firing such as ion pumping and glutamate neurotransmitter release. The energy supported neuronal activity of the baseline state (in the absence of external stimulation) and of the increments (during stimulation), while the baseline energies were much larger (Shulman et al., 1999). High energy consumption in the resting brain had been long known, but that usage had been considered to be distinct from the functional usage by neuronal firing (Creutzfeldt, 1975). However once <sup>13</sup>C MRS results showed that a majority of the brain energy supported activities associated with neuronal firing (Sibson et al., 1998), the high baseline energy could no longer be regarded as non-functional. Hence the underlying, but rarely expressed assumption of the computer theory of mind (Fodor, 2000), which required that the brain would be active only in response to a sensory or cognitive input, and in the absence of the need to process information would be dormant, was contradicted by the decreases in energy from the baseline level, reported by negative BOLD signals. These had implied a decrease in energy below zero, a description that made no sense (Shulman et al., 2002). Recent studies have investigated the neurophysiological basis of sustained negative BOLD signals (Shulman et al., 2007). While some studies have interpreted the negative BOLD signal to have a large hemodynamic component (Harel et al., 2002; Devor et al., 2005), others show there is a significant neuronal contribution to the negative BOLD signal (Shmuel et al., 2002; 2006).

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# fMRI and energy based neuroscience

The combination of fMRI, <sup>13</sup>C MRS, and electrophysiology has allowed the energy consumption of the many neurons in an fMRI voxel to be correlated with the electrical activity of ensembles of individual neurons in the same volume. Results from electrophysiological, fMRI, and <sup>13</sup>C MRS experiments are expressed in terms of the fundamental physical parameter of energy consumption: the cerebral metabolic rate of oxygen consumption (CMR<sub>O2</sub>) since essentially all brain energy comes from the oxidation of glucose (Siesjo, 1978).

The discovery that enabled this correlation across modalities and levels of observation was that the large majority of brain energy consumption supports events associated with neuronal signaling (Sibson et al., 1998). This association was established by <sup>13</sup>C MRS measurements of the flux from glucose to the Krebs cycle intermediates monitored by glutamate and then, in the same experiment, from glutamate to glutamine, which measured the neurotransmitter release and cycling. Since the normal mammalian brain obtains this energy almost completely from the oxidation of glucose, an adequate measure of energy consumption is obtained from measurements of CMR<sub>O2</sub> (Shulman et al., 2004; Raichle and Mintun, 2006). These experiments showed that a large majority of CMR<sub>O2</sub> is dedicated to the work (ion pumping, neurotransmitter cycling) associated with neuronal activity. The energetic consensus was accompanied by efforts to extract the incremental energetic component from the BOLD signal by calibrating fMRI (Hoge and Pike, 2001; Kida and Hyder, 2006) or more directly by <sup>15</sup>O PET or <sup>17</sup>O MRS (Gjedde et al., 2002; Zhu et al., 2002). The calibrated value of CMR<sub>O2</sub> from calibrated fMRI can be reinforced by independent measures of CMR<sub>O2</sub> (Hyder et al., 2001), as can be obtained from <sup>15</sup>O PET, <sup>13</sup>C MRS, or <sup>17</sup>O MRS (Raichle, 1988; Hyder et al., 2006; Zhu et al., 2002).

The second important question was whether task-induced changes in the energy consumption (i.e.,  $\Delta CMR_{O2}$ ) obtained by calibrated fMRI were reflected in the collective action of neuronal ensembles within an MRI voxel. The convergence between these apparently different levels of observation relies on thermodynamics – the fundamental relationship between work done and energy expended (Hyder et al., 2002). The microscopic behavior of the neuronal ensemble can be described by a histogram of their neuronal firing rates (Smith et al., 2002) from which the work done by the population can be calculated. By multiplying the number of neurons firing at any frequency by their respective firing rates, the relative energy consumption or  $CMR_{O2}$  for the neuronal ensemble can be related to the work by

$$CMR_{o2} = G\sum_{i} N_{i} v_{i}$$
<sup>[1]</sup>

where *i* spans the entire range of frequencies in the histogram,  $N_i$  is the number of cells firing at the frequency  $v_i$  in the histogram, and *G* is a scaling factor that accounts for neuronal density and metabolic rate per neuron (Attwell and Laughlin, 2001). This calculation assumes that energy expended by regular spiking neurons (Connors and Gutnick, 1990), and the coupled work including the changes in membrane potential before, during, and after firing in conjunction with neurotransmitter cycling and ion pumping, are linear with the firing rate of the neuronal ensemble (Siesjo, 1978; Attwell and Laughlin, 2001) If the *same* neuronal population is measured across different states (i.e.,  $N_i$  does not change in eq. [1]), then relative changes in CMR<sub>O2</sub> (where G is constant) can be related to shifts in firing rates within the neuronal ensemble. In rat brain, fMRI has measured changes in CMR<sub>O2</sub> between states differently activated (either by changing the anesthesia or introducing sensory stimulation) and found agreement with relative changes in CMR<sub>O2</sub> estimated by eq. [1] using

electrophysiological measurements of neuronal firing rates (Smith et al., 2002; Kida et al. 2006; Maandag et al., 2007).

In summary, this energetic consensus states that the large majority of energy consumption of the brain is produced by the oxidation of glucose and devoted to processes involved in neurotransmission. This principle combined with the excellent correlation between neuronal firing rates and their energy consumption, relates the activity of voxels of neuronal tissue, measured by calibrated fMRI, to firing rates of representative ensembles of neurons, by expressing both as changes in CMR<sub>O2</sub>.

# Effects of baseline energy on fMRI

To explore the neuronal foundations of baseline and incremental energetics, we conducted electrophysiological and fMRI studies in rats at two anesthetic states, characterized by very different baseline energies (Maandag et al., 2007); the lower energy state ( $\alpha$ -chloralose) was 40–60% lesser than the higher energy state (halothane). Forepaw stimulation was administered in both states to excite the contralateral primary somatosensory cortex (S1). There were major differences between the two states in their BOLD activations and in the firing rates of a representative neuronal ensemble. At high baseline there were weak activations in anterior brain regions (Fig. 1A), which included primary and secondary somatosensory cortices (S1, S2) in the contralateral side. In posterior areas, there were activations in secondary areas of visual and auditory cortices and small activations were mainly confined to the contralateral S1 (Fig. 1B) with insignificant activities elsewhere.

The neuronal firing rates were represented in histograms to depict each state. Neuronal histograms in the two states showed that the population can be divided into sub-groups of slow and rapid signaling neurons (i.e., SSN and RSN, respectively), where a greater SSN sub-population was observed in the lower (Fig. 2A) and a greater RSN sub-population in the higher energy baseline state (Fig. 2B). Halothane had nearly equal sub-populations in SSN and RSN, whereas  $\alpha$ -chloralose was heavily weighted towards SSN. The most conspicuous difference between the two anesthetized states of different energy was the dominance of RSN activity or energy under halothane in contrast to  $\alpha$ -chloralose. At high baseline energy a majority (80%) of total energy is used for RSN activity whereas the remainder (~20%) is used for SSN activity (i.e., RSN/SSN ratio is high). However at low baseline, the SSN activity accounts for a little more than half (60–70%) of total energy consumption and the remaining (30–40%) is used for RSN activity (i.e., RSN/SSN ratio is low).

The novelty of these results is that the SSN and RSN sub-groups correlated with the dissimilar delocalization of BOLD activations in the two states (Maandag et al., 2007). At high baseline energy, with greater RSN activity, widespread activations were observed throughout anterior and posterior brain regions, mainly of the contralateral hemisphere. However, at low baseline energy strong activations were mainly confined to the contralateral S1 with insignificant activity elsewhere. These recent experiments have related the results of fMRI measurements, reflecting the energy consumption of a voxel with sub-millimeter dimensions to the summed energy consumption of the microscopic neurons. Furthermore this relationship is not merely a description of a coupling between two parameters, nor is it a marker that from its perspective indicates a relationship, but rather, it is a measure of the equality of energy generated and consumed between two parameters. The agreement between the measured baseline and incremental values of  $CMR_{O2}$  (from <sup>13</sup>C MRS and BOLD) and the calculated  $CMR_{O2}$  (from neuronal histograms) we find in these studies established a thermodynamic basis of the energy activity coupling.

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observed under light anesthesia and in the awake state (MacDonald and Barth, 1995) but rarely detected when animals are under deep anesthesia (Franowicz and Barth, 1995). Conversely, low frequency (including  $\alpha$  band) activity is dominant under deep anesthesia (Jugovac et al., 2006). The  $\gamma$  band activity tends to be synchronized between the homologous sensorimotor regions of both hemispheres (Jones and Barth, 1997) and can be modified by variations in global activity (Engel et al., 1991). Our hypothesis is that the RSN activity supports intracortical signaling and synchronization, in accord with previous assignments of similar frequencies observed electrically as the  $\gamma$  band-type signaling in EEG (Ebner and Armstrong-James, 1990). We hypothesize that the RSN activity mediates communication between the activated sensory unit and distal cortical areas as shown by the correlation between high RSN activity in the activated somatosensory cortex and widespread BOLD activations. In other words, these data support the idea that the degree to which fMRI activity is delocalized is baseline-dependent and increases with the baseline energetic level. The electrophysiological correlate of this spread of activity noted by the delocalized BOLD signals is the amount of high frequency activity (RSN or  $\gamma$  band).

We propose a model that relates energy in the RSN sub-population to the degree of localization of BOLD signals. At states of high energy baseline, a large fraction of the energy supports the dominant RSN activity responsible for intracortical signaling across different regions. Ubiquitous intracortical interactions lead to widespread activations in other regions. At states with low energy baseline, the RSN activity consumes a much smaller fraction of the energy resulting in reduced intracortical signaling. Upon stimulation the attenuated intracortical signaling does not spread activations into other regions and thus most of the activity remains within the primary area.

This model does not make *a priori* assumptions that relate the activities in the resting state to detailed psychological activities. Instead it relates the observed SSN and RSN sub-populations and their associated energetics to the observed BOLD signal localization or lack thereof. It is important to note that these experiments are not only providing relations between macroscopic properties of brain activity and microscopic neuronal activity, but they also have begun to separate neuronal activity into sub-populations on the basis of firing rates and associated functions, which has implications for understanding the relationships between local processing within sensory units and global activity patterns of neural ensembles (Buzsaki, 2006). While our energy relationship provides a theoretical connection between the microscopic (electrophysiology) and the macroscopic (neuroimaging), identification of two subpopulations allow us to move slightly, but with some degree of reassurance, from the total neuronal population towards the important but distant complexity of heterogeneous activities of individual neurons (Adrian, 1941).

#### Empirical studies of brain function

In our opinion, the dynamic interplay between experimental results and scientific hypotheses described above reflects the excitement of science, the movement from one issue to the next that is raised in the course of study. In contrast to the assumptions of Cognitive Psychology that there were concepts of Mind in need of definition, we propose that mental activity can be studied by the reliable techniques of contemporary neurophysiology, certainly including fMRI (or PET), without making revolutionary a priori assumptions about its nature. Our methodology derives from the understanding of physics that Niels Bohr found when confronted with the uncertainty principle that destroyed hopes of causality at the quantum level. Bohr had to accept that causal explanations, the crown jewels of physics, were to be impossible at the levels revealed by quantum mechanics. His resolution was stated poignantly that "it is wrong to think that the task of physics is to find out how nature *is*. Physics concerns what we can

*say* about nature" (Petersen, 1963). While there are many, led by Albert Einstein, who rejected Bohr's view, there are similarities, we contend offered by this view between physics and the study of Mind. In any discussion of the nature of Mind it must be granted that now, particularly with the hopes of Cognitive Neuroscience dashed, objective scientific attempts to understand the popular preconceptions of Mind must be left for the distant future. Instead of starting with psychological conceptualizations of Mind in the hope they can be explained by brain activity, the energetic results have taught us to look for connections between neurophysiological findings and empirical, mental properties defined by observations. The influence of anesthetics and neuronal energetics upon the delocalization of brain activation and states of awareness that change with anesthetics (Franks, 2008) is a connection of this sort, one that is traced in these experiments.

In following these directions we are in accord with the methodology used in classical neuroscience. Textbooks of Neuroscience are devoted to the development and functioning of biochemical, physiological, and electrical mechanisms of brain properties which are sometimes connected with loosely defined state of Mind. Before the recent age of functional imaging, neuroscientific knowledge was derived from studies of lesions, anatomy, neurophysiology and neurochemistry. From these investigations, neuroscience provided some understanding of the working of the brain, and provided tangible insights into physiological mechanisms involved in complex mental states, like emotions. One example can illustrate the kinds of progress towards these modest goals made by "normal neuroscience". For example, estrogen induced up-regulation of oxytocin leads to anxiety reduction, observations of maternal behavior, social recognition and bonding. Although that up-regulation does not define anxiety or bonding, neither in a subjective nor in a definitive objective sense, still the chemical reaction provides a connection between biophysical processes and an emotional state. Biophysical studies of such connections provide hypotheses that relate knowledge from the molecular basis to physiology and emotions. Analogously, functional imaging, like <sup>13</sup>C MRS and electrical measurements are promising modern techniques of neurophysiology that can be used in the normal scientific study of the properties of brain.

# Shifting paradigm of psychological studies

The physiological studies of cerebral energetics combined with fMRI are profoundly changing the psychological interpretation of Cognitive Neuroimaging. Prominent early proponents of Cognitive Neuroscience, facing the growing experimental failings of modularity and cerebral localization, have been developing alternate descriptions of brain function that utilize neurophysiological results (Raichle and Mintun, 2006). In the past five years it would not be an exaggeration to say that the foundational conceptualization underlying brain imaging has undergone a revolutionary change eliminating the contributions of Cognitive Psychology and returning psychology to its empirical tradition. Since this change has been effected, in no small part, by the same functional imaging methods that were deployed in the service of the once dominant psychology, the fundamental nature of these changes is not immediately evident and must be emphasized. Basically, the view of brain activity has gone from stimuli inducing objective computer-like responses, to a view wherein the high brain activity, responds to perturbations from the internal and external worlds of the subject.

Emphasizing this paradigm shift is urgently needed, because research is being extended into ever more elaborate modules of mind, to the point where prominent scientific journals publish the cerebral localizations of Democratic and Republican political tendencies (Kaplan et al., 2007). The term "phrenological fMRI" has mockingly been used in reference to studies like this. How accurate this term is, becomes clear when one recalls the results of Fowler and Fowler who in 1836 localized and measured the degree of "republicanism" in the brain (Fowler and Fowler, 1836). These extensions of the differencing fMRI experiments to politics or other

fields, i.e., economics or criminology (Patel et al., 2007), claiming support from Cognitive Neuroimaging, are not justified, because modularity of brain and mind has not been supported by extensive scientific testing.

It is fitting but ironic that Marc Raichle, who played a prominent role in introducing Cognitive Psychology to fMRI experiments (Posner and Raichle, 1998) should now be actively disavowing those claims of a modular psychology as the neurophysiological results accumulate. Based upon the prevalence of negative BOLD signals and in view of the high baseline energy demonstrated by PET and <sup>13</sup>C MRS experiments, Gusnard and Raichle (2001) accepted that a high functional activity existed in the absence of explicit stimulation. They expanded on the early findings that the oxygen extraction fraction (OEF), which determined the fraction of oxygen extracted in a region for producing oxidative ATP, had been shown by PET to be quite constant across the cortex in the eyes closed resting state. Presumably this constancy reflected a structured anatomical coupling of local cerebral metabolism  $(CMR_{O2})$  and blood flow (CBF). Extending the meaning of the uniformity of the OEF at rest, Gusnard and Raichle (2001) defined "a baseline level of local neuronal activity". Because the BOLD signal is proportional to the difference between  $\Delta CBF$  and  $\Delta CMR_{O2}$ , an increase in OEF will reflect a decreased BOLD signal (and a decreased metabolism), while conversely a positive BOLD signal reflects a decreased OEF (and an increased metabolism). The connection between BOLD increases and increased metabolism has been supported by calibrated BOLD measurements (Davis et al., 1998; Hoge et al., 1999; Kida et al, 2000), as discussed above. The association of decreased BOLD signals with decreased metabolism, assumed in the Gusnard and Raichle (2001) definition of neuronal activity, was supported by subsequent calibration of negative BOLD signals (Shmuel et al., 2002; 2006; Uludag et al., 2004; Pasley et al., 2007; Shulman et al., 2007).

Based upon the magnitudes of metabolism as suggested by the energetics, Gusnard and Raichle (2001) interpreted the numerous observations of negative BOLD signal as decreases in metabolism or energy consumption from a resting baseline value during a variety of stimulations. A literature survey led them to the position that - "The presence of a consistent set of decreases in activity within a select set of brain areas strikingly independent of the goal directed behaviors with which they are associated suggests to us that specific brain functions unique to the baseline state itself are being temporarily suspended". They reported that in many experiments, the negative BOLD signals, generated in a wide variety of simple tasks, were confined to broad, reproducible areas of the cortex. Two such regions (the midline areas of the posterior cingulate and precuneous and the medial prefrontal cortex) were identified from cognitive experiments as being more active in the resting eyes closed state than when the brain is activated "in support of varying goal directed activities." They proposed that certain general psychological states were associated with these areas. These psychological states, described as monitoring sensory information, were "emotional biasing signals" that enter "decision making processes". These broad concepts are typical of traditional psychology and they cover intentions and emotions as well as cognition and reflect a return of a more comprehensive, qualitative psychology, such as was interrupted by the focus on cognitive processes in the 1970's. As empirical scientists, we are open to such broad alternate hypotheses since our studies of baseline energetics, as described above, relate quantitative neurophysiology to psychological terms like "awareness". However our terms, while similarly qualitative, differ in that they can be reproducibly observed as defined by anesthesiologists (Franks, 2008), and do not depend upon cognitive concepts but upon observable responses.

We do not find it valuable to postulate psychological states that characterize the "baseline" of brain activity because, much as we value physiological parameters like  $CMR_{O_2}$  and OEF, there is no reason to believe that there is a particular state of the brain called *the* baseline state or "the default mode". In our view "baseline" is an operational term, an adjective that defines a

property of a state of the system before it is perturbed by a stimulus. Hence the baseline state has a particular measurable property (i.e. the baseline energy or a particular baseline flow, or a baseline firing pattern or a baseline OEF, etc). The baseline state depends not only upon eyes being open or closed but also depends upon the degree of anesthesia, possibly the degree of anxiety, sleep or the level of blood alcohol, etc. Furthermore as shown in the anesthetized rat experiments, the properties of the baseline state (such as the baseline energy) influence the way in which the animal responds to stimulus. While our experiments do not define a particular baseline state, they do show that the response to a stimulus depends upon the energy of the unperturbed or "baseline" state. Correlating the energy level with the degree of awareness, which is an observable parameter (i.e., the response to a question or to a touch), we avoid the Cartesian assumptions of a state of "consciousness" and instead have an empirical connection between observables. Accordingly we feel that the conceptualizations of a "default mode" characteristic of a "baseline state" are psychological assumptions that do not help our neurophysiological studies of how the brain handles the individual's responses like "awareness".

While we share concerns about the value of "default mode" with views expressed recently by Morcum and Fletcher (2007), it should be evident that we come from a different corner. Morcum and Fletcher (2007) in a series of criticisms of the default mode, dismiss studies of the baseline activities because "they make no contributions to understanding cognition". They value the results of cognitive stimuli and are indifferent to findings about a particular state and recognize that intent and awareness are joined with cognition to identify the "default mode". Although we do not share their exclusive regard for cognitive concepts, still there is similarity to be found in our seeking, like them, to understand the changes in brain activity introduced by alterations in the external world. However in our studies the observations are in response to changes in the total energy of the state (by anesthetics) or the effect upon the response to physiological stimuli (sensory). We study the total activity in the absence and presence of sensory stimulation and thereby look to correlate changes in total brain activity with neurophysiological changes that support the changing brain function.

Rather than judging concepts and experiments by their contributions to specific cognitive concepts, as physical scientists we continue to value neurophysiological data like the energy-work relations of neurons. Our research goals are to connect such physical results with observables of rather unspecified mental functions like awareness. We do not seek cognitive modules of awareness in specific, well localized brain activity, since we now know that cognitive concepts or modules are not being localized by neuroimaging experiments. We do not believe that brain locations can overcome the limitations of defining concepts by words, in agreement with Wittgenstein. However just as general concepts in everyday speech have great usefulness, although not rigorously defined, so too we greet with pleasure recent approaches in which brain activations and energies are connected with observable and reproducible responses like "awareness". Recent neuroimaging results are telling us, not what the brain is, but rather are showing us the kinds of words that can profitably be used in talking about brain function.

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#### Fig. 1.

Averaged fMRI maps (from two subjects, two single runs, 30 s block design, forepaw stimulation) of anterior coronal slices (A) under halothane showed widespread activities beyond contralateral S1 and S2, whereas (B) under  $\alpha$ -chloralose demonstrated localized activation in contralateral S1. Darker regions represent greater overlap across experiments (i.e., reproducibility). All activation maps were thresholded at the same value (p < 0.02). From Mandaag et al (2007).

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# Fig. 2.

Total activity represented by distribution of firing rates (v; 10 s bins) in the S1 neuronal ensemble for (A) halothane and (B)  $\alpha$ -chloralose states. Activity under halothane are dominated by the RSN sub-group which seems unaffected by stimulation. The SSN sub-group shifts to higher frequencies upon stimulation are similar in both states, but more significant under  $\alpha$ -chloralose. From Mandaag et al (2007).