40th Anniversary Retrospective

Editor's Note: To commemorate the 40th anniversary of the Society for Neuroscience, the editors of *the Journal of Neuroscience* asked several neuroscientists who have been active in the society to reflect on some of the changes they have seen in their respective fields over the last 40 years.

A Paradigm Shift in Functional Brain Imaging

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Introduction

The history of brain imaging has paralleled the growth of the Society for Neuroscience, from its inception in 1973 with the introduction of x-ray computed tomography (CT) to the present (for a historical review, see Webb, 1990; Kevles, 1997; Raichle, 2000; Raichle, 2009). Since then, imaging of the human brain, first with positron emission tomography (PET) and now with magnetic resonance imaging (MRI), has become an increasingly important part of research in neurosciences, as well as the social sciences, and also an important face for brain research in the lay community. The thirst for information about brain function is universal, and imaging, for better or worse, has been used by many as a medium for the discussion.

Growth in functional imaging research has been particularly exceptional. Since its introduction in 1992 (Bandettini et al., 1992; Frahm et al., 1992; Kwong et al., 1992; Ogawa et al., 1992), functional MRI (fMRI) has accounted for nearly 12,000 papers along with 10,000 additional papers using PET, according to PubMed searches using the terms ["fMRI" and "brain"] and ["PET" and "brain"].

Functional brain imaging has followed a long tradition in neuroscience: studying neuronal responses to stimuli and activity during task performance. In this work, the role of bottom-up versus top-down (or feed-forward vs feed-back) causality is frequently discussed, reflecting a debate that extends back at least a century on the relative importance of intrinsic and evoked activity in brain function [for a comprehensive historical review, see Chapter 1 in the book by Llinas (2001)]. "Intrinsic activity" is ongoing neural and metabolic activity that is not directly associated with subjects' performance of a task. The distinction between intrinsic activity and task-evoked activity applies at many levels of neurophysiological examination, including events at the cellular level where ion channel proteins, receptors, and the components of signal transduction pathways turn over with half-lives of minutes, hours, days, and weeks (Marder and Goaillard, 2006). Brain imaging has recently entered this discussion with information that will likely be important in shaping future research. It

suggests to me an impending paradigm shift (Kuhn, 1996) brought about by surprising discoveries in imaging research that have occurred against a background of complementary work in electrophysiology and cell biology. In this essay I briefly review evidence that persuades me of this view.

Two views of brain function

Since the beginning of the 20th century and possibly earlier, two views of brain function have existed (Llinas, 2001). One view, pioneered by the early work of Sherrington (1906), 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 introduced by a disciple of Sherrington, T. Graham Brown (1914) [for a view of his work in a modern context, see the study by Yuste et al. (2005)]. The former has motivated most neuroscience research including that with functional neuroimaging. This is not surprising because experiments designed to measure brain responses to various stimuli and carefully designed tasks can be rigorously controlled, whereas evaluating the behavioral relevance of intrinsic activity can be an elusive enterprise. How do we adjudicate the relative importance of these two views in terms of their impact on brain function?

One means of evaluating the relative importance of evoked and intrinsic activity is to examine their cost in terms of brain energy consumption. In the average adult human, the brain represents ~2% of the total body weight but accounts for 20% of all the energy consumed (Clarke and Sokoloff, 1999). This high-energy consumption occurs in the resting state, a behavioral state characterized by quiet repose with either eyes closed or open, with or without visual fixation. Furthermore, relative to the very high rate of ongoing or "basal" energy consumption in humans, the additional energy consumption associated with evoked changes in brain activity is remarkably small, often <5% (Raichle and Mintun, 2006). This low figure likely applies to stimulus-independent thoughts (i.e., day dreaming) as well. 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 (Sokoloff et al., 1955) [for prescient early insights, the interested reader may also wish to read Creutzfeldt (1974)].

What is the nature of this ongoing intrinsic activity that commands such a large amount of the brain's energy resources? Measurements of brain energy metabolism using magnetic resonance spectroscopy (Sibson et al., 1997; Sibson et al., 1998; Shulman et al., 2001, 2004) in a variety of experimental settings have indicated that 60–80% of overall brain energy consumption is devoted to glutamate cycling and, hence, neuronal signaling. Complementary analyses using extant anatomic, physiologic, and metabolic data (Wong-Riley, 1989; Ames, 2000; Attwell and Laughlin, 2001; Lennie, 2003) to assess the cost of different components of excitatory signaling in the gray matter have arrived at similar conclusions. Such estimates leave for future consideration the demands placed on the brain's energy budget by the functional activity of inhibitory interneurons (Ackermann et al., 1984; McCasland and Hibbard, 1997; Waldvogel et al., 2000; Chatton et al., 2003; Patel et al., 2005; Buzsáki et al., 2007) and astrocytes (Pellerin and Magistretti, 1997; Magistretti and Chatton, 2005). That evidence notwithstanding, it is likely to remain the case that the majority of brain energy consumption is devoted to functionally significant intrinsic activity. The challenge, of course, is how to study these intrinsic brain processes. Functional brain imaging has provided some intriguing new insights.

Figure 1. *A*, *B*, A comparison of activity decreases during the performance of goal-directed tasks in the DMN (*A*) and spontaneous BOLD fluctuations (*B*) within the same network in the resting state derived from regions of interest placed in the posterior cingulate/precuneus (yellow arrow) or the medial prefrontal cortex (orange arrow). The remarkable degree of coherence between activities obtained from these two distant loci within the same system is evident on inspection of these time–activity curves. The degree of system-wide coherence within the DMN is shown in *C* when all voxels in the brain are examined for their correlation with a region of interest in the posterior cingulate/precuneus (yellow arrow in *A*). Such a well delineated pattern of coherence within a known system is typical of all large-scale cortical systems and their subcortical connections. This figure was adapted with permission from M. E. Raichle (2009).

Exploring intrinsic activity

It was a chance observation in neuroimaging, first with PET and later with 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 when compared with the 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 (Shulman et al., 1997). This study generated a set of iconic images of a constellation of brain regions now generally referred to as the default mode network or DMN (Fig. 1*A*) after our later paper on a default mode of brain function (Raichle et al., 2001) [for a historical perspective, see Raichle and Snyder (2007)]. The unique identity of this group of brain regions was amply confirmed in later meta-analyses by Jeffery Binder et al. (1999) at the Medical College of Wisconsin and Bernard Mazoyer et al. (2001) in France. Similar observations are now an everyday occurrence in laboratories throughout the world, leaving little doubt that the specific brain areas that make up the DMN, decrease their activity across a remarkably wide array of task conditions when compared with a passive control condition such as visual fixation. From this work has come an increasing appreciation of the many unique features of this network of areas [for example, see the studies by Buckner et al. (2008), Hagmann et al. (2008)].

The discovery of the DMN provided a new, large-scale view of the organization of the brain's intrinsic activity. However, the need for more detailed studies of intrinsic activity at a scale sug-
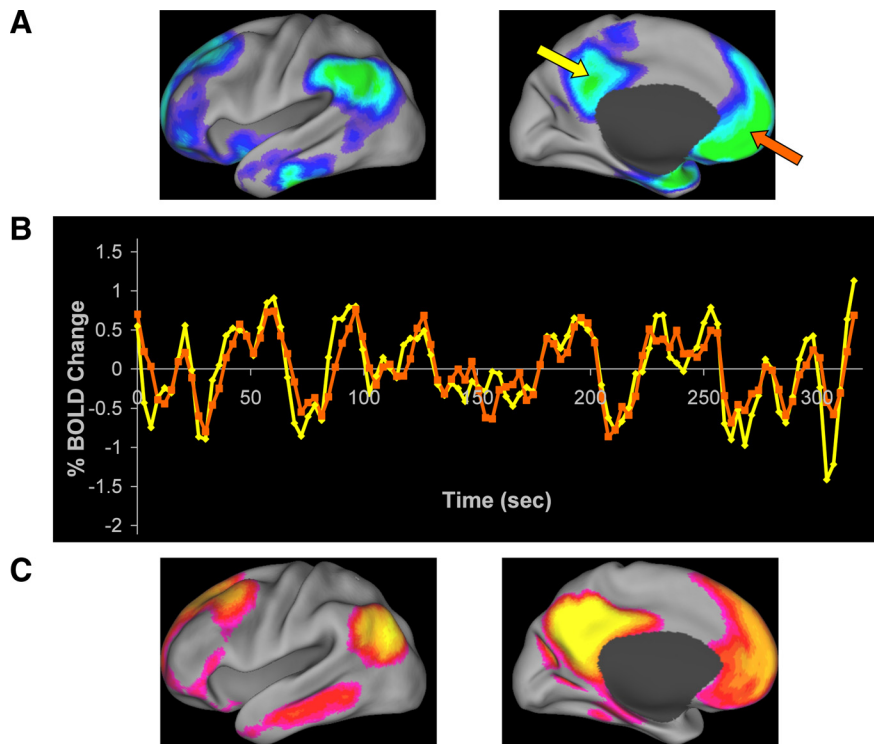
gested by the DMN was apparent. It was the discovery that the large-scale network organization of intrinsic activity also emerges from the study of patterns of spatial coherence in the spontaneous fluctuations (i.e., "noise") of the fMRI BOLD signal that provided the tool needed.

Spontaneous fluctuations in the fMRI BOLD signal

A prominent feature of fMRI is the noisiness of the raw BOLD signal (Fig. 1*B*), prompting researchers to average their data to increase the signal-to-noise ratio. As first shown by Bharat Biswal et al. (1995) in the human somatomotor system, a considerable fraction of this variance (i.e., noise) in the BOLD signal in the frequency range <0.1 Hz exhibits striking patterns of coherence within known brain systems (Fig. 1*C*).

The significance of this observation was brought forcefully to our attention when Michael Greicius et al. (2003) at Stanford University looked at the patterns of coherence in the DMN elicited by placing a region of interest in either the posterior cingulate cortex (Fig. 1*A*, yellow arrow) or the ventral medial prefrontal cortex (Fig. 1*A*, orange arrow). The resulting time–activity curves (Fig. 1*B*) reflected a pattern of coherence within the entire DMN (Fig. 1*C*). Similar patterns of resting state coherence have now been documented in most cortical systems in the human brain [for example, see the studies by Fox and Raichle (2007), Smith et al. (2009)], as well as in their subcortical connections (Zhang et al., 2008).

A number of additional observations make these surprising patterns of spatial coherence of interest. First, they appear to
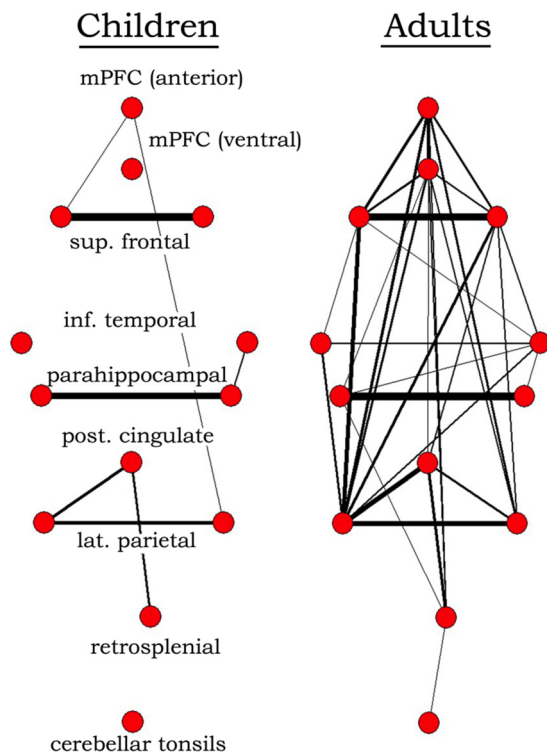
Figure 2. A graphic visualization of the correlation matrix within nodes of the DMN is presented in children (aged 7–9) on the left and adults (aged 21–31) on the right. The width of the line between two nodes depicts connection strength based on coherence of the resting-state fMRI BOLD signal (see Fig. 1). Noteworthy in these data is the differences in resting-state functional connectivity that accrue as the result of brain maturation. These data were reproduced with permission from D. A. Fair et al. (2008). inf., Inferior; lat., lateral; post., posterior; sup., superior.

transcend levels of consciousness, being present under anesthesia in humans (Greicius et al., 2008), monkeys (Vincent et al., 2007), and rats (Lu et al., 2007) (although in this study, as the level of anesthesia was increased the strength of coherence between the two cerebral hemispheres was diminished and finally eliminated). They are also present during the early stages of sleep in humans (Fukunaga et al., 2006; Larson-Prior et al., 2009). 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 (Christoff et al., 2009).

Second, resting state patterns of coherence respect patterns of anatomical connectivity in both monkeys (Vincent et al., 2007) and humans (Zhang et al., 2009), but they are not constrained by these anatomical connections (Vincent et al., 2007; Zhang et al., 2008). For example, the absence of monosynaptic connections between right and left primary visual cortex in the monkey (Vincent et al., 2007) 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 increases during development in humans. Illustrative in this regard is the DMN (Fig. 2). This observation is consistent with the role of experience and, possibly, spontaneous activity itself [for example, see the studies by Yuste (1997) and Huberman et al. (2008)] in sculpting and maintaining these functional relationships in the human brain.

Finally, spontaneous fluctuations in the BOLD signal contribute significantly to both variability in evoked signals (Fox et al., 2006) and to variability in the associated behavior (Fox et al.,

2007). 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.

The 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 the studies by Raichle and Mintun (2006), Khader et al. (2008), Logothetis (2008)]. The conclusion is that the fMRI BOLD signal is best correlated with local field potentials (LFPs). LFPs are complex signals arising from the integrated electrical activity in presynaptic and postsynaptic terminals of the brain and are recorded with microelectrodes placed within brain tissue. Brain electrical activity recorded from the scalp with EEG or from the surface of the brain with electrocorticography (ECoG) constitutes a summation of a population of LFPs. LFPs are usually described in terms of their band-limited frequency components (δ, 1–4 Hz; $\grave{e}$, 4–8 Hz; α, 8–12 Hz; β, 12–24 Hz; and, γ, 24–80 $^+$Hz).

Given the relationship between LFPs and BOLD, it is important here to focus on those LFP phenomena that exhibit frequencies similar to that of spontaneous BOLD fluctuations (i.e., 0.1–4.0 Hz). Two LFP phenomena fall into this category: fluctuations in the power of higher frequencies where particular attention has been paid to the gamma frequency band because of its association with cognition (Fries, 2009; Uhlhaas et al., 2009); and raw frequencies that approximate that of the spontaneous BOLD signal. These include the δ band (1–4 Hz) and infra-slow fluctuations or ISFs (Monto et al., 2008). ISFs are centered between 0.01 and 0.1 Hz (Vanhatalo et al., 2004; Monto et al., 2008) in the LFP frequency spectrum. These electrical potentials vary so slowly that they are sometimes called direct current (DC) potentials. ISFs are much less often recorded because of the amplifier requirements and concerns about artifacts (Khader et al., 2008). The δ frequency band and the ISFs have been combined and referred to as slow cortical potentials or SCPs (Rockstroh et al., 1989). Because it is likely that this envelope of frequencies is not functionally homogeneous (Steriade et al., 1993; Petersen et al., 2003; Watson et al., 2008) it is important to understand exactly what is reported. As these references indicate, an important additional phenomenon falls into this frequency range, namely "up and down states," which have important effects on neuronal function and behavior through rhythmic changes in cell excitability.

The research shows that the spontaneous fluctuations in the BOLD signal are best correlated with LFP activity in the range of the SCPs (Lu et al., 2007; He et al., 2008). Indeed, failure to consider SCPs in seeking electrical correlates of the BOLD signal have led some (Leopold, 2009; Sirotin and Das, 2009) to the erroneous conclusion that the BOLD signal and its metabolic/vascular underpinnings can operate independent of the brain's electrical activities. 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 REM and slow-wave sleep (He et al., 2008) and during anesthesia (Lu et al., 2007). In contrast, power in the gamma frequency band is only correlated spatially with the BOLD signal during wake and REM sleep (He et al., 2008) (see also Nir et al., 2008). This finding is consistent with the role of gamma-band coherence in the mental activities associated with conscious awareness (Fries, 2009; Uhlhaas et al., 2009).
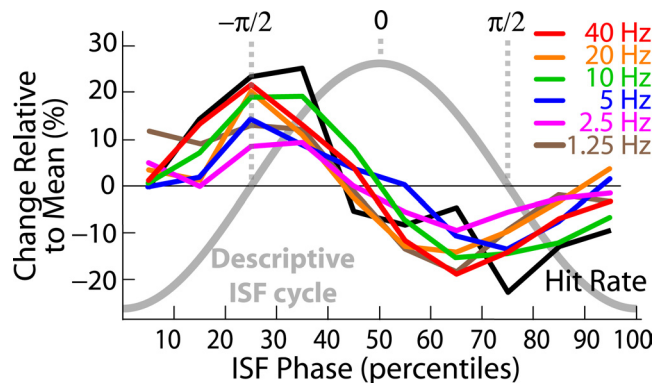
Figure 3. A depiction of cross-frequency coupling of EEG frequencies from 1 to 40 Hz within the phase of ISF. The thick gray line denotes a descriptive ISF cycle. It should be noted that the correlation of the 1–40 Hz oscillation amplitudes (colored lines) with the ISF is similar to that of the behavioral data (black line). This figure was reproduced with permission from S. Monto et al. (2008).

A broader view

Knowing that SCPs and spontaneous fluctuations in the BOLD signal are related provides a bridge to a highly relevant, rich, and diverse neurophysiologic literature on low-frequency oscillations/fluctuations [for example, see the studies by Rockstroh et al. (1989), Varela et al. (2001), Buzsáki and Draguhn (2004), Monto et al. (2008), and Schroeder and Lakatos (2009)]. Emerging from this extensive literature are several important themes.

First, SCPs and their BOLD counterpart (which includes optical imaging techniques) represent highly organized fluctuations in cortical excitability whose phase affects both evoked responses (Arieli et al., 1996; Fiser et al., 2004; Fox et al., 2006) and behavioral performance (Fox et al., 2007; Lakatos et al., 2008; Monto et al., 2008). Entrainment of SCPs to an expected, predictable stimulus [for example, see the studies by Lakatos et al. (2008), Montemurro et al. (2008), Gao et al. (2009), and Sirotin and Das (2009)] is an attractive means of matching predictions instantiated in intrinsic activity with the natural regularities of the environment (Bressler et al., 2008; Schroeder and Lakatos, 2008), a theme complementary to the concept of the "proactive" brain (Ingvar, 1985; Bar, 2009). An alternate state exists, as Schroeder and Lakatos (2008) posit when circumstances are unpredictable. Here, the brain may suppress low-frequency oscillations which, I would posit, may be seen as activity decreases in the DMN (Fig. 1A) (Fransson, 2006). This formulation provides one way of thinking about the give and take that exists between the DMN and what we have dubbed the task-positive network, a relationship instantiated even in the resting state (Fox et al., 2005, 2009; Popa et al., 2009).

Second, SCPs exhibit a remarkable relationship with other elements of the frequency spectrum of brain electrical activity (Monto et al., 2008) (Fig. 3) including the spiking activity of neurons (Montemurro et al., 2008). This cross-frequency coupling (i.e., nesting), with SCPs serving an overarching coordinating role within and across systems, provides the basis for integration in both space and time. One of the potential results of this, of course, might well be the emergence of consciousness (He and Raichle, 2009).

As we move forward, the scope of the inquiry will undoubtedly expand even further into the realm of cell biology where events related to ion channel proteins, synaptic receptors, components of signal transduction pathways (Marder and Goaillard, 2006), and even cellular redox states (Vern et al., 1998) exhibit temporal dynamics very similar to the work reviewed above. Integrating

across these many levels of analysis will obviously be challenging. Help will come from theoretical modeling approaches where creative work has already begun (Holcman and Tsodyks, 2006; Ghosh et al., 2008; Bullmore and Sporns, 2009). For all, the road ahead looks most exciting.

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