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Commentary

A default mode of brain function: A brief history of an evolving idea

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The concept of a default mode of brain function arose out of a focused need to explain the appearance of activity decreases in functional neuroimaging data when the control state was passive visual fixation or eyes closed resting. The problem was particularly compelling because these activity decreases were remarkably consistent across a wide variety of task conditions. Using PET, we determined that these activity decreases did not arise from activations in the resting state. Hence, their presence implied the existence of a *default mode*. While the unique constellation of brain areas provoking this analysis has come to be known as the *default system*, all areas of the brain have a high level of organized default functional activity. Most critically, this work has called attention to the importance of *intrinsic* functional activity in assessing brain behavior relationships.

> *"A science of the mind must reduce … complexities (of behavior) to their elements. A science of the brain must point out the functions of its elements. A science of the relations of mind and brain must show how the elementary ingredients of the former correspond to the elementary functions of the latter."*

William James (James, 1890).[1]

> *"...physiology and psychology, instead of prosecuting their studies, as some now recommend, more strictly apart one from another than at present, will find it serviceable for each to give to the results achieved by the other even closer heed than has been customary hitherto."*

Sir Charles Sherrington (Sherrington, 1906).[2]

> *"Confusion springs from a failure to distinguish between psychological, physiological and anatomical accounts."*

The Rt. Hon. Lord Brain (Brain, 1961).

Five years have now elapsed since the publication of our paper 'A Default Mode of Brain Function' (Raichle et al., 2001). That paper and those that followed (Gusnard and Raichle, 2001; Raichle and Gusnard, 2002, 2005; Raichle, 2006; Raichle and Mintun, 2006) have generated far more interest, discussion and controversy than we anticipated. In particular, it has recently been suggested that the very notion of a default mode of brain function has no utility (Morcom and Fletcher, 2007). Our objective here is to summarize the evidence that persuades us of the opposite perspective, which is that understanding how the brain works critically depends on the study of it's intrinsic activity (i.e., activity not directly related to identifiable sensory or motor events), including that present in the default mode.

Some of the controversy may, in part, be attributable to imprecise nomenclature. In functional neuroimaging, certain terms like "rest", "activation", "deactivation", "control state" and "baseline" are in current usage despite the fact that they are potentially misleading with respect to the concepts they are intended to describe (see Raichle and Mintun, 2006 for a more extended discussion). We hope that our operational definitions of these terms will be clarified by what follows.

Difficulty also arises because the field of neuroscience is rapidly expanding. Neuroscientists now are obliged to understand not only the concepts and strategies of cognitive psychology but also a wide array of behavioral disciplines covered under the rubric of social neuroscience (e.g., see Cacioppo et al., 2002, 2006). At the same time, behavioral scientists interested in relating their work to the brain are confronted by a rapidly increasing body of knowledge concerning the physiological correlates of functional neuroimaging signals (Logothetis et al., 2001; Attwell and Iadecola, 2002; Lauritzen, 2005). Understanding this work depends on complex concepts not only from neurophysiology but also from theoretical neuroscience (Olshausen and Field, 2005), cell biology (Attwell and Laughlin, 2001; Pellerin and

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[1] Volume 2, page 103.

[2] Page 387 in the 1906 book or page 385 in the Yale Paperbound issued in 1961.

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Magistretti, 2003; Lauritzen, 2005) and even genetics (Pezawas et al., 2005). It is easy to understand how investigators at all levels occasionally feel a sense of unease in dealing comprehensively with this agenda. Under such circumstances, it is tempting to retreat into the narrow confines of one's own area of expertise. Illustrative in this regard is the opinion that "the suggested link between the processing taking place at rest and its physiology is one that can have no direct relevance for neuroimaging" (Morcom and Fletcher, 2007). This statement arguably is true if one's experimental horizons are limited to conventional functional neuroimaging. We believe, however, that such a finite agenda will eventually be exhausted if not nourished by a broader consideration and understanding of the relevant physiology.

Intellectual tension between the psychological and physiological perspectives of brain function is a recurrent theme. Readers who were engaged by the quotations at the head of our article may wish to consult the late Donald O. Hebb's essay, "Alice in Wonderland or Psychology Among the Biological Sciences" (Hebb, 1965). Addressing his fellow psychologists, Hebb wrote,

> *"The clinical neurologist complains that psychologists are complicating the problem of aphasia; the neurosurgeon does not understand what the objections are to localizing a stuff called consciousness or memory or something else in this part of the brain or that. For their part, psychologists too often fail to keep themselves informed about what goes on in the neurological field and, in defense of such ignorance, too often deny that it has any relevance for their work—a position so preposterous and indefensible that it is hard to attack."*

Finally, there is another reason for difficulty and that lies in a difference in perspective regarding one's view of brain function. One view posits that the brain is primarily reflexive, driven by the momentary demands of the environment. The other view is that the brain's operations are mainly intrinsic involving the maintenance of information for interpreting, responding to and even predicting environmental demands. The former has motivated most neuroscience research including that with functional neuroimaging. This is likely the case because experiments designed to measure brain responses to controlled stimuli and carefully designed tasks can be rigorously controlled whereas evaluating the behavioral relevance of intrinsic brain activity can be an illusive enterprise.

The hypothesis that intrinsic activity is critical to brain function and behavior can be traced back over two millennia:

> *"The fact that the body is lying down is no reason for supposing that the mind is at peace. Rest is… far from restful."* Seneca[3] (Seneca, ~60 A.D. (1969))
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> *"…though all our knowledge begins with experience, it by no means follows that all arises out of experience. For, on the contrary, it is quite possible that our empirical knowledge is a compound of that which we receive through impressions, and that which the faculty of cognition supplies from itself…"* Immanuel Kant (Kant, 1781 (2004))
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> *"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 the object before us, another part (and it may be the larger part) always comes (in Lazarus's phrase) out of our own head."* William James (James, 1890)[4]
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> *"This concept, that the significance of incoming sensory information depends on the pre-existing functional disposition of the brain, is a far deeper issue than one gathers at first glance…"* Rodolfo Llinas (Llinas, 2001)[5]

Functional neuroimaging began with studies of the brain's responses to carefully controlled sensory, cognitive and motor events (Posner and Raichle, 1994). Such experiments fit well with the view of the brain as driven by the momentary environmental demands. More recently, advances in our understanding of brain function derived from neurophysiology (Buzsaki, 2006) as well as neuroimaging (Raichle, 2006; Raichle and Mintun, 2006) have provoked us to reassess the importance of ongoing or, intrinsic activity. The concept of a default mode of brain function (Raichle et al., 2001) was our introduction to this alternative perspective.

We present below a brief history of how the idea of a default mode of brain function arose and how it has led us to consider the importance of the brain's intrinsic activity. For more detailed discussions of the relevant physiology, cell biology, local circulation and metabolism (brain work) as they relate to neuroimaging we refer readers to our recent comprehensive review of these matters (Raichle and Mintun, 2006). For a comprehensive review of spontaneous neuronal activity we recommend the recent book by György Buzsaki (Buzsaki, 2006).

The history of a problem

By the early 1980s PET began to receive serious attention as a potential functional neuroimaging device in human subjects. (For a detailed historical account see Raichle, 2000). The study of human cognition with neuroimaging was aided greatly by the involvement of cognitive psychologists in the 1980s whose experimental strategies for dissecting human behaviors fit well with the emerging capabilities of functional brain imaging (Posner and Raichle, 1994). Subtracting functional images acquired in a task state from ones acquired in a control state was a natural extension of mental chronometry (Posner, 1986) in which one measures the time required to complete specific mental operations isolated by the careful selection of task and control states. This approach, in various forms, has dominated the cognitive neuroscience agenda ever since with remarkably productive results.

For the better part of a decade following the introduction of subtractive methodology to neuroimaging, the vast majority of changes reported in the literature were activity increases or *activations* as they were almost universally called. Activity increases but not decreases are expected in subtractions of a control condition from a task condition as long as the *assumption of pure insertion* is valid. To illustrate, using an example based on mental chronometry, say that one's control task requires a key press to a simple stimulus such as the appearance of a point of light in the

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[3] Page 111.

[4] Volume 1, page 28.

[5] Page 8.

visual field, whereas the task state of interest requires a decision about the color of the light prior to the key press. Assuming pure insertion, the response latency difference between conditions is interpretable as the time needed to perform a color discrimination. However, the time needed to press a key might be affected by the nature of the decision process itself, violating the assumption of pure insertion. More generally, the brain state underlying any action could have been altered by the introduction of an additional process. Interestingly, functional neuroimaging helped address the question of pure insertion by employing the device of *reverse subtraction*. Thus, in certain circumstances subtracting task state data from control state data revealed negative responses, or *task-specific deactivations* (for examples and further discussion of this interesting issue see Raichle et al., 1994; Petersen et al., 1998; Raichle, 1998). It was clearly shown, just as psychologists had suspected, that processes active in a control state could be modified when paired with a particular task. However, none of this work prepared us for nor anticipated "the problem".

'The problem,' as we now think of it, arose unexpectedly when we noted, quite by accident, that activity decreases were present in our subtraction images even when the control state was either visual fixation or eyes closed rest. What particularly caught our attention was the fact that, regardless of the task under investigation, the activity decreases almost always included the posterior cingulate and adjacent precuneus, a region we nicknamed MMPA for 'medial mystery parietal area'.

The first formal characterization of task-induced activity decreases (Shulman et al., 1997) generated a set of iconic images (Fig. 1A) whose unique identity was amply confirmed in later meta-analyses by Jeffery Binder and colleagues at the Medical College of Wisconsin (Binder et al., 1999) and Bernard Mazoyer and his colleagues (Mazoyer et al., 2001) in France. Similar observations are now an everyday occurrence in laboratories throughout the world leaving little doubt that a specific set of brain areas decrease their activity across a remarkably wide array of task conditions when compared to a passive control condition such as visual fixation.

The finding of a network of brain areas frequently seen to decrease its activity during goal directed tasks (Fig. 1A) was both surprising and challenging. Surprising because the areas involved had not previously been recognized as a system in the same way we might think of the motor or visual system. And, challenging because initially it was unclear how to characterize their activity in a passive or resting condition.

For us the issue of characterizing activity decreases came to a head in 1998 when a paper we were attempting to publish was rejected because of the way in which we characterized activity

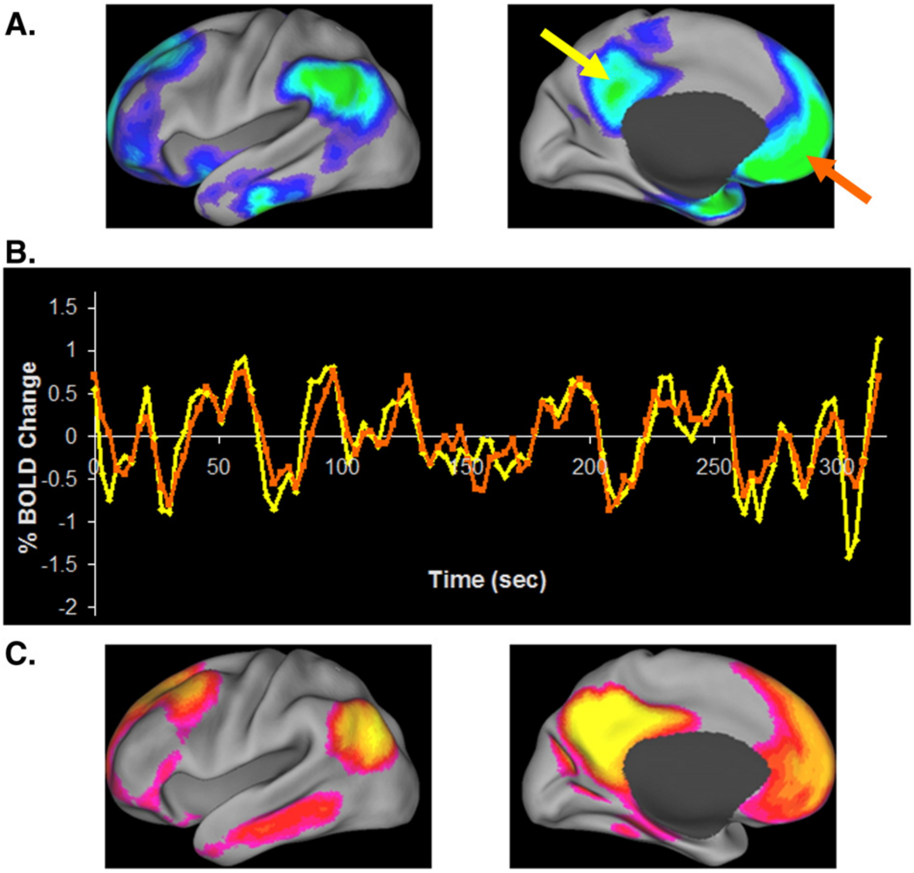

Fig. 1. Performance of a wide variety of tasks has called attention to a group of brain areas (A) that decrease their activity during task performance (data adapted from Shulman et al., 1997). If one records the spontaneous fMRI BOLD signal activity in these areas in the resting state (arrows, A) what emerges is a remarkable similarity in the behavior of the signals between areas (B). Using these fluctuations to analyze the network as a whole (Fox et al., 2005; Vincent 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 that the ongoing organization of the human brain likely provides a critical context for all human behaviors. These data were adapted from our earlier published work (Shulman et al., 1997; Gusnard and Raichle, 2001; Raichle et al., 2001; Fox et al., 2005).

changes of the type seen in Fig. 1A.[6] One of the referees wrote, “This is the most controversial aspect of this paper as it (1) cannot be ruled out that these signal changes are actual activations in the so-called resting state and (2) the physiological mechanisms underpinning a genuine BOLD signal decrease remain a matter of speculation”.[7]

It was clear that we needed a way to determine whether or not task-induced activity decreases were simply ‘activations’ present in the absence of an externally-directed task and an explanation regarding why they should appear in both PET and fMRI functional neuroimaging studies. In wrestling with these difficult issues two things came to mind that, together, we felt offered us an opportunity to move forward.[8]

First, the manner in which functional neuroimaging was conducted with fMRI carried with it a physiological definition of activation that could be measured with PET. This definition arose from quantitative circulatory and metabolic PET studies demonstrating that when brain activity increases *transiently* above a resting state, blood flow increases more than oxygen consumption (Fox and Raichle, 1986; Fox et al., 1988). As a result, the amount of oxygen in blood increases locally as the ratio of oxygen consumed to oxygen delivered falls. This ratio is known as the oxygen extraction fraction or the OEF. Activation can then be defined physiologically as a transient local decrease in the oxygen extraction or, if you like, a transient increase in oxygen availability.

The practical consequence of this observation was to lay the physiological groundwork for functional MRI using blood oxygen level dependent or BOLD contrast, (Thus, MRI is sensitive to the level of blood oxygenation; Thulborn et al., 1982; Ogawa et al., 1990, 1992; Kwong et al., 1992). Using this quantitative definition of activation we asked whether ‘activations’ were present in a passive state such as visual fixation or eyes closed rest. But activation must be defined relative to something. How was that to be accomplished if there was no ‘control’ state for eyes closed rest or visual fixation?

The definition of a control state for eyes closed rest or visual fixation arose from a *second* critical piece of physiological information. Researchers using PET for the quantitative measurement of brain oxygen consumption and blood flow had long appreciated the fact that, across the entire brain, blood flow and oxygen consumption are closely matched when one lies in a PET scanner with eyes closed resting or during visual fixation (see Lebrun-Grandie et al., 1983 for one of the earliest references; also Raichle et al., 2001). This is observed despite a nearly 4-fold difference in oxygen consumption and blood flow between gray and white matter and variations in both measurements of greater than 30% within gray matter itself. As a result of this close matching of blood flow and oxygen consumption at rest, the OEF is strikingly uniform throughout the brain. This well-established observation led us to the hypothesis that if this observation (a uniform OEF at rest) was correct then activations, as defined above, were likely absent in the resting state (Raichle et al., 2001). We decided to test this hypothesis.

Using PET to quantitatively assess regional OEF, we examined two groups of normal subjects in the resting state and initially confined our analysis to those areas of the brain frequently exhibiting the aforementioned imaging signal decreases (Fig. 1A). In this analysis we found no evidence that these areas were activated in the resting state; that is, the *average* OEF in these areas did not differ significantly from other areas of the brain. We concluded that the regional decreases, observed commonly during task performance, represented the presence of functionality that was ongoing (i.e., sustained as contrasted to transiently activated[9]) in the resting state and attenuated only when resources were temporarily reallocated during goal-directed behaviors; hence our original designation of them as *default functions* (Raichle et al., 2001). Thus, from a metabolic/physiologic perspective, these areas (Fig. 1A) could not be distinguished from other areas of the brain in the resting state.

After performing the above analysis (Raichle et al., 2001) on the aforementioned areas (Fig. 1A), we searched our data for any other areas that might exhibit evidence of activation in the resting state and found none (Raichle et al., 2001).[10] This observation is important in suggesting that aspects of the brain’s intrinsic functionality are *not* confined to those areas that we designated as a *default network* (Fig. 1A) and is consistent with the observation that activity decreases do occur in other areas of the brain in a more task specific manner (Drevets et al., 1995; Kawashima et al., 1995; Ghatan et al., 1998; Somers et al., 1999; Smith et al., 2000; Amedi et al., 2005; Shmuel et al., 2006).[11]

The importance of using PET rather than fMRI to define a physiologic baseline state of the brain needs to be emphasized. Our work was critically dependent on the ability of PET to provide absolute, quantitative and reproducible measurements of regional blood flow and oxygen consumption in the human brain. PET is uniquely suited to do so, operating as it does with tracer techniques that have been validated against objective standards (Raichle et al., 1983; Mintun et al., 1984; Martin et al., 1987). fMRI as it is conventionally practiced using BOLD imaging does not offer a similar absolute reference (Aguirre et al., 2002; Detre and Wang, 2002) and, hence, estimated changes in parameters such as oxygen consumption must be viewed with caution until further work is done to determine their validity (e.g., see Kim et al., 1999).

Furthermore, when fMRI is employed comparisons are always made between two states closely spaced in time because baseline BOLD signal, for reasons currently not understood, does not remain constant. Some have concluded, therefore, that a functional imaging baseline cannot be defined. We appreciate the potential for confusion particularly when terms like control state, control condition and baseline are used interchangeably, which occurs frequently in the imaging literature. While the term physiologic baseline, as we have defined it (Gusnard and Raichle, 2001; Raichle et al., 2001), is not appropriately applied to fMRI data directly, it is clear that the terms control state and control condition

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[6] The study, never published, was a comparison of PET and fMRI.

[7] Such a response was not surprising given the work with reverse subtractions in dealing with the assumption of pure insertion.

[8] What follows is a brief synopsis of complex physiological observations. For readers interested in more details we recommend our recent review dealing in depth with this subject (Raichle and Mintun, 2006).

[9] It should be noted that with sustained increases in activity (i.e., activations) the OEF gradually returns towards its pre-activation levels Mintun et al. (2002).

[10] Readers of our paper (Raichle et al., 2001) will note that we observed *increases* in the OEF (so-called “deactivations”) in areas of extrastriate visual cortex. This finding had been noticed many years before in the earliest investigations of the OEF in humans (Lebrun-Grandie et al., 1983). Interested readers may wish to consult our paper for a more complete discussion of this finding.

[11] It should also be noted that the work of Shmuel and colleagues (Shmuel et al., 2006) provided us with the first direct evidence that activity decreases seen with fMRI represented actual reductions in neuronal activity.

may be applied equally well to both PET and fMRI imaging techniques. And, importantly, when low level control states such as eyes closed rest or visual fixation are used, the results from both imaging techniques are virtually identical (Raichle, 1998; Simpson et al., 2000).

Intrinsic brain activity

Having arrived at the view that the brain has a default mode of function through our analysis of activity decreases, we began to take seriously claims that there was likely much more to brain function than that revealed by experiments manipulating momentary demands of the environment. Two bodies of information have been especially persuasive.

First is the cost of intrinsic activity, which far exceeds that of evoked activity (for a review of this literature see Raichle and Mintun, 2006). It should suffice here to remind readers that, depending on the approach used, it is estimated that 60% to 80% of the brain's enormous energy budget is used to support communication among neurons, functional activity by definition. The additional energy burden associated with momentary demands of the environment may be as little as 0.5% to 1.0% of the total energy budget. This cost-based analysis alone implies that intrinsic activity may be at least as important as evoked activity in understanding overall brain function.

Second is the remarkable degree of functional organization exhibited by intrinsic activity. For us this organization was first revealed in the activity decreases we and others observed in our studies with functional neuroimaging (Fig. 1A). More striking, however, have been the patterns of activity revealed in the analysis of the "noise" in the fMRI BOLD signal when subjects are resting quietly in the scanner with their eyes closed or simply maintaining visual fixation.

A prominent feature of fMRI is that the unaveraged signal is quite noisy (Fig. 1B) prompting researchers to average their data to reduce this 'noise' in the signals they seek. As it turns out, a considerable fraction of the variance in the BOLD signal in the frequency range below 0.1 Hz appears to reflect spontaneous fluctuating neuronal activity that exhibits striking patterns of coherence within known brain systems (Fig. 1C) even in the absence of observable behaviors associated with those systems. Additionally these patterns of coherence are remarkably consistent among individuals as well as across subject groups. The value of studying resting state BOLD fluctuations has been well articulated (Buckner and Vincent, in press). But what does intrinsic activity represent?

One possibility is that intrinsic activity simply represents unconstrained, spontaneous cognition—our daydreams or, more technically, stimulus-independent thoughts (SITS; Antrobus, 1968; McGuire et al., 1996; Mason et al., 2007). But from a cost perspective SITS are highly unlikely to account for more energy consumption than that elicited by responding to controlled stimuli, which accounts for a very small fraction of total brain activity (Raichle and Mintun, 2006). Most telling is the recent observation that spatially coherent, spontaneous BOLD activity is present even under general anesthesia (Vincent et al., in press). This important observation suggests that intrinsic activity cannot simply be a reflection of conscious mental activity. Rather, it likely reflects a more fundamental or intrinsic property of brain functional organization.

Among the possible functions of this intrinsic (default) activity is facilitation of 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 (Salinas and Sejnowski, 2001; Laughlin and Sejnowski, 2003; Abbott and Chance, 2005; Haider 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". Another well-known example first demonstrated in the visual system of the cat is the 'Sprague effect' (Sprague, 1966). 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; Kersten et al., 2004; Knill and Pouget, 2004). 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. This is a theme presciently enunciated many years ago by the late David Ingvar in his memorable essay "Memory of the Future" (Ingvar, 1985).

An important question for researchers interested in how brain instantiates behavior is how to incorporate studies of intrinsic brain activity into an already busy program of work devoted to evoked activity. Some, of course, will elect not to do so. But as we pointed out earlier, such a limited approach will eventually be exhausted if not nourished by a broader consideration and understanding of the relevant neurobiology. What is required is an expanded framework upon which to base such a research agenda. Neuroscience and the behavioral sciences *together* must provide that framework which is one that we heartily endorse.

Cognitive neuroscientists for their part will need to become more familiar with a broad range of approaches to the study of spontaneous activity of neurons (Arieli et al., 1996; Kenet et al., 2003; Leopold et al., 2003; Buzsaki and Draguhn, 2004; Kay, 2005; Foster and Wilson, 2006). In this regard, descriptions of slow fluctuations (nominally, <1 Hz) in neuronal membrane polarization–so-called up and down states–are intriguing (Petersen et al., 2003; Hahn et al., 2006; Isomura et al., 2006; Luczak et al., 2007). Not only does their temporal frequency correspond to that of the spontaneous fluctuations in the fMRI BOLD signal, but their functional consequences may be relevant to an understanding of the variability in task-evoked brain activity as well as behavioral variability in human performance. Neuroscientists for their part need to be aware of the expanded view of intrinsic activity afforded by neuroimaging and the potential to relate this not only to their own work at the cellular level but also to the behavior we all seek to understand.

Appendix A

This brief appendix directly addresses selected points raised by Morcom and Fletcher (M&F; Morcom and Fletcher, 2007) more directly than was done in the main text. Our responses are intended to clarify certain points and to provide additional background that some may find useful in discussions of the default mode, the default system, the physiologic baseline and intrinsic activity.

> *M&F: a default or intrinsic mode of functioning derives from the observation that "a consistent network of brain regions shows high levels of activity when no explicit task is performed and subjects are asked simply to rest."*

A *default mode* of functioning was initially inferred on the basis of two related observations: first, certain areas of the brain consistently decrease activity when subjects engage in goal-directed tasks as compared to simply resting quietly with the eyes closed or visually fixating; and, second, this network of areas was not physiologically 'activated' in the resting state. While initially attributed specifically to a specific system, now often called the *default network*, we now appreciate that all parts of the brain exhibit a *default mode* of functioning that largely reflects their ongoing intrinsic activity.

> *M&F: "The importance of this putative 'default mode' is asserted on the basis of the substantial energy demand associated with the resting state and of the suggestion that rest entails a finely tuned balance between metabolic demand and regionally regulated blood supply."*

A finely tuned balance between metabolic demand and regionally regulated blood supply is not unique to the resting state or the default system. It is characteristic of all areas of the brain at all times. It is important to appreciate in this regard that blood flow is not simply regulated in relation to oxygen consumption as traditionally envisioned. Rather, a complex interplay between glycolysis, oxidative phosphorylation, blood flow and cellular physiology (in astrocytes and neurons alike) is played out in the course of functional activities (Raichle and Mintun, 2006).

The brain's substantial energy demand (20% of the entire body's) is a more broadly important matter (Raichle, 2006). Recent evidence clearly indicates that a majority of this cost is directly related to the functioning of the brain. In this regard it should be noted that transmitter cycling is a correlate of transmitter release and uptake, and, hence neuronal signaling. Transmitter cycling has computational significance.

> *M&F: The case for a default mode comprises three related ideas. The first is that the resting state constitutes an absolute baseline, and is therefore a fixed point relative to which all cognitive and physiological states can and should be considered.*

To restate, the baseline as defined in our work is a physiological referent not a behavioral one. It is, therefore, only appropriately applied to PET and not to fMRI. On the other hand, 'control state' and 'control condition' (whichever term is preferred) can be equally well applied to PET and fMRI. We remain convinced that using a low level control state in addition to other more complex ones enhances the interpretability of functional imaging data (e.g., consider the interpretational complexities in the study by Simpson and colleagues (Simpson et al., 2001) that are discussed in greater detail in Gusnard and Raichle, 2001).

> *M&F: "The second is the notion that the level of neural activity in this resting state is substantial and therefore functionally important, with changes produced by task demands representing just the 'tip of the iceberg'."*

Correct. Event-related changes in cerebral blood flow and glucose uptake are no more than 10% of the physiologic baseline in typical cognitive paradigms. Concomitant changes in energy utilization are on the order of 1% (for addition discussion see Raichle and Mintun, 2006).

> *M&F: "It would follow that cognitively driven fluctuations cannot be interpreted except in the context of the default system."*

This is true of *all* parts of the brain because they all exhibit ongoing intrinsic activity, a *default mode* if you will. Task-related responses in any part of the nervous system should ultimately be understood in relation to local intrinsic activity.

> *M&F: "We conclude that despite the interesting characteristics of rest as baseline in terms of oxygen balance, these are not relevant to studies that seek to understand how neural activity underpins cognitive processing."*

Traditional views of brain energy metabolism posited that all energy for brain function came from the metabolism of glucose to carbon dioxide and water. The discovery that this simple relationship is not correct (Fox et al., 1988) not only provided the physiological basis for fMRI but also opened up new ways of thinking about the neural events underlying cognitive processing. Links such as this across levels of analysis and intellectual inquiry should be at the heart of any enterprise that hopes to understand how brain instantiates behavior.

> *M&F: "While we accept that a high level of energy expenditure of the brain at 'rest' indicates that the resting state is active, we do not agree that this activity has a special status compared with that in any other task, or that the brain energy budget is informative about the nature of the 'default mode'."*

The important distinction is not between "rest" and "task" but rather between intrinsic and evoked activity. To define "rest" as simply a task with unspecified cognitive content obscures what we believe to be the important and essential distinction between intrinsic and evoked activity. That upwards of 90% of the brain's functional activity, as measured in energy terms, is devoted to intrinsic and not evoked activity inescapably leads one to give to the study of intrinsic activity an increased level of attention, well above that which it has heretofore received. To do otherwise is to prematurely limit the level of understanding achievable in our quest to understand how brain instantiates behavior. Determining the contribution of intrinsic activity to behavior is challenging but, in our view, should be a major neuroscience objective.

> *M&F: "We conclude that even if there is empirical consistency in the patterns of activity observed at rest, and a subjective appeal to the notion that when we rest we are in a default state because there is no explicit task to perform, these are insufficient grounds for affording the resting state a privileged status in accounts of human behavior."*

Again, our argument is quite simply that the fundamental distinction to be made is between intrinsic and evoked activity. Resting quietly but awake in a scanner affords one an opportunity to view intrinsic activity but we would not argue that this is the only way. Sleep and general anesthesia (Vincent et al., in press) also come to mind. As experimental strategies develop distinctions between intrinsic and evoked during task performance may also become increasingly feasible in the context of functional neuroimaging (e.g., see Fox et al., 2006). But we should always keep in mind that this work cannot precede effectively in a vacuum. Success will require a dialogue with other levels of analysis.

> *M&F: In most instances the aims of cognitive neuroscience are best served by the study of specific task manipulations rather than "rest."*

We would agree that the aims of cognitive neuroscience will continue to be served by the study of specific task manipulations but not exclusively so. To base the agenda on this approach alone misses the exciting opportunities afforded by an integration of approaches across disciplines and levels of analysis. To do so also has the potential to blind one to the real reason we have a brain, which is not to reminisce about the past nor react in the moment but, rather, to envision the future.

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