

The Brain's Default Mode Network

Marcus E. Raichle

Washington University School of Medicine, St. Louis, Missouri 63110;
email: marc@npg.wustl.edu

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Abstract

The brain's default mode network consists of discrete, bilateral and symmetrical cortical areas, in the medial and lateral parietal, medial prefrontal, and medial and lateral temporal cortices of the human, nonhuman primate, cat, and rodent brains. Its discovery was an unexpected consequence of brain-imaging studies first performed with positron emission tomography in which various novel, attention-demanding, and non-self-referential tasks were compared with quiet repose either with eyes closed or with simple visual fixation. The default mode network consistently decreases its activity when compared with activity during these relaxed nontask states. The discovery of the default mode network reignited a longstanding interest in the significance of the brain's ongoing or intrinsic activity. Presently, studies of the brain's intrinsic activity, popularly referred to as resting-state studies, have come to play a major role in studies of the human brain in health and disease. The brain's default mode network plays a central role in this work.

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INTRODUCTION

It has been 17 years since Shulman et al. (1997) first noted that a constellation of areas in the human cerebral cortex consistently reduced its activity while performing various novel, non-self-referential, goal-directed tasks (Shulman et al. 1997) when these tasks were compared with a control state of quiet repose (i.e., a resting state of eyes closed or visual fixation). That these localized reductions in activity were occurring at all was surprising, and their consistency across a wide variety of tasks made it all the more remarkable. The immediate challenge was to prove that these activity decreases were not due to activations in the resting state caused by experimentally uncontrolled cognition.

In 2001 we used positron emission tomography (PET) measurements of regional blood flow and oxygen consumption to show, by established metabolic criteria for activation, that areas consistently exhibiting activity reductions during task performance were not activated in the resting state. Our article was titled, “A Default Mode of Brain Function” (Raichle et al. 2001). We concluded that the brain areas observed to decrease their activity during attention-demanding, goal-directed tasks were not activated in the resting state but, rather, were indicative of a heretofore-unrecognized organization within the brain’s intrinsic or ongoing activity. Parenthetically, it had not occurred to us that others would anoint the constellation of areas exhibiting this unique behavior as the brain’s default mode network. The name obviously caught on.

Research on the brain’s default mode network and the brain’s intrinsic activity more generally has moved in many directions producing a literature that has become quite extensive. In preparing this review, we examined this literature to look for general trends, which we summarize in **Figure 1** for the interested reader. Rather than attempting a detailed analysis of this entire body of work, I focus on topics within it that have been of particular interest to me and that provide a sense of the future of this work.

This article begins with a review of our initial work because of its centrality in establishing the legitimacy of the brain’s default mode network.

DISCOVERY

By the early 1980s, PET began to receive serious attention as a potential functional neuroimaging device in human subjects (Raichle 2009). The study of human cognition with neuroimaging was aided greatly by the involvement of cognitive psychologists in the 1980s. Their experimental strategies for dissecting human behaviors fit well with the emerging capabilities of functional brain

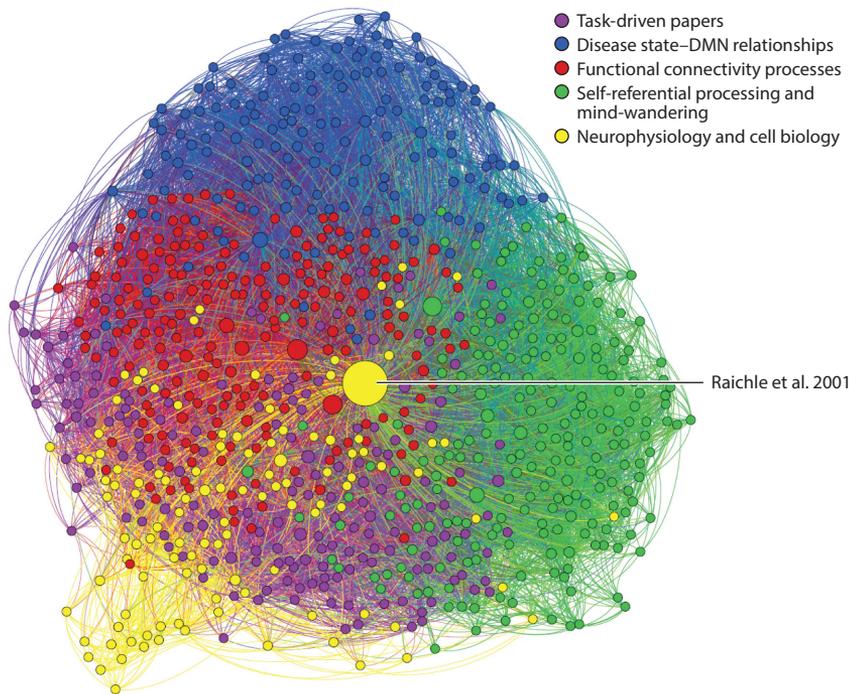


Figure 1

The evolving literature on the default mode network (DMN). Since the publication of “A Default Mode of Brain Function” (Raichle et al. 2001), nearly 3,000 papers have been published on this topic. To identify the broad topics of inquiry in the DMN field, we conducted a search for papers citing Raichle et al. (2001). The search returned 2,988 papers with digital object identifiers in the Information Sciences Institute (ISI) database. ISI was then used to return the reference list for each of the 2,988 papers. These data were used to construct a $2,988 \times 2,988$ binary adjacency matrix, in which each element (i, j) indicated whether paper i cited paper j . Once constructed, the adjacency matrix was imported into Gephi, the open-source network visualization tool. To simplify the network graph, all nodes with degrees (number of citations from other papers in the network) less than or equal to 20 were removed. The number of network modules was then determined using a fast, modularity-optimization method included within Gephi. Each node was assigned to a specific module, and each module was assigned a unique color for visualization purposes. A topic was assigned to each module by identifying the focus of the highest cited papers within each module. Finally, the size of each node within the graph was weighted according to the node degree. This algorithm represents a data-driven approach to identify clusters of papers with common citation patterns. Each cluster represents a broad topic of investigation in the DMN field. The purple cluster contains task-driven papers typical of cognitive neuroscience. Papers in the blue cluster are broadly focused on the relationship between disease states and the DMN. Papers in the red cluster concentrate on functional connectivity processes. The green cluster is composed of papers on self-referential processing and mind wandering. Articles in the yellow cluster are related to neurophysiology and cell biology. At the center, in yellow, is Raichle et al. (2001).

imaging (Posner & Raichle 1994) 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 (e.g., see Price 2012).

For the better part of the decade following the introduction of subtractive methodology to neuroimaging, the vast majority of changes reported in the literature were activity increases (or activations, to use the jargon of the cognitive neuroscience field). 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 not violated. 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 visual field, whereas the task state 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 the 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 be altered by introducing an additional process.

Functional neuroimaging helped address the issue 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 (Gusnard & Raichle 2001). Investigators clearly showed, 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 or anyone else for the experiment in which the control state was rest (i.e., simply lying quietly but awake in a scanner with eyes closed or visually fixating on a crosshair).

One of the guiding principles of cognitive psychology at that time was that a control state must explicitly contain all the elements of the associated task state other than the one element of interest (e.g., seeing a word versus reading the same word). Using a control state of rest would clearly seem to violate that principle. Despite our commitment to the strategies of cognitive psychology in our experiments, we routinely obtained resting-state scans in all our experiments, a habit largely carried over from experiments involving simple sensory stimuli (Fox et al. 1986) in which the control state was simply the absence of the stimulus (i.e., a resting state). At some point in our work, and I do not recall the motivation, I began to look at the resting-state scans minus the task scans. What immediately caught my attention was the fact that regardless of the task under investigation, the activity decreases almost always included the posterior cingulate and the adjacent precuneus.

The first formal characterization of task-induced activity decreases from a resting state was a meta-analysis of 9 PET studies, involving 134 subjects, by my colleague Gordon Shulman (Shulman et al. 1997). This study generated an iconic image of a network of cortical areas that decreased in activity while performing various attention-demanding, largely non-self-referential tasks (**Figure 2**). The unique identity of this network was confirmed a short time later by Jeffrey Binder and colleagues at the Medical College of Wisconsin (Binder et al. 1999) and Bernard Mazoyer and his colleagues in France (Mazoyer et al. 2001). Similar observations are now an everyday occurrence in laboratories worldwide as investigators seek to understand the role of this network in brain function (**Figure 1**).

Finding a network of brain areas frequently seen to decrease its activity during attention-demanding tasks was both surprising and challenging: surprising because the areas involved had not previously been recognized as a system in the same way that 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. Were they simply activations present in the resting state? And why should they appear in both PET and functional magnetic resonance imaging (fMRI)? Two things came to mind that offered a way forward.

First, the manner in which functional imaging was conducted with fMRI carried with it a physiological definition of activation that could be measured with PET. This definition arose from the quantitative circulatory and metabolic PET studies, which demonstrated that when brain activity increases transiently above a resting state, blood flow increases more than oxygen consumption (reviewed in Raichle & Mintun 2006). As a result, the amount of oxygen in blood

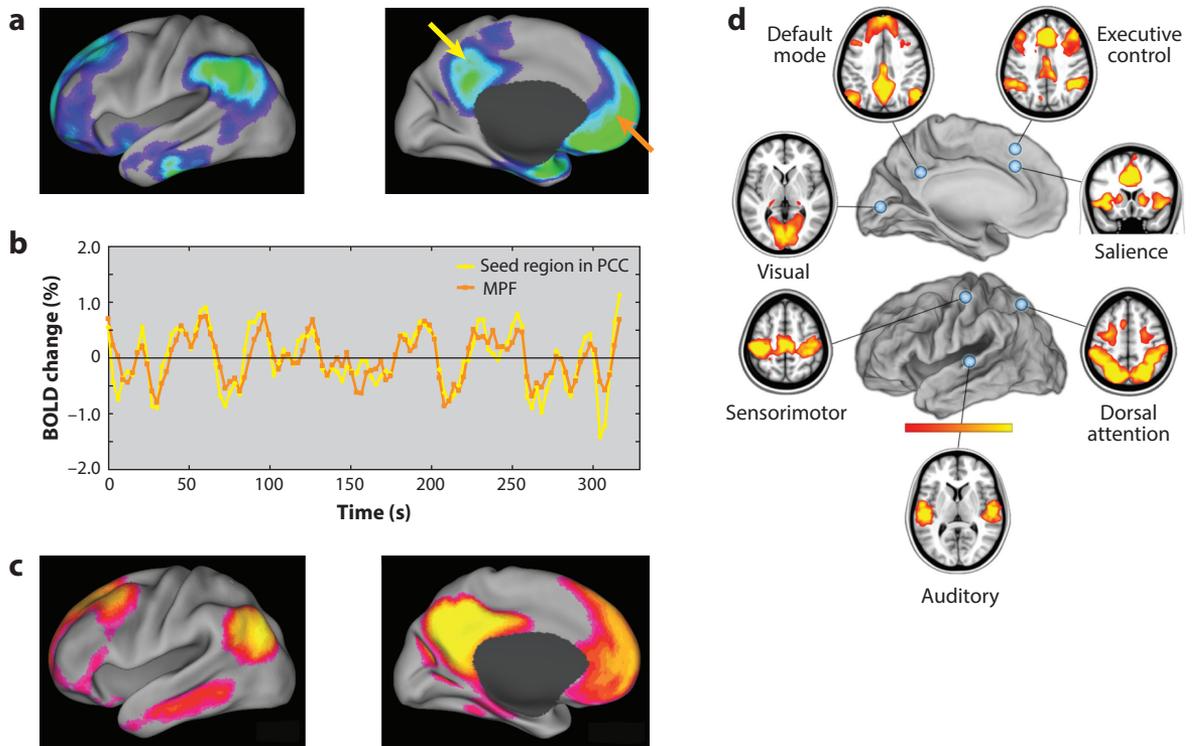


Figure 2

Views of the default mode network from the perspective of activity decreases during task performance (*a*) and resting-state functional connectivity (*b* and *c*), and in relation to other networks that exhibit resting-state patterns of functional connectivity (*d*). The yellow and orange arrows in panel *a* denote the source of the BOLD resting-state, time-activity curves shown in panel *b*. Abbreviations: BOLD, blood-oxygen-level-dependent; MPF, medial prefrontal cortex; PCC, precuneus and posterior cingulate cortex. Elements of this figure were adapted from Raichle (2010, 2011).

increases locally as the ratio of oxygen consumed to oxygen delivered falls. This ratio is known as the oxygen extraction fraction (OEF). Activation can then be defined physiologically as a transient local decrease in the OEF, which results in a local increase in oxygen availability.

The practical consequence of this observation was to lay the physiological basis for fMRI using blood-oxygen-level-dependent (BOLD) contrast (Bandettini et al. 1992, Frahm et al. 1992, Kwong et al. 1992, Ogawa et al. 1990, Thulborn et al. 1982). Using this quantitative definition of activation, we asked whether activation was present in a resting state. But activation must be defined relative to something. How was a comparison 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 the second critical piece of physiological information. Researchers using PET to quantitatively measure 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 resting quietly in a PET scanner (Lebrun-Grandie et al. 1983, Raichle et al. 2001). This is observed despite a nearly fourfold difference in oxygen consumption and blood flow between gray and white matter and variations of greater than 30% within gray matter. 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 hypothesize that if this observation (i.e., a uniform OEF at rest) was correct then activations, as defined above, were likely absent in the resting state. We decided to test this hypothesis.

Using PET to quantitatively assess regional OEF, we examined two groups of normal subjects in the resting state, confining our analysis initially to the regions shown in **Figure 2**. We found no evidence that these cortical areas were activated when compared with other areas (i.e., the OEF was uniform). We concluded that the regional decreases observed commonly during task performance represented the presence of an organized functionality that was ongoing in the resting state and that this functionality was attenuated in the presence of an attention-demanding, non-self-referential task. On the basis of this perspective, we titled our paper “A Default Mode of Brain Function,” not suspecting at the time that the focus of our analysis would become known as the brain’s default mode network. We (Drevets et al. 1995) and others (Amedi et al. 2005, Ghatan et al. 1998, Kawashima et al. 1995, Shmuel et al. 2006, Smith et al. 2000, Somers et al. 1999) had noted other more task-specific deactivations, consistent with the idea that a default mode of brain function is broadly based across all brain systems (a hypothesis that received substantial support from functional studies of the brain’s resting state).

RESTING STATE

The discovery of the default mode network 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 default mode network, could be revealed by studying spatial coherence patterns in the spontaneous fluctuations (i.e., noise) in the fMRI BOLD signal during the resting state (for more detailed reviews, see Raichle 2010, 2011).

A prominent feature of fMRI is the noise in the raw BOLD signal. This has prompted researchers to average their data to increase the signal and reduce noise. As first shown by Bharat Biswal and colleagues (1995) in the human somatomotor system, a considerable fraction of this noise exhibits striking patterns of coherence within known brain systems.

The significance of this observation was brought forcefully to our attention when Michael Greicius and colleagues considered the coherence patterns in the default mode network (Greicius et al. 2003) elicited by placing a region of interest in either the posterior cingulate cortex (**Figure 2a**, *yellow arrow*) or the ventral medial prefrontal cortex (**Figure 2a**, *orange arrow*). The resulting time-activity curves (**Figure 2b**) reflected a coherence pattern within the entire default mode network (**Figure 2c**). Similar patterns of resting-state coherence have now been documented in most cortical systems in the human brain (**Figure 2d**; for recent reviews, see Fox & Raichle 2007, Smith et al. 2009, Snyder & Raichle 2012) as have their subcortical connections (Zhang et al. 2008).

FUNCTIONS

The Components of the Default Mode Network

A frequently asked question, which has an incomplete answer at this time, is, “What is the function of the default mode network?” There are several ways to approach answering the question. I begin by summarizing what we know about the behavioral functions associated with the major anatomical subdivisions of the default mode network in humans and note the themes that have emerged from this perspective (see also Andrews-Hanna et al. 2010b). I then tackle some of the more fundamental insights that have emerged from studies of the default mode network and intrinsic activity that inject a note of caution in interpreting too literally the behavioral data obtained from humans.

The default mode network is divided into roughly three major subdivisions: the ventral medial prefrontal cortex; the dorsal medial prefrontal cortex; and the posterior cingulate cortex and adjacent precuneus plus the lateral parietal cortex (approximately Brodmann area 39). These general subdivisions are easily appreciated in **Figure 2a**. Another area that has been associated frequently with the default mode network is the entorhinal cortex.

The ventral medial prefrontal cortex (VMPC) is an area about which much is known in terms of its cytoarchitectonics and anatomical connectivity, thanks to the work of such people as Joel Price (e.g., see Ongür & Price 2000) and Helen Barbas (Barbas 2007). Although most of this work has been done in nonhuman primates, evidence suggests that most of what was learned from nonhuman primates exists in humans (Ongür & Price 2000). From this work we know that the VMPC is a critical element in a network of areas that receive sensory information from the external world and the body via the orbital frontal cortex and convey that information to structures such as the hypothalamus, the amygdala, and the periaqueductal gray matter of the midbrain. This anatomical circuitry alone has much to say about the potential role of this component of the default mode network as a sensory-visceromotor link concerned with social behavior, mood control, and motivational drive, all of which are important components of an individual's personality.

Since the publication of the paradigmatic patient Phineas Gage (for a detailed review of this fascinating case, see Damasio et al. 1994), there have been many reports of striking personality changes and deviant social behavior appearing in premorbidly normal individuals after damage to the VMPC (Bechara et al. 1997, Damasio & Van Hoesen 1983).

Imaging studies in normal individuals have shown that the emotional state of the subject has a direct effect on the activity level in the VMPC component of the default mode network. In studies of performance anxiety induced by task difficulty, the degree to which VMPC decreased its activity in concert with other elements of the default mode network was directly proportional to the subject's anxiety level while performing the task. With high anxiety, the VMPC decreased little if at all. As anxiety decreased with practice on the task activity so too did activity in the VMPC (Simpson et al. 2001b). In a companion study, Simpson et al. (2001a) induced anticipatory anxiety in normal subjects by having them anticipate a painful shock to the fingers of one hand. Activity decreases in the VMPC were inversely correlated with anxiety self-rating, such that the least anxious subjects exhibited the largest reductions, whereas the most anxious subjects showed no significant reduction or a slight increase. Taken together, these two studies illustrate that activity in the VMPC component of the default mode network reflects a dynamic balance between focused attention and a subject's emotional state and may occur from a functionally active baseline (i.e., a default state).¹

Elements of the VMPC actually increase their activity in association with disruptions in bodily homeostasis. This change is nicely illustrated in association with the autonomic responses to stepped hypoglycemia [i.e., increase in heart rate and plasma levels of epinephrine, norepinephrine, and pancreatic polypeptide (Teves et al. 2004)], even when typical symptoms of hypoglycemia are mild.

Finally, the discovery that the agranular, subgenual portion of the VMPC had reduced blood flow and glucose consumption in addition to a reduced volume in familial bipolar and unipolar

¹When dealing with an active baseline state, the nature of a control state becomes critical in interpreting the effect of a task on brain activity. Thus, if an attention-demanding control task is used as a baseline, it is likely to be associated with a reduction in activity within the VMPC. When this reduction is coupled with a task of interest that also incorporates an element of emotional processing, the difference between the baseline established by the control task and the task of interest will, in all likelihood, appear as an increase. Thus, what others report as an increase should, on occasion, be regarded more properly as a decrease, which more accurately reflects the changes in neural activity (Gusnard & Raichle 2001).

depressives (Drevets et al. 1997) has led not only to greater insight into the functional anatomy of mood disorders but also to treatment of intractable depression by stimulating this area with chronically implanted electrodes (Mayberg et al. 2005).

Although it is immediately adjacent, the dorsal medial prefrontal cortex (DMPC) can be distinguished from the VMPC by its association with self-referential judgments. An example of this comes from our earlier work (Gusnard et al. 2001) in which subjects were asked to make a self-referential judgment (i.e., pleasant or unpleasant) about emotionally valenced pictures from the International Affective Picture System (IAPS) (Lang et al. 1997). Increases in activity were observed in the DMPC and accompanied by decreases in the VMPC, consistent with the fact that attention-demanding tasks attenuate emotional processing.

The posterior cingulate cortex and the medial precuneus are prominent features of the default mode network and were the first to come to our attention. These areas, along with the lateral parietal components of the default mode network, have been consistently associated with successful recollection of previously studied items (for a review of this literature, see Vincent et al. 2006). The same paper presents resting-state functional connectivity MRI, demonstrating a significant relationship between the hippocampal formation and the posterior elements of the default mode network. In a subsequent study, Shannon and colleagues (2013) demonstrated that this hippocampal-parietal memory network exhibits remarkable diurnal variation being strongly present in the evening and absent in the morning after a normal night's sleep. This finding suggests that the relationship between the hippocampal formation and the posterior elements of the default mode network are sensitive to the cumulative experiences of wake and that sleep resets this relationship each day. Parenthetically, these dramatic diurnal variations in the functional connectivity of the default mode network should be considered when planning experiments designed to study the role of the default mode network in memory and learning.

To summarize, data from humans suggest that the default mode network instantiates processes that support emotional processing (VMPC), self-referential mental activity (DMPC), and the recollection of prior experiences (posterior elements of the default mode network). These functional elements of the default mode network can be differentially affected during task performance by the nature of the task [e.g., presence or absence of an emotional component or an element of self-reference (Andrews-Hanna et al. 2010b, Gusnard et al. 2001)]. However, regardless of the details of a particular task, the default mode network always begins from a baseline of high activity, with small changes in this activity made to accommodate the requirements of a particular task. The available evidence indicates that the functions of the default mode network are never turned off but, rather, carefully enhanced or attenuated.

Spontaneous Cognition

Because the default mode network was first identified with the resting state, it has been appealing to many (**Figure 1**) to associate default mode network functionality with the mental state that commonly accompanies a relaxed state of quiet repose, namely daydreaming, mind wandering, or stimulus-independent thoughts (e.g., see Andrews-Hanna et al. 2010a). Furthermore, spontaneous cognition routinely involves thoughts about one's personal past and future, which fits comfortably with identified functionality in the default mode network in humans (see above). However, several factors lead this author to believe that focusing solely on spontaneous cognition ignores the possibility of a much more fundamental role for the default mode network in brain function. Following are observations to support this viewpoint.

Spontaneous activity, in contrast with spontaneous cognition, is the major factor contributing to the high cost of brain function in humans. Although the adult human brain is only 2% of the

body weight, it consumes 20% of the body's energy budget (Clarke & Sokoloff 1999). Relative to the high rate of ongoing energy consumption, which is devoted largely to functional activity (reviewed in Raichle & Mintun 2006), the additional energy consumption associated with task-evoked changes in brain activity is small, usually less than 5% locally (Raichle & Mintun 2006). There is no reason to suppose that unconstrained thoughts are more energy demanding than are constrained ones, leaving much to be explained about the nature of spontaneous activity.

Additionally, the general features of the default mode network have now been identified in the monkey (Vincent et al. 2007), cat (Popa et al. 2009), rat (Lu et al. 2012), and mouse (Stafford et al. 2014). Visually comparing the topography of the default mode network in the rat, monkey, and human (**Figure 3**) evokes a sense of similarity, but the details show clear differences. For example, in the human, the lateral parietal component is approximately in Brodmann area 39. Monkeys do not have a comparable parietal area. In the rat, the lateral parietal component resides in primary sensory cortices. Similarities are most evident along the midline, but here again, differences emerge from the details. Regardless of the details of the anatomy, if one accepts the idea that a default mode network is an integral component of the mammalian brain, which remains to be firmly established, it seems clear that the mental states of rats and humans, let alone nonhuman primates,

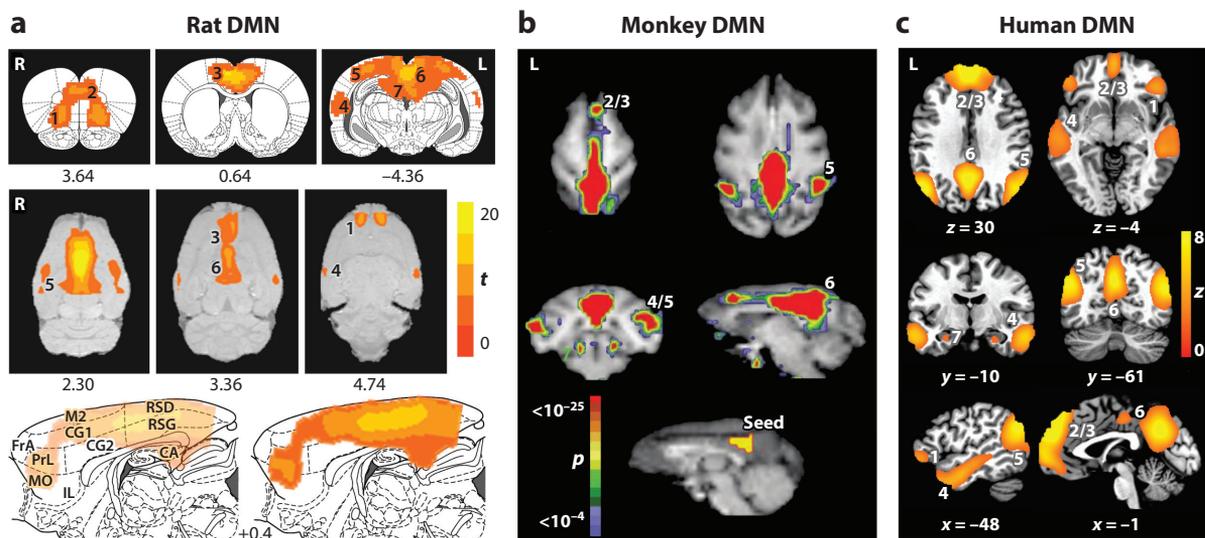


Figure 3

Comparison of the default mode network (DMN) in rat, monkey, and human. For the rat DMN (*a*, top panel): significant clusters include 1, orbital cortex; 2, prelimbic cortex (PrL); 3, cingulate cortex (CG1, CG2); 4, auditory/temporal association cortex (Au1, AuD, AuV, TeA); 5, posterior parietal cortex (PPC); 6, retrosplenial cortex, which corresponds to the posterior cingulate cortex (PCC) in humans; 7, hippocampus (CA1). The middle panel shows the connectivity maps in the axial plane. Note the strong connectivity between the prefrontal and posterior cingulate cortices, which can best be visualized in the sagittal plane (*bottom*, medial-lateral: +0.4 mm). Other abbreviations: FrA, frontal association cortex; MO, medial orbital cortex; R, right; RSG/RSD, granular/dysgranular retrosplenial cortex. Color bar indicates t scores ($N = 16$, thresholded at $t > 5.6$, corrected $p < 0.05$). Numbers below images are approximate coordinates relative to bregma. For the monkey DMN (*b*): 2/3, dorsal medial prefrontal cortex; 4/5, lateral temporoparietal cortex (including area 7a and superior temporal gyrus); 6, posterior cingulate/precuneus cortex; and 7, posterior parahippocampal cortex. The monkey DMN map was derived using the cross-correlation method with the seed region as shown in the figure. For human DMN (*c*): significant clusters include 1, orbital frontal cortex; 2/3, medial prefrontal cortex/anterior cingulate cortex; 4, lateral temporal cortex; 5, inferior parietal lobe; 6, posterior cingulate/retrosplenial cortex; 7, hippocampus/parahippocampal cortex ($N = 39$, thresholded at $z > 2.1$, corrected $p < 0.05$). This figure was adapted courtesy of *PNAS* and Lu et al. (2012).

differ substantially. A future research focus on the evolution of the default mode network will likely help us to understand its functions more deeply.

Finally, patterns of resting-state functional connectivity appear to 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) and also during the early stages of sleep in humans (Fukunaga et al. 2006, Larson-Prior et al. 2009). These observations make it unlikely that the coherence patterns and the intrinsic activity they represent are primarily the result of unconstrained, conscious cognition [i.e., mind wandering or daydreaming (Christoff et al. 2009)].

Balance

I turn now to two examples from our own work that have influenced my thinking about the default mode network. Both relate to the concept of a functional balance between the default mode network and other brain systems and the resulting implications for our understanding of the function of the default mode network.

The first example comes from a highly cited paper in our early work on the default mode network and resting-state functional connectivity (Fox et al. 2005). This paper called attention to the presence of anticorrelations in the resting state between the default mode network and what we dubbed the “task-positive network”. The latter consisted of what is more conventionally called the dorsal attention network (DAN; Corbetta & Shulman 2002, Fox et al. 2006) and elements of frontoparietal control networks (Fair et al. 2007, Seeley et al. 2007). Even though controversy surrounded the data-processing procedures that revealed this relationship (for a detailed discussion, see Fox et al. 2009), the intuitive appeal of the observation has remained strong because it captured a relationship between the default mode network and the DAN that had been well characterized by the performance of novel, attention-demanding tasks (i.e., increases in the DAN accompanied by decreases in the default mode network). An apt metaphor that often comes to mind is “losing one’s self in one’s work.”

Our work on the anticorrelations not only reinforced interest in resting-state imaging studies with fMRI of the brain’s intrinsic activity, but also stimulated an important neurophysiological exploration of this relationship by Pare and his colleagues (Popa et al. 2009). Instrumenting cats with chronic indwelling electrodes, investigators recorded unit activity and local field potentials in the cat homologues of the default mode network and the DAN across the sleep-wake cycle and during variations in attentional demands. Noteworthy was the observation that anticorrelations between the two networks occurred ~20% of the time, whereas correlations were present for the remaining 80% of the time; these observations suggested a variable relationship between cooperation and antagonism. Furthermore, during increased attentional demands, firing rates within the cat default mode network actually increased despite a reduction in local field potential (LFP) power, which suggests that the default mode network may play an enhanced role during increased attentional demands.

To fully appreciate the potential significance of the work by Pare and colleagues (Popa et al. 2009), one must note a critical difference with the data manipulations employed in resting-state fMRI, which first revealed the anticorrelations between the default mode network and DAN (Fox et al. 2005; a more detailed discussion is presented in Fox et al. 2009). In the fMRI experiment, the data were prepared by removing a signal common to all areas of the brain (i.e., the so-called global signal). By doing so, correlations between the default mode network and the DAN, if hidden within this signal, would be removed. In the work of Pare and colleagues, no such maneuver was performed. If, in fact, this observation explains the difference between the neurophysiological

observations in cats (i.e., anticorrelations present only part of the time) and those in humans (i.e., anticorrelations present all the time in the resting state), then our understanding of the relationship between the default mode network [i.e., a self-centered predictive model of the world (Raichle 2010)] and the DAN (i.e., detector of novel environmental features) must be reconsidered. Is attention, as conventionally defined, limited to conscious perception of environmental novelty? Or does attention also involve a nonconscious component that orients us to the predictive regularities of the environment upon which we base most of our behaviors? We must take a more nuanced approach to our understanding of the resources of the brain in which networks such as the default mode network and the DAN are always “on” but adjusting subtly their relationships. Understanding the dialogue between the default mode network and the DAN is likely a critical place to begin this work.

The second example is a resting-state fMRI study we performed on 107 juvenile offenders (Shannon et al. 2011), in whom we could relate with remarkable accuracy organizational features of their brains to their levels of impulsivity. In this study, we found that in less impulsive juveniles and normal controls, motor-planning regions were correlated with brain networks associated with spatial attention and executive control. In more impulsive juveniles, these motor-planning regions were correlated with the default mode network. Our results suggested that the balance between the default mode network and the networks controlling spatial attention and executive control was critical in determining the output of cortical motor-planning areas and, ultimately, the subject’s level of impulsivity. To further explore the relationship between impulsivity and neural development, we studied functional connectivity of the same motor-planning regions in 95 typically developing individuals across a wide age span. The change in functional connectivity with age mirrored that of impulsivity: Younger subjects tended to exhibit functional connectivity similar to the more impulsive incarcerated juveniles, whereas older subjects exhibited a less impulsive pattern. It seems reasonable to suggest that the default mode network is playing a critical role in the organization and expression of preplanned, reflexive behaviors that are critical to our existence in a complex world but when unconstrained by the social and physical constraints of the environment become impulsive and destructive. These opposing forces are captured nicely in the book by Daniel Kahneman, *Thinking, Fast and Slow* (Kahneman 2011).

Anatomy

Finally, the potential importance of the default mode network to brain organization is captured in studies focused on its connective anatomy. This is exemplified by the work of Hagmann and colleagues (2008). By using diffusion spectrum imaging, these researchers noninvasively mapped cortico-cortical axonal pathways in humans. The analysis of their data revealed a structural core within the posterior medial and parietal cerebral cortices as well as distinct temporal and frontal modules. Brain regions within this structural core constitute connector hubs that link all major structural models. The structural core they identified contained regions that form the posterior components of the default mode network. They also compared measures of structural connectivity with measures of resting-state functional connectivity and concluded that there was a substantial correspondence between the two measures. The conclusion they drew from their work was that this structural core, centered as it were on the posterior elements of the default mode network, is important for functional integration. Additional studies of this type (e.g., see van den Heuvel & Sporns 2011) complement and expand on the perspective put forth by Hagmann and colleagues and places the default mode network at the center of the brain’s organization both structurally and functionally.

SUMMARY

The brain's default mode network is a relative newcomer to discussions about brain organization and function, but it invigorates discussions that go back many years regarding the basic nature of brain function. One view espoused by Sherrington (1906) posited that the brain is primarily reflexive, driven by the momentary demands of the environment. The other view was put forth by Sherrington's student T. Graham Brown (1914) that the brain's operations were mainly intrinsic, involving the acquisition and maintenance of information for interpreting, responding to, and even predicting environmental demands (for a more recent perspective, see Llinas 2001, Raichle 2010, Yuste et al. 2005). The latter view clearly seems to be on the ascendency, with a rapidly increasing interest in the ongoing activity of the brain, which must construct and maintain an operational model of the world and implement it on the basis of highly impoverished sensory information (Raichle 2010). One of the features of that activity is its large-scale functional organization, in which the default mode network appears to be playing a commanding role. Our challenge is to better define that role, which will likely force us to rethink well-established concepts such as attention and to seek the involvement of scientists at all levels of inquiry. Although this review did not consider issues from a cellular perspective, such views are commanding increasing attention, even as they relate to the default mode network in humans (e.g., see Goyal et al. 2014). Inspection of **Figure 1** demonstrates a major interest in the role of intrinsic activity, and particularly the default mode network, in disease. This is likely to be an exciting frontier in the years ahead as we take a fresh look at such diseases as Alzheimer's (Buckner et al. 2008, Vlassenko et al. 2010) and depression (Drevets et al. 1997, Greicius et al. 2004, Mayberg et al. 2005), which defy simple explanation. The default mode network is likely to figure prominently in all these areas of inquiry, the more so as we come to understand its true role in brain function.

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LITERATURE CITED

- Amedi A, Malach R, Pascual-Leone A. 2005. Negative BOLD differentiates visual imagery and perception. *Neuron* 48:859–72
- Andrews-Hanna JR, Reidler JS, Huang C, Buckner RL. 2010a. Evidence for the default network's role in spontaneous cognition. *J. Neurophysiol.* 104:322–35
- Andrews-Hanna JR, Reidler JS, Sepulcre J, Poulin R, Buckner RL. 2010b. Functional-anatomic fractionation of the brain's default network. *Neuron* 65:550–62
- Bandettini PA, Wong EC, Hinks RS, Tikofsky RS, Hyde JS. 1992. Time course EPI of human brain function during task activation. *Magn. Reson. Med.* 25:390–97
- Barbas H. 2007. Specialized elements of orbitofrontal cortex in primates. *Ann. N. Y. Acad. Sci.* 1121:10–32
- Bechara A, Damasio H, Tranel D, Damasio AR. 1997. Deciding advantageously before knowing the advantageous strategy. *Science* 275:1293–95
- Binder JR, Frost JA, Hammeke TA, Bellgowan PS, Rao SM, Cox RW. 1999. Conceptual processing during the conscious resting state: A functional MRI study. *J. Cogn. Neurosci.* 11:80–93
- Biswal B, Yetkin FZ, Haughton VM, Hyde JS. 1995. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn. Reson. Med.* 34:537–41
- Brown TG. 1914. On the nature of the fundamental activity of the nervous centres; together with an analysis of the conditioning of rhythmic activity in progression, and a theory of the evolution of function in the nervous system. *J. Physiol.* 48:18–46

- Buckner RL, Andrews-Hanna JR, Schacter DL. 2008. The brain's default network: anatomy, function, and relevance to disease. *Ann. N. Y. Acad. Sci.* 1124:1–38
- Christoff K, Gordon AM, Smallwood J, Smith R, Schooler JW. 2009. Experience sampling during fMRI reveals default network and executive system contributions to mind wandering. *PNAS* 106:8719–24
- Clarke DD, Sokoloff L. 1999. Circulation and energy metabolism of the brain. In *Basic Neurochemistry. Molecular, Cellular and Medical Aspects*, ed. BW Agranoff, GJ Siegel, pp. 637–70. Philadelphia: Lippincott-Raven
- Corbetta M, Shulman GL. 2002. Control of goal-directed and stimulus-driven attention in the brain. *Nat. Rev. Neurosci.* 3:201–15
- Damasio AR, Van Hoesen GW. 1983. Emotional disturbances associated with focal lesions of the limbic frontal lobe. In *Neuropsychology of Human Emotion*, ed. KM Heilman, P Satz, pp. 85–110. New York: Guilford Press
- Damasio H, Grabowski T, Frank R, Galaburda AM, Damasio AR. 1994. The return of Phineas Gage: clues about the brain from the skull of a famous patient. *Science* 264:1102–5
- Drevets WC, Burton H, Videen TO, Snyder AZ, Simpson JR Jr., Raichle ME. 1995. Blood flow changes in human somatosensory cortex during anticipated stimulation. *Nature* 373:249–52
- Drevets WC, Price JL, Simpson JR Jr., Todd RD, Reich T, et al. 1997. Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* 386:824–27
- Fair DA, Dosenbach NU, Church JA, Cohen AL, Brahmbhatt S, et al. 2007. Development of distinct control networks through segregation and integration. *PNAS* 104:13507–12
- Fox MD, Corbetta M, Snyder AZ, Vincent JL, Raichle ME. 2006. Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. *PNAS* 103:10046–51
- Fox MD, Raichle M. 2007. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat. Rev. Neurosci.* 8:700–11
- Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. 2005. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *PNAS* 102:9673–78
- Fox MD, Zhang D, Snyder AZ, Raichle ME. 2009. The global signal and observed anticorrelated resting state brain networks. *J. Neurophysiol.* 101:3270–83
- Fox PT, Mintun MA, Raichle ME, Miezin FM, Allman JM, Van Essen DC. 1986. Mapping human visual cortex with positron emission tomography. *Nature* 323:806–9
- Frahm J, Bruhn H, Merboldt KD, Hänicke W. 1992. Dynamic MR imaging of human brain oxygenation during rest and photic stimulation. *J. Magn. Reson. Imaging* 2:501–5
- Fukunaga M, Horovitz SG, van Gelderen P, de Zwart JA, Jansma JM, et al. 2006. Large-amplitude, spatially correlated fluctuations in BOLD fMRI signals during extended rest and early sleep stages. *Magn. Reson. Imaging* 24:979–92
- Ghatan PH, Hsieh JC, Petersson KM, Stone-Elander S, Ingvar M. 1998. Coexistence of attention-based facilitation and inhibition in the human cortex. *NeuroImage* 7:23–29
- Goyal MS, Hawrylycz M, Miller JA, Snyder AZ, Raichle ME. 2014. Aerobic glycolysis in the human brain is associated with development and neotenus gene expression. *Cell Metab.* 19:49–57
- Greicius MD, Kiviniemi V, Tervonen O, Vainionpää V, Alahuhta S, et al. 2008. Persistent default-mode network connectivity during light sedation. *Hum. Brain Mapp.* 29:839–47
- Greicius MD, Krasnow B, Reiss AL, Menon V. 2003. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *PNAS* 100:253–58
- Greicius MD, Srivastava G, Reiss AL, Menon V. 2004. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *PNAS* 101:4637–42
- Gusnard DA, Akbudak E, Shulman GL, Raichle ME. 2001. Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *PNAS* 98:4259–64
- Gusnard DA, Raichle ME. 2001. Searching for a baseline: functional imaging and the resting human brain. *Nat. Rev. Neurosci.* 2:685–94
- Hagmann P, Cammoun L, Gigandet X, Meuli R, Honey CJ, et al. 2008. Mapping the structural core of human cerebral cortex. *PLOS Biol.* 6:e159
- Kahneman D. 2011. *Thinking, Fast and Slow*. New York: Penguin
- Kawashima R, O'Sullivan BT, Roland PE. 1995. Positron-emission tomography studies of cross-modality inhibition in selective attentional tasks: closing the "mind's eye." *PNAS* 92:5969–72

- Kwong KK, Belliveau JW, Chesler DA, Goldberg IE, Weisskoff RM, et al. 1992. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *PNAS* 89:5675–79
- Lang PJ, Bradley MM, Cuthbert BN. 1997. *International Affective Picture System (IAPS): Technical Manual and Affective Ratings*. Gainesville, Fla.: Natl. Inst. Ment. Health (NIMH) Cent. Study Emot. Atten.
- Larson-Prior LJ, Zempel JM, Nolan TS, Prior FW, Snyder AZ, Raichle ME. 2009. Cortical network functional connectivity in the descent to sleep. *PNAS* 106:4489–94
- Lebrun-Grandié P, Baron JC, Soussaline F, Loch'h C, Sastre J, Bousser MG. 1983. Coupling between regional blood flow and oxygen utilization in the normal human brain. A study with positron tomography and oxygen 15. *Arch. Neurol.* 40:230–36
- Llinas RR. 2001. *I of the Vortex: From Neurons to Self*. Cambridge, MA: MIT Press
- Lu H, Zou Q, Gu H, Raichle ME, Stein EA, Yang Y. 2012. Rat brains also have a default mode network. *PNAS* 109:3979–84
- Lu H, Zuo Y, Gu H, Waltz JA, Zhan W, et al. 2007. Synchronized delta oscillations correlate with the resting-state functional MRI signal. *PNAS* 104:18265–69
- Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, et al. 2005. Deep brain stimulation for treatment-resistant depression. *Neuron* 45:651–60
- Mazoyer B, Zago L, Mellet E, Bricogne S, Etard O, et al. 2001. Cortical networks for working memory and executive functions sustain the conscious resting state in man. *Brain Res. Bull.* 54:287–98
- Ogawa S, Lee TM, Kay AR, Tank DW. 1990. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *PNAS* 87:9868–72
- Ongür D, Price JL. 2000. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cereb. Cortex* 10:206–19
- Popa D, Popescu AT, Pare D. 2009. Contrasting activity profile of two distributed cortical networks as a function of attentional demands. *J. Neurosci.* 29:1191–201
- Posner MI, Raichle ME. 1994. *Images of Mind*. New York: Freeman
- Price CJ. 2012. A review and synthesis of the first 20 years of PET and fMRI studies of heard speech, spoken language and reading. *NeuroImage* 62:816–47
- Raichle ME. 2009. A brief history of human brain mapping. *Trends Neurosci.* 32:118–26
- Raichle ME. 2010. Two views of brain function. *Trends Cogn. Sci.* 14:180–90
- Raichle ME. 2011. The restless brain. *Brain Connect.* 1:3–12
- Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. 2001. A default mode of brain function. *PNAS* 98:676–82
- Raichle ME, Mintun MA. 2006. Brain work and brain imaging. *Annu. Rev. Neurosci.* 29:449–76
- Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, et al. 2007. Dissociable intrinsic connectivity networks for salience processing and executive control. *J. Neurosci.* 27:2349–56
- Shannon BJ, Dosenbach RA, Su Y, Vlessenko AG, Larson-Prior LJ, et al. 2013. Morning-evening variation in human brain metabolism and memory circuits. *J. Neurophysiol.* 109:1444–56
- Shannon BJ, Raichle ME, Snyder AZ, Fair DA, Mills KL, et al. 2011. Premotor functional connectivity predicts impulsivity in juvenile offenders. *PNAS* 108:11241–45
- Sherrington CS. 1906. *The Integrative Action of the Nervous System*. New Haven, CT: Yale Univ. Press
- Shmuel A, Augath M, Oeltermann A, Logothetis NK. 2006. Negative functional MRI response correlates with decreases in neuronal activity in monkey visual area V1. *Nat. Neurosci.* 9:569–77
- Shulman GL, Fiez JA, Corbetta M, Buckner RL, Miezin FM, et al. 1997. Common blood flow changes across visual tasks: II. Decreases in cerebral cortex. *J. Cogn. Neurosci.* 9:648–63
- Simpson JR Jr., Drevets WC, Snyder AZ, Gusnard DA, Raichle ME. 2001a. Emotion-induced changes in human medial prefrontal cortex: II. During anticipatory anxiety. *PNAS* 98:688–93
- Simpson JR Jr., Snyder AZ, Gusnard DA, Raichle ME. 2001b. Emotion-induced changes in human medial prefrontal cortex: I. During cognitive task performance. *PNAS* 98:683–87
- Smith AT, Singh KD, Greenlee MW. 2000. Attentional suppression of activity in the human visual cortex. *NeuroReport* 11:271–77
- Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, et al. 2009. Correspondence of the brain's functional architecture during activation and rest. *PNAS* 106:13040–45

- Snyder AZ, Raichle ME. 2012. A brief history of the resting state: the Washington University perspective. *NeuroImage* 62:902–10
- Somers DC, Dale AM, Seiffert AE, Tootell RB. 1999. Functional MRI reveals spatially specific attentional modulation in human primary visual cortex. *PNAS* 96:1663–68
- Stafford JM, Jarrett BR, Miranda-Dominguez O, Mills BD, Cain N, et al. 2014. Large-scale topology and the default mode network in the mouse connectome. *PNAS* 111:18745–50
- Teves D, Videen TO, Cryer PE, Powers WJ. 2004. Activation of human medial prefrontal cortex during autonomic responses to hypoglycemia. *PNAS* 101:6217–21
- Thulborn KR, Waterton JC, Matthews PM, Radda GK. 1982. Oxygenation dependence of the transverse relaxation time of water protons in whole blood at high field. *Biochim. Biophys. Acta* 714:265–70
- van den Heuvel MP, Sporns O. 2011. Rich-club organization of the human connectome. *J. Neurosci.* 31:15775–86
- Vincent JL, Patel GH, Fox MD, Snyder AZ, Baker JT, et al. 2007. Intrinsic functional architecture in the anaesthetized monkey brain. *Nature* 447:83–86
- Vincent JL, Snyder AZ, Fox MD, Shannon BJ, Andrews JR, et al. 2006. Coherent spontaneous activity identifies a hippocampal-parietal mnemonic network. *J. Neurophysiol.* 96:3517–31
- Vlassenko AG, Vaishnavi SN, Couture L, Sacco D, Shannon BJ, et al. 2010. Spatial correlation between brain aerobic glycolysis and amyloid- β (A β) deposition. *PNAS* 107:17763–67
- Yuste R, MacLean JN, Smith J, Lansner A. 2005. The cortex as a central pattern generator. *Nat. Rev. Neurosci.* 6:477–83
- Zhang D, Snyder AZ, Fox MD, Sansbury MW, Shimony JS, Raichle ME. 2008. Intrinsic functional relations between human cerebral cortex and thalamus. *J. Neurophysiol.* 100:1740–48