

Feature Review

Two views of brain function

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Traditionally studies of brain function have focused on task-evoked responses. By their very nature, such experiments tacitly encourage a reflexive view of brain function. Although such an approach has been remarkably productive, it ignores the alternative possibility that brain functions are mainly intrinsic, involving information processing for interpreting, responding to and predicting environmental demands. Here I argue that the latter view best captures the essence of brain function, a position that accords well with the allocation of the brain's energy resources. Recognizing the importance of intrinsic activity will require integrating knowledge from cognitive and systems neuroscience with cellular and molecular neuroscience where ion channels, receptors, components of signal transduction and metabolic pathways are all in a constant state of flux.

The brain is not primarily reflexive

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 out of our own head.

William James (1890)

This prescient comment by William James, to be found in Volume 2 (p. 103) of his monumental work *The Principles of Psychology* [1], captures the essence of a debate ongoing in the 19th century, and possibly earlier, surrounding two views of brain function. One view, pioneered by the work of Sir Charles Sherrington [2], 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 acquisition and maintenance of information for interpreting, responding to and even predicting environmental demands, a view espoused by one of Sherrington's disciples T. Graham Brown [3] (for more recent perspectives see [4,5]).

The view that the brain is primarily reflexive has motivated most neuroscience research including that with functional neuroimaging. This is not surprising 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 activity (i.e. ongoing neural and metabolic activity which is not directly associated with subjects' performance of a task) can be an elusive enterprise. Unfortunately, the success of studying evoked

activity has caused us to lose sight of the possibility that our experiments reveal only a small fraction of the actual functional activity performed by our brain.

Two challenges face a consideration of the view that the brain's operations are mainly intrinsic. First, how do we adjudicate the merits of such a claim? The answer comes primarily from a consideration of the considerable cost of running the brain most of which is devoted to its ongoing, internal functional activity. And, second, if the claim is correct then how do we unlock the mysteries of intrinsic activity? The answer will come from a serious consideration of multiple levels of inquiry ranging from cognitive and systems neuroscience to cell biology and metabolism.

Adjudicating the merits of intrinsic activity

Cost

One of the most persuasive arguments for the importance of intrinsic activity emerges from a consideration of its relative cost in terms of brain energy consumption. In the average adult human, the brain represents about 2% of the total body weight yet it accounts for 20% of all the energy consumed [6], 10 times that predicted by its weight alone.

Relative to this very high rate of ongoing energy consumption in the resting state (Box 1), the additional energy consumption associated with changes in brain activity is remarkably small, often less than 5% (Figure 1). From these data it is clear that the brain's enormous energy consumption is little affected by task performance, an observation first made more than 50 years ago by Louis Sokoloff, Seymour Kety and their colleagues [7] but rarely cited.

What is the nature of this ongoing intrinsic activity that commands such a large amount of the brain's energy resources? Assessments of brain energy metabolism using a variety of approaches ([8–12] for review see [13]) indicate that from 60 to 80% of overall brain energy consumption is devoted to glutamate cycling and, hence, neural signaling processes. Such estimates leave for future consideration the demands placed on the brain's energy budget by the activity of inhibitory interneurons [14–19] and astrocytes [20,21]. That evidence notwithstanding it is probable that the majority of brain energy consumption is devoted to functionally significant intrinsic activity.

Sensory information

Complementary information on the importance of intrinsic activity comes from consideration of sensory information. It might surprise some to learn that visual information is significantly degraded as it passes from the eye to the visual cortex. Thus, of the unlimited information available from

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Box 1. The Resting State

The *resting state* is here viewed as a behavioral state characterized by quiet repose usually with eyes closed but occasionally, in the experimental setting, with eyes open with or without visual fixation (visual fixation as a resting state proxy probably only applies to humans where maintaining visual fixation is near effortless compared to monkeys who must be coerced). We presume that during the resting state subjects experience an ongoing state of conscious awareness largely filled with stimulus-independent thoughts (SITs; [148]) or, more popularly, day dreaming or mind wandering [47,149]. It is important to distinguish between the resting state, defined behaviorally, and the state of the brain that accompanies the resting state. The brain is never physiologically *at rest* as evidenced by ongoing intrinsic activity and a very high energy consumption that varies little between the resting state and engagement in attention-demanding tasks (Figure 1).

the environment, only about 10^{10} bits/sec are deposited in the retina. Because of a limited number of axons in the optic nerves (approximately 1 million axons in each) only $\sim 6 \times 10^6$ bits/sec leave the retina and only 10^4 make it to layer IV of V1 [22,23]. These data clearly leave the impression that visual cortex receives an impoverished representation of the world, a subject of more than passing interest to those interested in the processing of visual information [24]. Parenthetically, it should be noted that estimates of the bandwidth of conscious awareness itself (i.e. what we ‘see’) are in the range of 100 bits/sec or less [22,23].

Reinforcing this impression of the brain’s ‘isolation’ is the fact that the number of synapses in the lateral geniculate nucleus of the thalamus and in layer IV of primary visual cortex devoted to incoming visual information is less

than 10% of the total number of synapses in both locations [25]. Various proposals have been made concerning the interpretation of these anatomical data [26,27] but the fact remains that the brain must interpret, respond to and even predict environmental demands from seemingly impoverished data. An explanation for its success in doing so must lie in significant measure with intrinsic brain processes that link representations residing *broadly* within brain systems to incoming sensory information [28]. The challenge, of course, is how to study these intrinsic brain processes at the appropriate spatial and temporal scales.

Unlocking the mysteries of intrinsic activity

Since the introduction of electroencephalography (EEG) in humans by Hans Berger in 1929 [29] (for an English translation of this important work see [30]) it has been clear that ongoing spontaneous electrical activity is a prominent feature in EEG. In referring to the spontaneous activity Berger rhetorically asked [29] ‘Is it possible to demonstrate the influence of intellectual work upon the human electroencephalogram, insofar as it has been reported here?’ He then concluded that ‘Of course, one should not at first entertain too high hopes with regard to this, because mental work, as I explained elsewhere, adds only a small increment to the cortical work which is going on continuously and not only in the waking state’. As has been demonstrated in subsequent research, extensive averaging of the EEG has been used to significantly attenuate if not eliminate this seemingly random, ongoing activity leaving only predictably occurring, task-induced changes or event-related potentials (ERPs) as they are

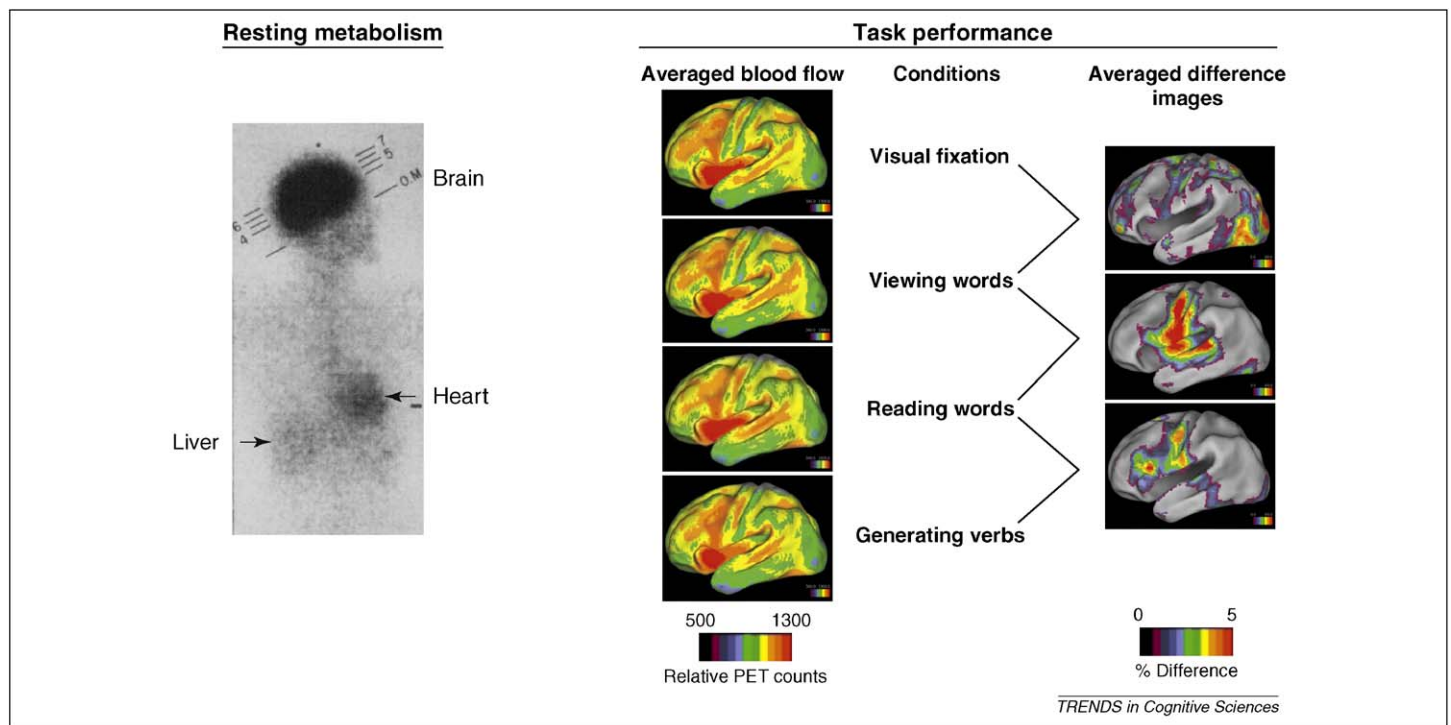


Figure 1. In the resting state (Box 1) brain blood flow accounts for 11% of the cardiac output and brain metabolism accounts for 20% of the energy consumption of the body, overshadowing the metabolism of other organs such as the heart, liver and skeletal muscle as shown on the left (above) in this classic image of whole body glucose consumption. Reproduced, with permission, from [142]. The changes in regional blood flow associated with task performance are often no more than 5% of the resting blood flow of the brain from which they were derived (center) and, hence, only discernable in difference images averaged across subjects as shown above on the left (data adapted from Petersen *et al.* [143]). These modest modulations in ongoing circulatory and metabolic activity rarely affect the overall rate of brain blood flow and metabolism during even the most arousing perceptual and vigorous motor activity [7,126,144–146].

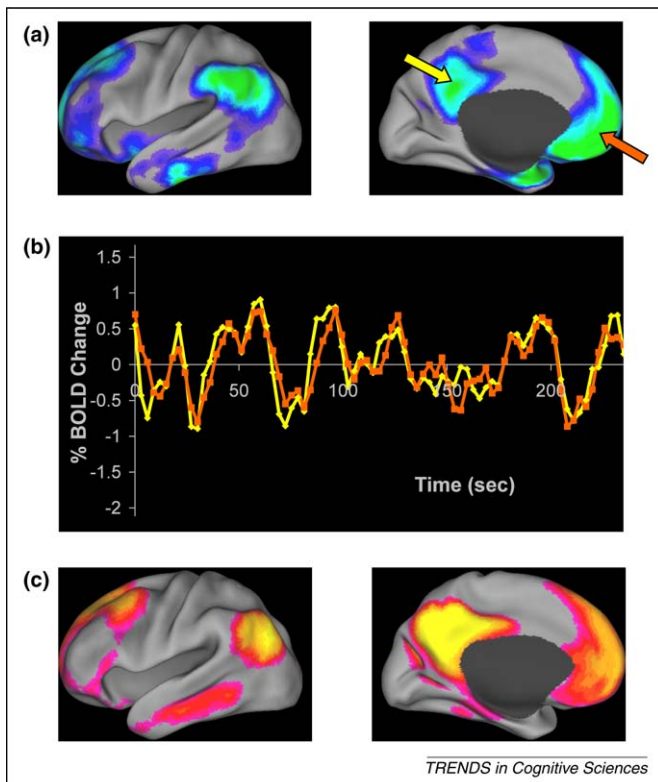


Figure 2. Performance of a wide variety of tasks has called attention to a group of brain areas (a) that decrease their activity during task performance (data adapted from [31]). These areas are often referred to as the brain's DMN [32]. If one records the spontaneous fMRI BOLD signal activity in these areas in the resting state (arrows, a) what emerges is a remarkable similarity in the behavior of the signals between areas (b), a phenomenon originally described by Biswal and colleagues in the somatomotor cortex [147] and later in the DMN by Greicius and colleagues [38]. Using these fluctuations to analyze the network as a whole reveals a level of functional organization (c) that parallels that seen in the task-related activity decreases (a).

known generally. This strategy is analogous to image subtraction and averaging (Figure 1) with similar, unfortunate consequences for ongoing intrinsic activity.

It was a chance observation in neuroimaging first with positron emission topography (PET) and later with functional magnetic resonance imaging (fMRI) that actually provided a new perspective on what to look for in studying the brain's intrinsic activity. This was the occurrence of activity decreases during the performance of goal-directed tasks compared with the resting state.

Activity decreases from a resting state

The first formal characterization of task-induced activity decreases from a resting state was a large meta-analysis of published PET data from our group [31]. This study generated a set of iconic images of a constellation of brain regions now generally referred to as the default mode network (DMN) (Figure 2A) after our later paper on a *default mode of brain function* [32] (Box 2). Jeffery Binder and colleagues [33] and Bernard Mazoyer and colleagues confirmed the unique identity of this group of brain regions in later meta-analyses. Similar observations are now an everyday occurrence in numerous laboratories, leaving little doubt that a specific set of brain areas decrease their activity across a remarkably wide array of task conditions when compared with a passive control condition such as visual fixation.

Box 2. Questions for future research:

- To what extent does phase resetting of SCPs account for the evoked BOLD response?
- How are the many functions of glucose allocated during development and how is this regulated?
- What functions of glucose contribute to the persistent increase in aerobic glycolysis following learning and are these the same functions deployed during development?
- Are spontaneous fluctuations in cortical excitability related to aerobic glycolysis and, if so, how?
- How is the striking overall increase in brain energy consumption from waking distributed among brain systems?
- Why does the DMN succumb to Alzheimer's disease and what, if any, is the role of aerobic glycolysis in this unique vulnerability?

The finding of a network of brain areas frequently seen to decrease its activity from a resting state during goal-directed tasks (Figure 2A) 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 arising as it did in a passive or resting condition. It was conceivable that these activity decreases were simply activations present in a poorly constrained resting state.

It was clear that we needed a way to determine whether or not task-induced activity decreases were simply 'activations' in the absence of an externally directed task. To initiate our inquiry we employed quantitative PET measurements of regional brain blood flow and oxygen consumption to define a physiologic baseline. The details of this work have been recounted on several occasions [13,32,35,36] and, thus, will not be repeated here. Suffice to say that this work allowed us to move forward on the assumption that activity within the DMN did not represent conventional activations in the resting state but, rather, a new view of the organization of the brain's intrinsic activity that we dubbed 'a default mode of brain function' [32]. It is important to note that the DMN is not unique in exhibiting both high levels of baseline metabolic activity and organized functional activity in the resting state. It is a property of all brain systems and their subcortical connections as I will detail later.

The discovery of the DMN made apparent the need for additional ways to study the large-scale intrinsic organization of the brain. A major step forward was the discovery that this large-scale network organization, including but not limited to the DMN, could be revealed by the study of patterns of spatial coherence in the spontaneous fluctuations (i.e. noise) in the fMRI blood oxygen level dependent (BOLD) signal.

Spontaneous fluctuations in the fMRI BOLD signal

A prominent feature of fMRI is the noise in the raw BOLD signal. This has prompted researchers to average their data to increase signal and reduce noise. As first shown by Bharat Biswal and colleagues in the human somatomotor system [37], a considerable fraction of this noise exhibits striking patterns of coherence within known brain systems.

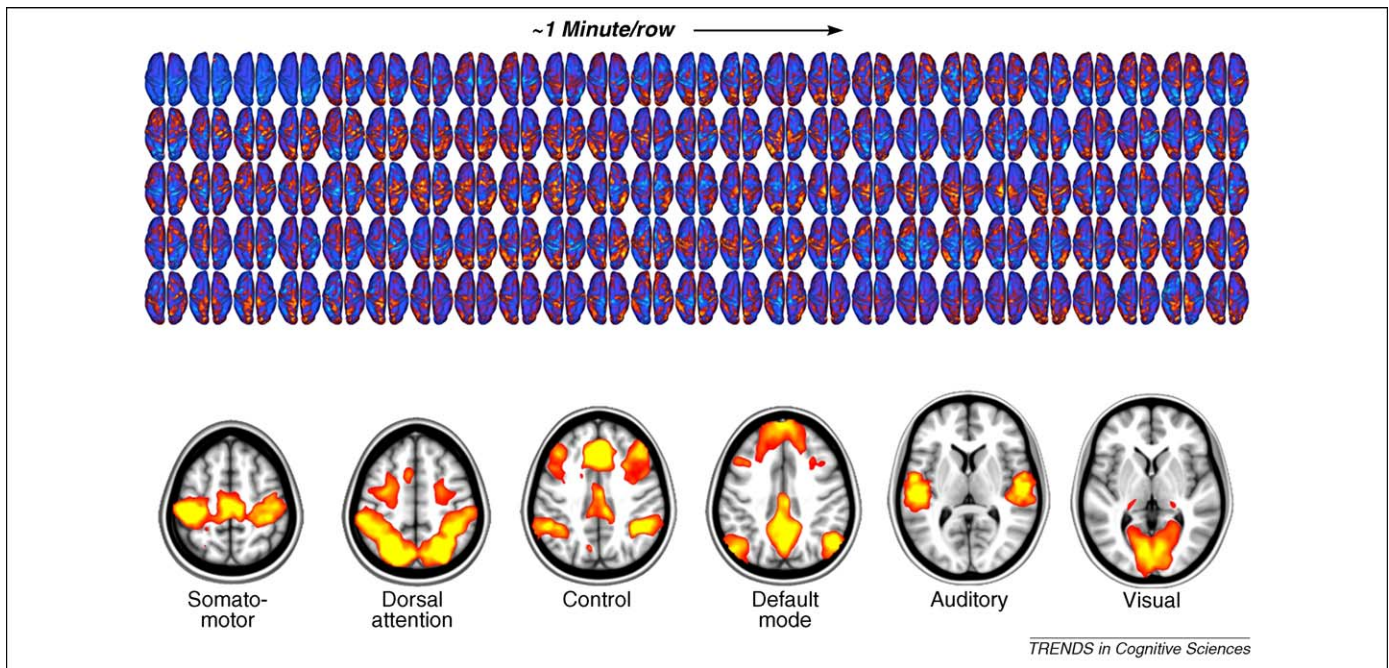


Figure 3. From the fluctuating patterns of intrinsic activity seen in the human brain with fMRI BOLD imaging (top) striking patterns of spatial coherence within known brain systems (bottom) can be extracted. A single subject example of data from which these patterns are derived is shown (top). These data were obtained continuously over a period of 5 minutes (each row is one minute, each frame is 2.3 seconds). It is instructive to occasionally view the data in this way because it helps one understand the slowly moving, somewhat fluid nature of the process. An interpolated version of these data in a video format is available on the web (ftp://imaging.wustl.edu/pub/raichlab/restless_brain). The patterns of spatial coherence shown on the bottom are obtained by placing a seed region in a single focus within a system and then correlating the activity in that seed region with the rest of the brain. A more complete description of the data processing steps leading to such images is presented elsewhere along with alternate strategies [140]. Shown are six major brain networks analyzed in this way: visual, sensorimotor, auditory, default mode, dorsal attention and executive control.

The significance of this observation was brought forcefully to our attention when Michael Greicius and colleagues looked at the patterns of coherence in the DMN [38] elicited by placing a region of interest in either the posterior cingulate cortex (yellow arrow, Figure 2A) or the ventral medial prefrontal cortex (orange arrow, Figure 2A). The resulting time-activity curves (Figure 2B) reflected a pattern of coherence within the entire DMN (Figure 2C). Similar patterns of resting state coherence have now been documented in most cortical systems in the human brain (Figure 3; for a recent review see [39,40]) as well as their subcortical connections [41].

Several additional observations made about these surprising patterns of spatial coherence are of interest. First, they seem to transcend levels of consciousness, being present under anesthesia in humans [42], monkeys [43] and rats [44] and also during the early stages of sleep in humans [45,46]. These observations make it unlikely that the patterns of coherence and the intrinsic activity they represent are primarily the result of unconstrained, conscious cognition (i.e. mind-wandering or day dreaming [47]).

Second, although resting state patterns of coherence do respect patterns of anatomical connectivity in both the monkey [43] and human brain [41], it is clear that they are not constrained by these anatomical connections. Thus, the absence of monosynaptic connections between brain areas (e.g. right and left primary visual cortex [43]) does not preclude the existence of functional connectivity as expressed in the maps of resting state coherence.

Third, the strength of coherence between nodes within systems varies with age and disease. Developmental

changes have been particularly well demonstrated in the DMN [48]. Such observations are consistent with the role of experience and, possibly, spontaneous activity itself in sculpting and maintaining these functional relationships in the human brain [49,50]. At the other end of the life spectrum, data indicate that the young adult pattern in the DMN might recede as one passes into the sixth decade of life and beyond [51] even in healthy older persons. Even more interesting are three recent studies demonstrating disruption in DMN coherence in cognitively normal older persons harboring DMN amyloid plaques [52–54]. In this regard it should be recalled that the DMN seems to be the target of Alzheimer’s disease [55]. Disruption in the resting state coherence between nodes of a system might well prove to be a very sensitive early indicator of disease [56].

Finally, spontaneous fluctuations in the BOLD signal contribute significantly to both variability in evoked signals [57] and to variability in the associated behavior [58]. These observations become important as we consider the neurophysiologic correlates of the spontaneous BOLD fluctuations. What follows is a brief description of the direction the neurophysiologic work is taking beginning with the electrical correlates of the fMRI BOLD signal.

Neurophysiology of BOLD

There has been an active effort to ascertain the electrical correlates of the fMRI BOLD signal (for summaries of this work from different perspectives see [13,59,60]). The conclusion from this work is that the fMRI BOLD signal is best correlated with local field potentials (LFPs), that is, the complex signals arising from the integrated electrical activity in pre- and postsynaptic terminals of the brain,

which are recorded with microelectrodes placed within brain tissue. Brain electrical activity recorded from the scalp with EEG or from surface of the brain with electrocorticography (ECoG) constitutes a summation of a population of LFPs. LFPs are conventionally described in terms of their band-limited frequency components (delta, 1–4 Hz; theta, 4–8 Hz; alpha, 8–12 Hz; beta, 12–24 Hz; and gamma, >24 Hz).

Given the relationship between LFPs and BOLD it is important to focus on those LFP phenomena that exhibit frequencies similar to that of spontaneous BOLD fluctuations (i.e. 0.01–4.0 Hz). Two LFP phenomena fall into this category: fluctuations in the power of higher frequencies (i.e. their power spectral density), where particular attention has been paid to the gamma frequency band [61] because of its association with cognition [62,63]; and, raw frequencies that approximate that of the spontaneous BOLD signal. These include the delta band (1–4 Hz), up-and-down states (~0.8 Hz; [64–67]) and infra-slow fluctuations (ISFs) (0.01 and 0.1 Hz [68,69]). ISFs are sometimes called direct current (DC) potentials, referring to their amplification requirements. ISFs are much less often recorded because of the amplifier requirements and concerns about artifacts [59]. Often all three (delta, up-and-down states and ISFs) are subsumed under the designation slow cortical potentials (SCPs) [70,71]. In the present discussion I will use the term SCPs recognizing that it probably includes all three phenomena to an as yet unspecified extent.

The research shows that the spontaneous fluctuations in the BOLD signal are best correlated with LFP activity in the range of the SCPs ([44,71]). As is the case with the BOLD signal (see above), the spatial patterns of coherence exhibited by SCPs are maintained across levels of consciousness ranging from wakefulness to rapid eye movement (REM) and slow wave sleep [71] and during anesthesia [44]. By contrast, power in the gamma frequency band is only correlated spatially with the BOLD signal during wake and REM sleep ([71]; see also [72]). This finding is consistent with the role of gamma-band coherence in the mental activities associated with conscious awareness [62,63]. It should be noted that failure to consider SCPs in seeking electrical correlates of the BOLD signal has led some to propose that the BOLD signal and its metabolic/vascular underpinnings can operate independent of the brain's electrical activity [73,74].

Knowing that SCPs and spontaneous fluctuations in the BOLD signal are related provides a bridge to a highly relevant neurophysiologic literature on low frequency oscillations (e.g. see [69,70,75–77]). Emerging from this literature are several informative themes.

SCPs and possibly the spontaneous fluctuations in brain oxygenation as seen by fMRI BOLD and optical imaging techniques [78] represent fluctuations in cortical excitability (for review see [77]). These fluctuations in cortical excitability have a remarkable effect on other elements of the LFP frequency spectrum ([69]; Figure 4) as well as the spiking activity of neurons [79,80]. This coupling or nesting with SCPs serving an important coordinating role provides a logical structure for the integration of functional activity. Not surprisingly the phase of the SCPs affects both evoked

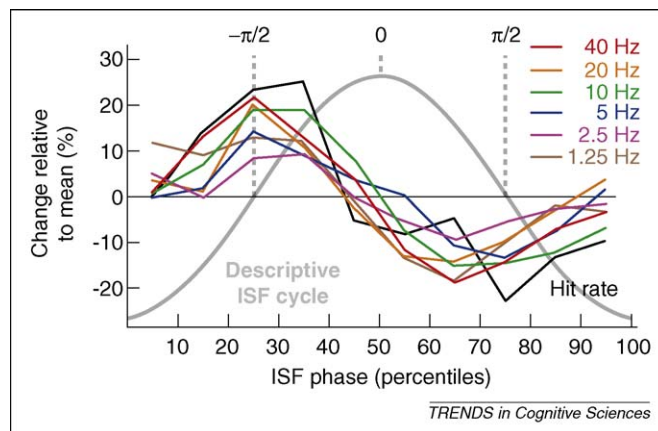


Figure 4. EEG oscillations (1–40 Hz) are nested in the ISFs of the EEG (0.01–0.1 Hz). The correlation of the 1–40 Hz oscillation amplitudes (colored lines) with the ISFs is similar to that of the behavior (black line). The ISF phase ranges from $-\pi$ to π in bins of 10 percentiles. The thick gray line denotes a descriptive cycle of the ISFs. Reproduced, with permission, from [69].

responses [28,57,81,82] and behavioral performance [58,69,83]. One among many results of this functional organization might well be the emergence of conscious awareness [84]. However, the story does not end there.

Although each major brain system can be identified by a unique pattern of spatial coherence the brain does not operate as an assemblage of independent systems. Coordination among brain systems is aided by the fact that brain systems are not created equal. Rather, there seems to be a federation of hierarchically organized *hubs* in the brain whose influence extends across the boundaries of systems [85,86]. Remarkably, at the top of this hierarchy is the DMN. Thus, not surprisingly, the brain is not a free-for-all among independent systems but a federation of interdependent components hierarchically organized.

SCPs provide a window on how the brain matches its predictions to changing environmental contingencies. Schroeder and Lakatos [77] view this as one mode of attending in which the phase of the SCPs is shifted to match the predictable patterns of incoming information, a process dubbed *phase resetting*. As a result, responses are enhanced and performance is improved (see also [69,87,88]). This mode, and it might well be the dominant mode, occurs in a seemingly effortless manner fitting, in a sense, the idea of a default mode of brain function involving the ongoing coordinated activity of all of its systems. It provides a means of connecting the concept of an intrinsic mode of brain function designed to organize information for interpreting, responding to and even predicting environmental events [89,90] into register with the naturally occurring but ever changing regularities unfolding in the environment.

Obviously, the world in which we live is not entirely predictable. This calls for a complementary strategy in which SCPs are temporarily suppressed in a setting in which task performance requires considerable effort (i.e. goal-directed attention) because of novelty and uncertainty (for review see [77]). This is precisely the circumstance in which we have come to expect activity decreases in the DMN (Figure 2A) and increased activity in brain areas associated with goal-directed attention [91,92]. It is of

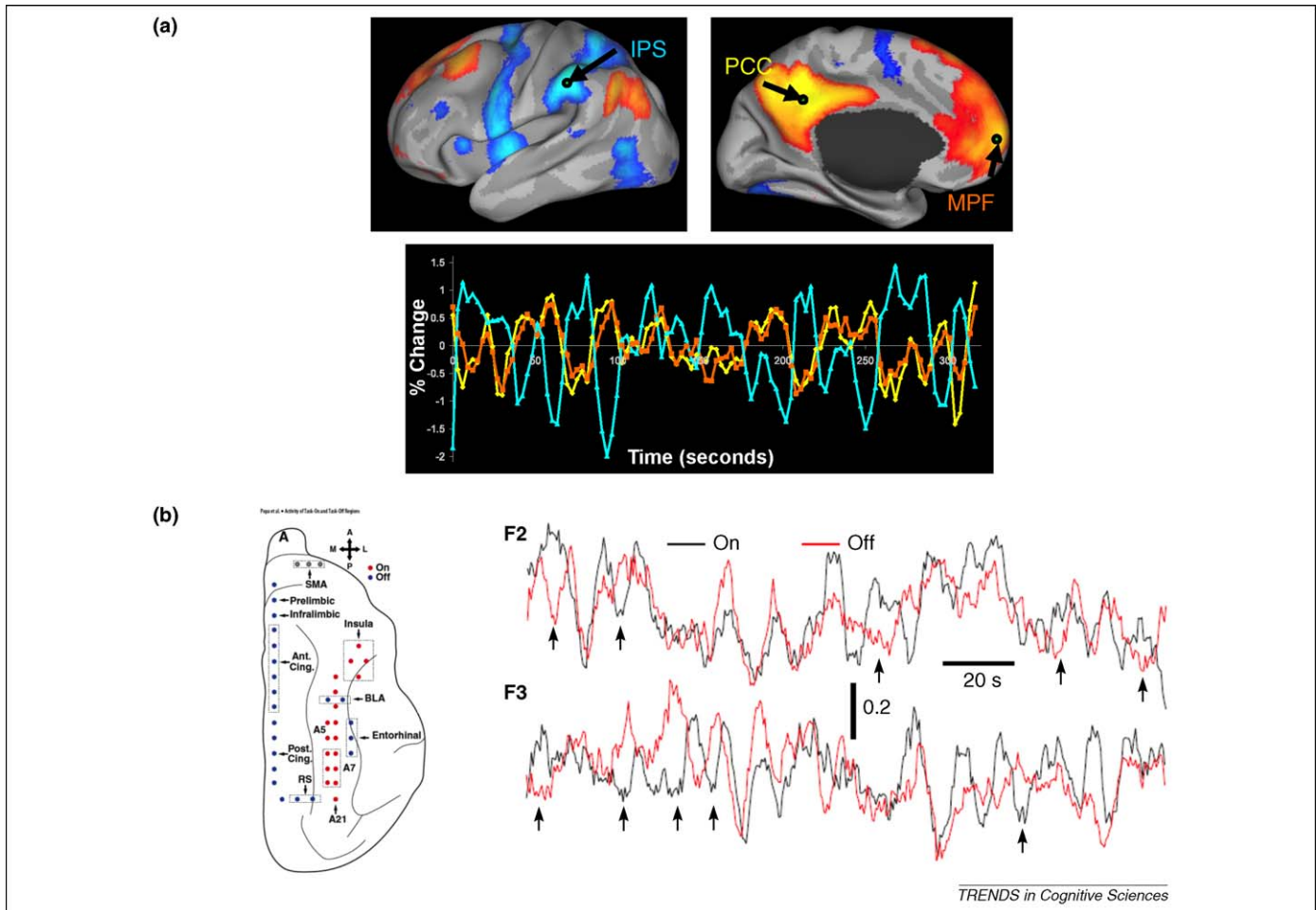


Figure 5. A. Intrinsic defined anti-correlated networks in the awake human observed with resting state fMRI. Positive nodes are significantly correlated with seed regions involved in focused attention and working memory (attention-positive seeds), and significantly anti-correlated with seed regions routinely deactivated during attention-demanding cognitive tasks (i.e. DMN). Negative nodes are significantly correlated with attention-negative seeds and significantly anti-correlated with attention-positive seeds. Reproduced, with permission, from [94]. B. Slow LFP power fluctuations in the awake cat reveal anti-correlated networks. These recordings were obtained from chronically implanted microelectrodes situated in the putative homolog of the DMN (midline blue electrodes) and regions thought to correspond to the attention-positive seeds in the human brain (blue). In these two recording epochs (F2 and F3) anticorrelations (arrows) alternated with periods of correlation between the two brain regions. Anticorrelations were present approximately 20% of the time. Reproduced, with permission, from [95]. This percentage dropped significantly during REM and slow wave sleep (personal communication, Denis Pare).

interest that this give-and-take relationship between the DMN and these latter systems is also seen in their spontaneous activity in the resting state (Figure 5; [93–95]) indicating that the brain is continuously trying to strike a balance between the expected and the unpredictable.

Digging deeper

Pursuing an understanding of the brain's intrinsic activities need not stop with the neurophysiology. Understanding the underlying cell biology is also relevant not only in understanding brain imaging signals but also what these signals actually reveal about brain function (see [36] for an extended discussion of this argument). Functional brain imaging studies actually provide some clues as to how this inquiry might proceed and the intellectual disciplines likely to contribute. I begin from the perspective of fMRI BOLD signal physiology.

One of the surprising observations made with PET was that blood flow increased much more than oxygen consumption during task-induced increases in brain activity ([96,97]; Figure 6). The physiological consequences of this

are that local blood deoxyhemoglobin decreases simply because the supply of oxygen transiently increases more than demand [96,97]. Importantly, deoxyhemoglobin is an MRI contrast agent which causes signal loss in direct proportion to its concentration. The combination of the physiology associated with an increase in brain activity (i.e. an increase in blood flow > an increase in oxygen consumption) with the physical properties of deoxyhemoglobin as an endogenous contrast agent led to the concept of the BOLD signal ([98]; for a recent historical review see [99]). Since its introduction in 1992 [100–103] BOLD fMRI has accounted for nearly 12 000 papers according to an informal PubMed search using the terms “fMRI” and “brain”. For some, interest in the biology of the BOLD signal ends here. However, the most interesting part of the story could yet be told.

Overlooked by many in discussions of the biology of the BOLD signal has been the task-induced increase in aerobic glycolysis (i.e. glucose metabolized by the brain in excess of that needed for oxidative phosphorylation despite the presence of adequate oxygen; Figure 6). This

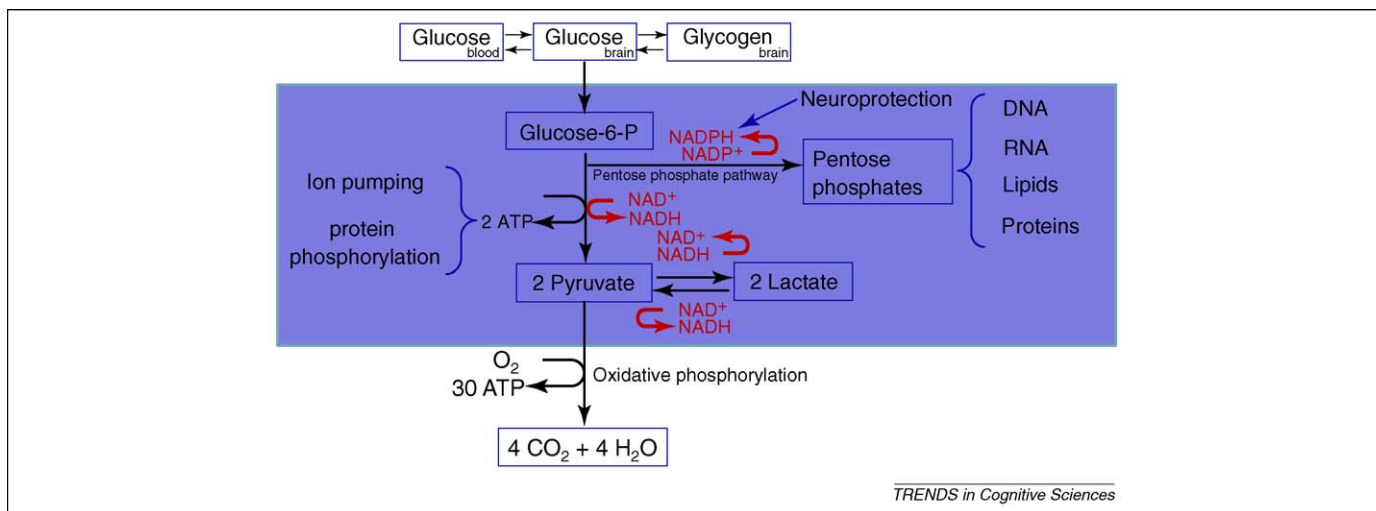


Figure 6. A simplified schematic of brain glucose metabolism highlighting (in blue) the features discussed in this review. For most neuroscientists glucose is viewed as the brain's fuel, providing substrate for oxidative phosphorylation where it is metabolized to carbon dioxide and water in the course of producing 30+ molecules of ATP. Because glucose produces only 2 ATP outside of oxidative phosphorylation it has been easy to overlook its many other important contributions to the activities of the brain. As highlighted in blue in this figure and discussed in detail in the text these other contributions of glucose are of considerable importance. Glucose is the source of 2-carbon fragments for the synthesis of nucleic acids, lipids and proteins; this occurs via the pentose phosphate pathway. This makes glucose important for both building the brain and remodeling it as needed for memory and learning. As glucose traverses its several pathways it also has an important effect on the brain's redox state (i.e. the ratio of NAD^+ to NADH) which is critical for the handling of reactive oxygen species and the management of apoptosis. Finally, the small number of ATP produced by glucose metabolism itself are important because they are delivered to critical membrane-related processes such as the Na,K-ATPase pump and can be produced much faster than the ATP derived from oxidative phosphorylation.

unexpected task-induced increase in aerobic glycolysis actually reflects an increase rather than a *de novo* appearance of aerobic glycolysis. Aerobic glycolysis is actually present in the normal adult human brain at rest accounting for between 12 and 15% of the glucose metabolized [104,105]. Remarkably this ongoing aerobic glycolysis is not distributed uniformly in the adult human brain. Rather it exhibits elevated levels in the DMN and adjacent areas of the dorsolateral prefrontal cortex and low levels in the cerebellum and the medial temporal lobes [106]. Together these surprising observations stimulated us to review the various roles that aerobic glycolysis might play in addition to the production of energy via oxidative phosphorylation.

Through a series of important experiments beginning in the early 1990s [107] Pellerin and Magistretti were able to establish that one source of the task-induced increases in aerobic glycolysis is the energy demands of the membrane pump Na,K-ATPase in astrocytes [107]. Increases in activity in the adult mammalian brain are largely caused by the release of the excitatory neurotransmitter glutamate. Glutamate is removed from the synapse by uptake into astrocytes in a sodium dependent process. Sodium must then be removed from the astrocyte by Na,K-ATPase . The energy needed for this process comes from aerobic glycolysis that produces a net 2 ATP per molecule of glucose consumed. One might argue that it is inefficient to fuel such a critical pump by aerobic glycolysis given such a low yield of ATP for each molecule of glucose used (Figure 6). However, the advantage aerobic glycolysis has over oxidative phosphorylation is that the ATP is produced much faster (at least 2 times faster; [108]). Thus, where speed is important, such as at an excitatory synapse, one might posit that aerobic glycolysis is the way to go. Regardless of the reason it is the case that Na,K-ATPase is

fueled by aerobic glycolysis in all membrane systems in which it is found [109–112] with lactate as a byproduct. Lactate can be converted to pyruvate and enter the Krebs cycle where most of the brain's ATP is produced stimulating much debate as to the importance of lactate as an energy substrate for neurons [13,113–116]. Some lactate, of course, simply leaves the brain in flowing blood.

Obviously, Na,K-ATPase is not confined to the astrocytes [112]; it functions in neurons as well. For example, Na,K-ATPase is an important constituent of the postsynaptic density where it resides along with the enzymatic machinery for glycolysis. There Na,K-ATPase is crucially involved in the regulation of AMPA receptor turnover and thereby synaptic strength [117]. The degree to which AMPA receptor associated Na,K-ATPase activity contributes to ongoing as well as task-induced increases in aerobic glycolysis remains to be determined but its association with processes involved in learning and memory emerges directly from this observation.

Given the similarity between the task-evoked BOLD signal and the resting state BOLD signal it is tempting to assume that they represent a similar underlying physiology (i.e. fluctuations in blood flow and aerobic glycolysis that are greater than those in oxygen consumption). Such an assumption would be consistent with the hypothesis that SCPs represent changes in membrane excitability discussed earlier. Unfortunately, our current knowledge of the temporal dynamics of synaptic glutamate concentrations and glucose utilization in adjacent cells is insufficient to support this hypothesis. Work presently ongoing in several laboratories seeks to fill this void [118].

Aerobic glycolysis has several important functions in addition to fueling membrane pumps such as Na,K-ATPase and providing substrate for oxidative phosphorylation (Figure 6). The task of unraveling the details of these

functions has been the province of cancer biologists [119,120] who were stimulated by Otto Warburg's seminal observations in the 1920s that cancer cells forsake oxidative phosphorylation for aerobic glycolysis [121]. Because of the treatment implications for cancer it has been crucial to understand why cells choose glycolysis over oxidative phosphorylation, an adaptation that seems designed to prevent cell death. What follows are some highlights of this work and their implications for neuroscience.

One of the important functions performed by glycolysis is to provide substrate for biosynthesis. This proceeds via the pentose phosphate pathway (Figure 6) where carbon is provided for the synthesis of nucleotides, fatty acids, lipid membranes and proteins. This is obviously important for actively proliferating cancer cells. With its role in cellular biosynthesis in mind it is of interest to recall what we know about levels of aerobic glycolysis ongoing in the human brain.

As noted earlier, aerobic glycolysis represents between at least 12 and 15% of the total amount of glucose consumed by the adult brain [104,105]. Interestingly, this percentage is 30% in the term, human infant [122] and, remarkably, is nearly 100% in the premature infant [123,124]. These much higher values in the premature infant would certainly be consistent with the role of glucose in biosynthesis but we know little of its fate in the premature and infant brain. Because considerable development occurs between birth and early adulthood it would be of interest to know how the percentage of aerobic glycolysis varies during this time period; here available data are incomplete.

Brain glucose metabolism reaches adult levels by age 2, it is twice that adult level by about age 9 [125] and it then returns to adult levels by the early 20s [125]. This trajectory parallels the proliferation of synapses in the brain and their eventual pruning as the adult brain is sculpted. What we do not know over this crucial period of brain development is how glucose consumption is partitioned between oxidative phosphorylation and its other functions because parallel measurements of oxygen consumption are not available. However, it seems reasonable to posit that aerobic glycolysis might be a considerable fraction. Why? Consider the following. If all of the glucose metabolized in the brain of a 9 year old were going to oxidative phosphorylation and the amount of glucose consumed was twice that of the adult then instead of the brain accounting for 20% of the entire energy budget of the body [7] brain metabolism would account for upwards of 40% of the body's energy budget. Clearly this is unlikely and probably not sustainable. More probable is that aerobic glycolysis accounts for a significant fraction of this extra glucose consumption, a fact that we must establish in future research.

As noted above, even in the adult human at rest aerobic glycolysis is present. Furthermore, it not only increases during task performance but can remain elevated for an extended period after task performance [126] even though blood flow and oxygen consumption have returned to control levels. This observation would be consistent with the hypothesis that aerobic glycolysis is, in part, a signal of

experience-dependent biosynthetic processes in the brain. Supportive of this idea are diurnal variations in brain energetic and aerobic glycolysis.

Measurements of whole brain blood flow, oxygen consumption and glucose utilization across the day-night cycle [127,128] reveal that they are all significantly higher in the evening than in the morning. Whole brain oxidative phosphorylation increases almost 20% [127], a remarkable increase when one considers it in relation to the magnitude of task-induced changes (Figure 1). Aerobic glycolysis, as a percentage of the total glucose consumption, almost doubles, increasing from 11% in the morning to 19% in the late evening [127]. This parallels nicely the experience-dependent diurnal variation in synaptic strength posited by Tononi and Cirelli in their synaptic homeostasis hypothesis [129] and is consistent with the view so eloquently expressed by Eve Marder who notes that 'while neurons live and function well for decades... ion channels, synaptic receptors and the signal conduction pathways are constantly turning over in the membrane and being replaced, with half-lives of minutes, hours, days or weeks' (see introductory paragraph in [130]). Little wonder why we sleep, we can ill afford not to!

Finally, aerobic glycolysis is critical for the long-term survival of cancer cells as well as neurons because of its role in the regulation of apoptosis [131,132]. This is accomplished through management of the brain's redox state (i.e. the ratio of NAD^+ to NADH) which glucose does via the pentose phosphate shunt (Figure 6). Unfortunately, our knowledge of the ongoing activity of the pentose phosphate pathway is presently insufficient to relate it to the dynamics of cell turnover in the brain during development as well as the moment-to-moment experiences in the adult. It is noteworthy that the redox state of the brain fluctuates on about the same timescale as does its intrinsic activity, as expressed by the spontaneous BOLD fluctuations and the SCPs [133], and is a significant determinant of the responsiveness of the brain vasculature [134–136]. Our understanding of these important relationships is regrettably incomplete at the moment.

The way forward

As we move forward the scope of the inquiry into the brain's intrinsic activities is poised to expand. Integrating the necessary levels of analysis will obviously be challenging and will demand the willingness to accept the multidisciplinary nature of the task. Help will come also from theoretical modeling approaches where creative work has already begun [137–139].

Although research on the brain's intrinsic activity has much to offer with regard to our understanding of normal brain function, it is also likely to provide many new insights into the devastating array of diseases afflicting the human brain. This possibility has not been lost on investigators who are already pursuing vigorously a wide variety of diseases (for a detailed review of the surprising number of papers already pursuing intrinsic activity as a window on disease see [140]). Studying the brain in health and disease through the organization of its intrinsic activity not only addresses a dominant feature of its functional activity but does so with an approach that can be

applied without the constraints imposed by task performance because nothing is required of the subject other than the ability to remain still in a scanner.

Finally, we might need to rethink our understanding of the fMRI BOLD signal in terms of its relationship to task-evoked activity. We have struggled in the past to relate the sluggish responsiveness of the BOLD signal to rapidly changing electrical events in the brain all the while ignoring the fact that the temporal characteristics of the fMRI BOLD signal match almost perfectly the SCPs and other functionally important cellular and biochemical processes. We should ask whether task-induced changes in the fMRI BOLD signal are not, as we have posited, sluggish responses to rapidly changing electrical events but rather a reflection of changes in the slow components of the brain's intrinsic activity in response to changing environmental contingencies. Several observations related to anticipatory changes in the fMRI BOLD signal mimicking task-evoked changes [74,141] are consistent with this hypothesis as are much earlier observations in the ERP literature related to slowly varying anticipatory signals such as the contingent negative variation [70]. Such a formulation would be consistent with much of the research reviewed here and put our interpretation of the fMRI BOLD signal on a firmer biological footing.

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