The Brain's Default Network

Anatomy, Function, and Relevance to Disease

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Thirty years of brain imaging research has converged to define the brain's default network—a novel and only recently appreciated brain system that participates in internal modes of cognition. Here we synthesize past observations to provide strong evidence that the default network is a specific, anatomically defined brain system preferentially active when individuals are not focused on the external environment. Analysis of connectional anatomy in the monkey supports the presence of an interconnected brain system. Providing insight into function, the default network is active when individuals are engaged in internally focused tasks including autobiographical memory retrieval, envisioning the future, and conceiving the perspectives of others. Probing the functional anatomy of the network in detail reveals that it is best understood as multiple interacting subsystems. The medial temporal lobe subsystem provides information from prior experiences in the form of memories and associations that are the building blocks of mental simulation. The medial prefrontal subsystem facilitates the flexible use of this information during the construction of self-relevant mental simulations. These two subsystems converge on important nodes of integration including the posterior cingulate cortex. The implications of these functional and anatomical observations are discussed in relation to possible adaptive roles of the default network for using past experiences to plan for the future, navigate social interactions, and maximize the utility of moments when we are not otherwise engaged by the external world. We conclude by discussing the relevance of the default network for understanding mental disorders including autism, schizophrenia, and Alzheimer's disease.

Key words: **default mode; default system; default network; fMRI; PET; hippocampus; memory; schizophrenia; Alzheimer**

Introduction

A common observation in brain imaging research is that a specific set of brain regions—referred to as the default network—is engaged when individuals are left to think to themselves undisturbed (Shulman et al. 1997, Mazoyer et al. 2001, Raichle et al. 2001). Probing this phenomenon further reveals that other kinds of situations, beyond freethinking, engage the default network. For example, remembering the past, envisioning future events, and considering the thoughts and perspectives of other people all activate multiple regions within the default network (Buckner & Carroll 2007). These observations prompt one to ask such questions as: What do these tasks and spontaneous cognition share in common? and what is the significance of this network to adaptive function? The default network is also disrupted in autism, schizophrenia, and Alzheimer's disease, further encouraging one to consider how the functions of the default network might be important to understanding diseases of the mind (e.g., Lustig et al. 2003, Greicius et al. 2004, Kennedy et al. 2006, Bluhm et al. 2007).

Motivated by these questions, we provide a comprehensive review and synthesis of findings about the

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brain's default network. This review covers both basic science and clinical observations, with its content organized across five sections. We begin with a brief history of our understanding of the default network (section I). Next, a detailed analysis of the anatomy of the default network is provided including evidence from humans and monkeys (section II). The following sections concern the role of the default network in spontaneous cognition, as commonly occurs in passive task settings (section III), as well as its functions in active task settings (section IV). While recognizing alternative possibilities, we hypothesize that the fundamental function of the default network is to facilitate flexible self-relevant mental explorations—simulations—that provide a means to anticipate and evaluate upcoming events before they happen. The final section of the review discusses emerging evidence that relates the default network to cognitive disorders, including the possibility that activity in the default network augments a metabolic cascade that is conducive to the development of Alzheimer's disease (section V).

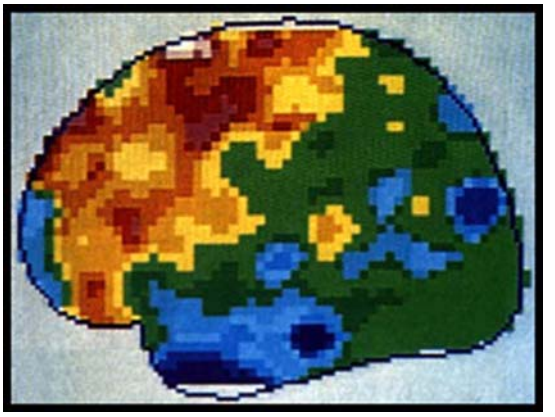


FIGURE 1. An early image of regional cerebral blood flow (rCBF) at rest made by David Ingvar and colleagues using the nitrous oxide technique. The image shows data averaged over eight individuals to reveal a "hyperfrontal" activity pattern that Ingvar proposed reflected "spontaneous, conscious mentation" (Ingvar 1979). Ingvar's ideas anticipate many of the themes discussed in this review (see Ingvar 1974, 1979, 1985).

I. A Brief History

The discovery of the brain's default network was entirely accidental. Evidence for the default network began accumulating when researchers first measured brain activity in humans during undirected mental states. Even though no early studies were explicitly designed to explore such unconstrained states, relevant data were nonetheless acquired because of the common practice of using rest or other types of passive conditions as an experimental control. These studies revealed that activity in specific brain regions increased during passive control states as compared to most goal-directed tasks. In almost all cases, the exploration of activity during the control states occurred as an afterthought—as part of reviews and meta-analyses performed subsequent to the original reports, which focused on the goal-directed tasks.

Early Observations

A clue that brain activity persists during undirected mentation emerged from early studies of cerebral metabolism. It was already known by the late 19th century that mental activity modulated local blood flow (James 1890). Louis Sokoloff and colleagues (1955) used the Kety-Schmidt nitrous oxide technique (Kety & Schmidt 1948) to ask whether cerebral metabolism changes globally when one goes from a quiet rest state to performing a challenging arithmetic problem—a task that demands focused cognitive effort. To their surprise, metabolism remained constant. While not their initial conclusion, the unchanged global rate of metabolism suggests that the rest state contains persistent brain activity that is as vigorous as that when individuals solve externally administered math problems.

The Swedish brain physiologist David Ingvar was the first to aggregate imaging findings from rest task states and note the importance of consistent, regionally specific activity patterns (Ingvar 1974, 1979, 1985). Using the xenon 133 inhalation technique to measure regional cerebral blood flow (rCBF), Ingvar and his colleagues observed that frontal activity reached high levels during rest states (Fig. 1). To explain this unexpected phenomenon, Ingvar proposed that the "hyperfrontal" pattern of activity corresponded "to undirected, spontaneous, conscious mentation, the 'brain work,' which we carry out when left alone undisturbed" (Ingvar 1974). Two lasting insights emerged from Ingvar's work. First, echoing ideas of Hans Berger (1931), his work established that the brain is not idle when left undirected. Rather, brain activity persists in the absence of external task direction. Second, Ingvar's observations suggested that increased activity during rest is localized to specific brain regions that prominently include prefrontal cortex.

The Era of Task-Induced Deactivation

Ingvar's ideas about resting brain activity remained largely unexplored for the next decade until positron emission tomography (PET) methods for brain imaging gained prominence. PET had finer resolution and

sensitivity to deep-brain structures than earlier methods and, owing to the development of isotopes with short half-lives (Raichle 1987), typical PET studies included many task and control conditions for comparison. By the mid-1990s several dozen imaging studies were completed that examined perception, language, attention, and memory. Scans of rest-state brain activity[a] were often acquired across these studies for a control comparison, and researchers began routinely noticing brain regions more active in the passive control conditions than the active target tasks—what at the time was referred to as "deactivation."

The term "deactivation" was used because analyses and image visualization were referenced to the target, experimental task. Within this nomenclature, regions *relatively* more active in the target condition (e.g., reading, classifying pictures) compared to the control task (e.g., passive fixation, rest) were labeled "activations"; regions less active in the target condition than the control were labeled "deactivations." Deactivations were present and often the most robust effect in many early PET studies. One form of deactivation for which early interest emerged was activity reductions in unattended sensory modalities because of its theoretical relevance to mechanisms of attention (e.g., Haxby et al. 1994, Kawashima et al. 1994, Buckner et al. 1996). A second form of commonly observed deactivation was along the frontal and posterior midline during active, as compared to passive, task conditions. There was no initial explanation for these mysterious midline deactivations (e.g., Ghatan et al. 1995, Baker et al. 1996).

A particularly informative early study was conducted while exploring brain regions supporting episodic memory. Confronted with the difficult issue of defining a baseline state for an autobiographical memory task, Andreasen and colleagues (1995) explored the possibility that spontaneous cognition makes an important contribution to rest states. Much like other studies at the time, the researchers included a rest condition as a baseline for comparison to their target conditions. However, unlike other contemporary studies, they hypothesized that autobiographical memory (the experimental target of the study) inherently involves internally directed cognition, much like the spontaneous cognition that occurs during "rest" states. For this reason, Andreasen and colleagues explored both the rest and memory tasks referenced to a third control condition that involved neither rest nor episodic memory. Their results showed that similar brain regions were engaged during rest and memory as compared to the nonmemory control. In addition, to better understand the cognitive processes associated with the rest state, they informally asked their participants to subjectively describe their mental experiences.

Two insights originated from this work that foreshadow much of the present review's content. First, Andreasen et al. (1995) noted that the resting state "is in fact quite vigorous and consists of a mixture of freely wandering past recollection, future plans, and other personal thoughts and experiences." Second, the analysis of brain activity during the rest state revealed prefrontal midline regions as well as a distinct posterior pattern that included the posterior cingulate and retrosplenial cortex. As later studies would confirm, these regions are central components of the core brain system that is consistently activated in humans during undirected mental states.

Broad awareness of the common regions that become active during passive task states emerged with a pair of meta-analyses that pooled extensive data to reveal the functional anatomy of unconstrained cognition. In the first study, Shulman and colleagues (1997) conducted meta-analysis of task-induced deactivations to explicitly determine if there were common brain regions active during undirected (passive) mental states. They pooled data from 132 normal adults for which an active task (word reading, active stimulus classification, etc.) could be directly compared to a passive task that presented the same visual words or pictures but contained no directed task goals. Using a similar approach, Mazoyer et al. (2001) aggregated data across 63 normal adults that included both visually and aurally cued active tasks as compared to passive rest conditions.

These two analyses revealed a remarkably consistent set of brain regions that were more active during passive task conditions than during numerous goal-directed task conditions (spanning both verbal and nonverbal domains and visual and auditory conditions). The results of the Shulman et al. (1997) meta-analysis are shown in FIGURE 2. This image displays the full cortical extent of the brain's default network. The broad generality of the rest activity pattern across so many diverse studies reinforced the intriguing possibility that a common set of cognitive processes was used spontaneously during the passive-task states. Motivated by this idea, Mazoyer et al. (2001) explored the content of spontaneous thought by asking participants to describe their musings following the scanned rest periods. Paralleling the informal observations by

[a]PET and functional MRI (fMRI) both measure neural activity indirectly through local vascular (blood flow) changes that accompany neuronal activity. PET is sensitive to changes in blood flow directly (Raichle 1987). fMRI is sensitive to changes in oxygen concentration in the blood which tracks blood flow (Heeger and Ress 2002). For simplicity, we refer to these methods as measuring brain activity in this review.

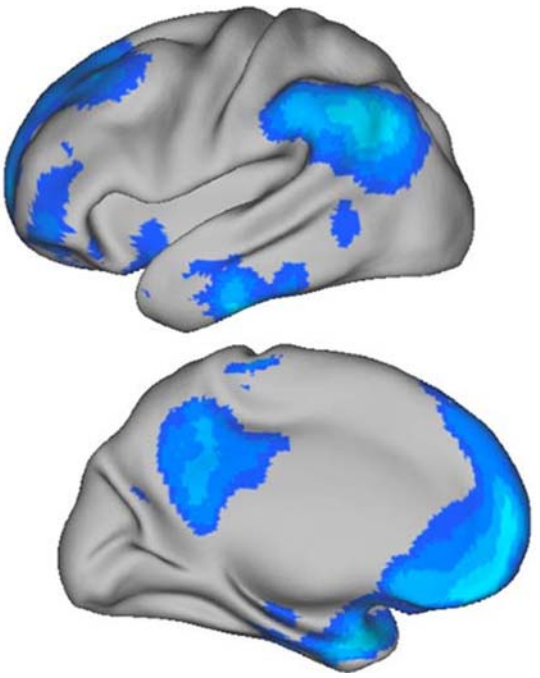


FIGURE 2. The brain's default network was originally identified in a meta-analysis that mapped brain regions more active in passive as compared to active tasks (often referred to as task-induced deactivation). The displayed positron emission tomography (PET) data include nine studies (132 participants) from Shulman et al. (1997; reanalyzed in Buckner et al. 2005). Images show the medial and lateral surface of the left hemisphere using a population-averaged surface representation to take into account between-subject variability in sulcal anatomy (Van Essen 2005). Blue represents regions most active in passive task settings.

Ingvar and Andreasen et al., they noted that the imaged rest state is associated with lively mental activity that includes "generation and manipulation of mental images, reminiscence of past experiences based on episodic memory, and making plans" and further noted that the subjects of their study "preferentially reported autobiographical episodes."

Emergence of the Default Network as Its Own Research Area

The definitive recent event in the explication of the default network came with the a series of publications by Raichle, Gusnard, and colleagues (Raichle et al. 2001, Gusnard & Raichle 2001, Gusnard et al. 2001). A dominant theme in the field during the previous decade concerned how to define an appropriate baseline condition for neuroimaging studies. This focus on the baseline state was central to the evolving concept of a default network. Many argued that passive conditions were simply too unconstrained to be useful as control states. Richard Frackowiak summarized this widely held concern: "To call a 'free-wheeling' state, or even a state where you are fixating on a cross and dreaming about anything you like, a 'control' state, is to my mind quite wrong" (Frackowiak 1991). (For recent discussion of this ongoing debate see Morcom and Fletcher 2007, Buckner & Vincent 2007, Raichle & Snyder 2007). As a result of this uneasiness in interpreting passive task conditions, beyond the few earlier studies mentioned, there was a general trend not to thoroughly report or discuss the meaning of rest state activity.

Raichle, Gusnard, and colleagues reversed this trend dramatically with three papers in 2001 (Raichle et al. 2001, Gusnard & Raichle 2001, Gusnard et al. 2001). Their papers directly considered the empirical and theoretical implications of defining baseline states and what the specific pattern of activity in the default network might represent. Several lasting consequences on the study of the default network emerged. First, they distinguished between various forms of task-induced deactivation and separated deactivations defining the default network from other forms of deactivation (including attenuation of activity in unattended sensory areas). Second, they compiled a considerable array of findings that drew attention to the specific anatomic regions linked to the default network and what their presence might suggest about its function. A key insight was that the medial prefrontal regions consistently identified as part of the default network are associated with self-referential processing (Gusnard et al. 2001, Gusnard & Raichle 2001). Most importantly, the papers brought to the forefront the exploration of the default network as its own area of study (including providing its name, which, as of late 2007, has appeared as a keyword in 237 articles). Our use of the label "default network" in this review stems directly from their labeling the baseline rest condition as the "default mode."[b] Their reviews made clear that the default network is to be studied as a fundamental neurobiological system with physiological and cognitive properties that distinguish it from other systems.

The default network is a brain system much like the motor system or the visual system. It contains a set of interacting brain areas that are tightly functionally

[b]References to the default mode appear in the literature on cognition prior to the introduction of the concept as an explanation for neural and metabolic phenomena. Giambra (1995), for example, noted that "Task-unrelated images and thoughts may represent the normal default mode of operation of the self-aware." Thus, the concept of a default mode is converged upon from both cognitive and neurobiological perspectives.

TABLE 1. Core regions associated with the brain's default network

REGION	ABREV	INCLUDED BRAIN AREAS
Ventral medial prefrontal cortex	vMPFC	24, 10 m/10 r/10 p, 32ac
Posterior cingulate/retosplenial cortex	PCC/Rsp	29/30, 23/31
Inferior parietal lobule	IPL	39, 40
Lateral temporal cortex†	LTC	21
Dorsal medial prefrontal cortex	dMPFC	24, 32ac, 10p, 9
Hippocampal formation††	HF+	Hippocampus proper,EC, PH

Notes: Region, abbreviation, and approximate area labels for the core regions associated with the default network in humans. Labels correspond to those originally used by Brodmann for humans with updates by Petrides and Pandya (1994), Vogt et al. (1995), Morris et al. (2000), and Öngür et al. (2003). Labels should be considered approximate because of the uncertain boundaries of the areas and the activation patterns. †LTC is particularly poorly characterized in humans and is therefore the most tentative estimate. ††HF+ includes entorhinal cortex (EC) and surrounding cortex (e.g., parahippocampal cortex; PH).

connected and distinct from other systems within the brain. In the remainder of this review, we define the default network in more detail, speculate on its function both during passive and active cognitive states, and evaluate accumulating data that suggest that understanding the default network has important clinical implications for brain disease.

II. Anatomy of the Default Network

The anatomy of the brain's default network has been characterized using multiple approaches. The default network was originally identified by its consistent activity increases during passive task states as compared to a wide range of active tasks (e.g., Shulman et al. 1997, Mazoyer et al. 2001, FIG. 2). A more recent approach that identifies brain systems via intrinsic activity correlations (e.g., Biswal et al. 1995) has also revealed a similar estimate of the anatomy of the default network (Greicius et al. 2003, 2004). More broadly, the default network is hypothesized to represent a brain system (or closely interacting subsystems) involving anatomically connected and interacting brain areas. Thus, its architecture should be critically informed by studies of connectional anatomy from nonhuman primates and other relevant sources of neurobiological data.

In this section, we review the multiple approaches to defining the default network and consider the specific anatomy that arises from these approaches in the context of architectonic and connectional anatomy in the monkey. We highlight two observations. First, all neuroimaging approaches converge on a similar estimate of the anatomy of the default network that is largely consistent with available information about connectional anatomy (TABLE 1). Second, the intrinsic architecture of the default network suggests that it comprises multiple interacting hubs and subsystems. These anatomic observations provide the foundation on which the upcoming sections explore the functions of the default network.

Blocked Task-Induced Deactivation

Because PET imaging requires about a minute of data accumulation to construct a stable image, the brain's default network was initially characterized using blocked task paradigms. Within these paradigms, extended epochs of active and passive tasks were compared to one another. During these epochs brain activity was averaged over blocks of multiple sequential task trials—hence the label "blocked." Shulman et al. (1997) and Mazoyer et al. (2001) published two seminal meta-analyses based on blocked PET methods to identify brain regions consistently more active during passive tasks as compared to a wide range of active tasks. Tasks spanned verbal and nonverbal domains (Shulman et al. 1997) and auditory and visual modalities (Mazoyer et al. 2001). In total, data from 195 subjects were aggregated across 18 studies in the two meta-analyses.

FIGURE 2 displays the original data of Shulman et al. visualized on the cortical surface to illustrate the topography of the default network; the data from Mazoyer et al. (not shown) are highly similar. FIGURE 3 shows a third meta-analysis of blocked task data from a series of 4 fMRI data sets from 92 young-adult subjects (Shannon 2006). In this meta-analysis of fMRI data, the passive tasks were all visual fixation and the active tasks involved making semantic decisions on visually presented words (data from Gold & Buckner 2002, Lustig & Buckner 2004). Across all the variations, a consistent set of regions increases activity during passive tasks when individuals are left undirected to think to themselves.

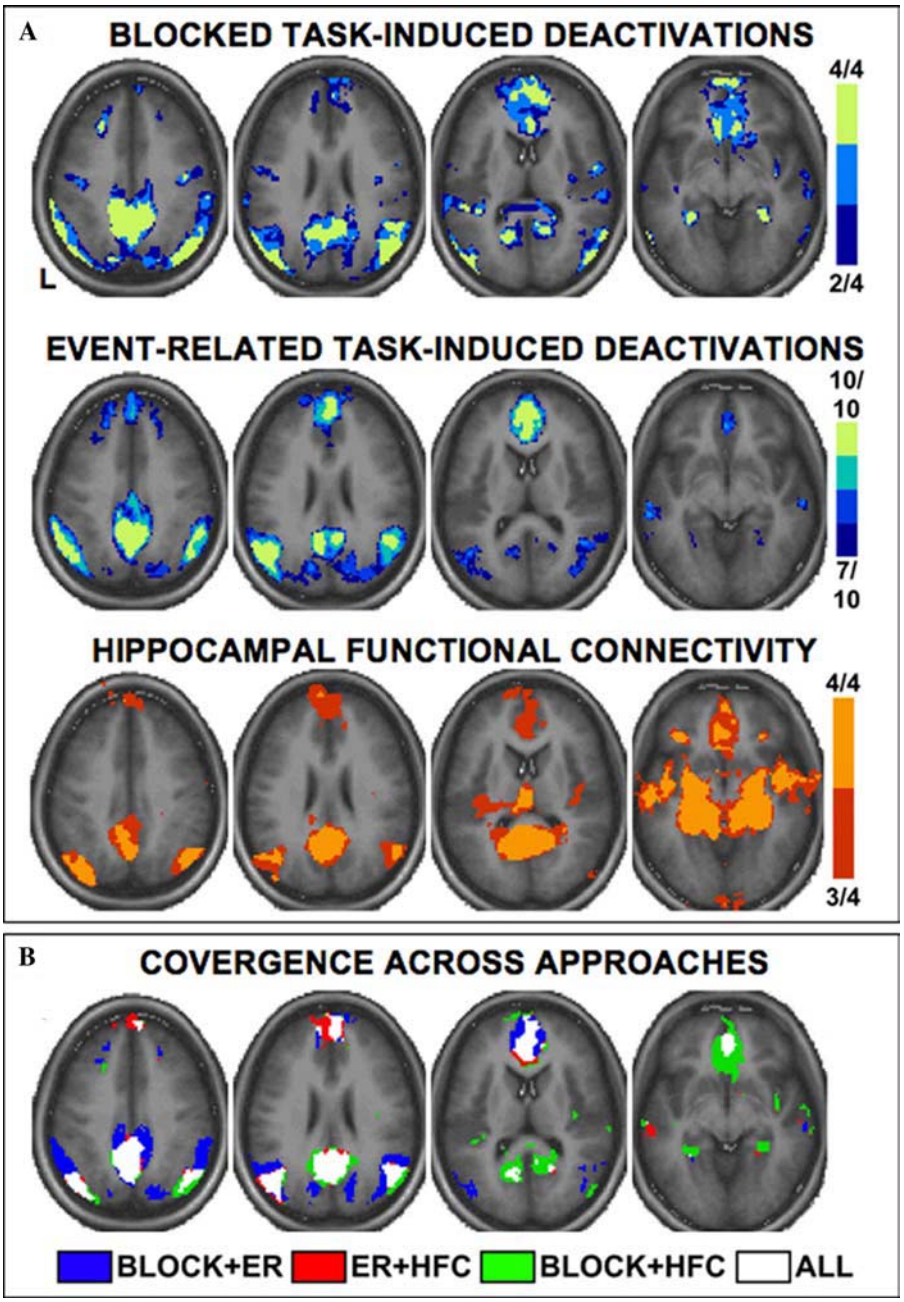


FIGURE 3. The brain's default network is converged upon by multiple, distinct fMRI approaches. **(A)** Each row of images shows a different fMRI approach for defining the default network: blocked task-induced deactivation (top row), event-related task-induced deactivation (middle row), and functional connectivity with the hippocampal formation (bottom row). Within each approach, the maps represent a meta-analysis of multiple data sets thereby providing a conservative estimate of the default network (see text). Colors reflect the number of data sets showing a significant effect within each image (color scales to the right). **(B)** The convergence across approaches reveals the core regions within the default network (legend at the bottom). Z labels correspond to the transverse level in the atlas of Talairach and Tournoux (1988). Left is plotted on the left. Adapted from Shannon (2006).

Event-Related, Task-Induced Deactivation

An alternative to defining the anatomy of the default network based on blocked tasks is to perform a similar analysis on individual task events. Rapid event-related fMRI makes possible such an analysis by presenting task trials at randomly jittered time intervals, typically 2 to 10 seconds apart. The reason to perform such an analysis is the possibility that extended epochs are required to elicit activity during passive epochs, as might be the case if blocked task-induced deactivations arise from slowly evolving signals or sustained task sets that are not modulated on a rapid time frame (e.g., Dosenbach et al. 2006).

FIGURE 3 illustrates the results of a meta-analysis of studies from Shannon (2006) that uses event-related fMRI data to define the default network. In total, data from 49 subjects were pooled for this analysis. The data are based on semantic and phonological classification tasks from Kirchhoff et al. (2005; $n = 28$) as well as a second sample of event-related data that also involved semantic classification (Shannon 2006; $n = 21$). As can be appreciated visually, the default network defined based on event-related data is highly similar to that previously reported using blocked data. Thus, the differential activity in the default network between passive and active task states can emerge rapidly, on the order of seconds or less.

Functional Connectivity Analysis

A final approach to defining the functional anatomy of the default network is based on the measurement of the brain's intrinsic activity. At all levels of the nervous system from individual neurons (Tsodyks et al. 1999) and cortical columns (Arieli et al. 1995) to whole-brain systems (Biswal et al. 1995, De Luca et al. 2006), there exists spontaneous activity that tracks the functional and anatomic organization of the brain. The patterns of spontaneous activity are believed to reflect direct and indirect anatomic connectivity (Vincent et al. 2007a) although additional contributions may arise from spontaneous cognitive processes (as will be described in a later section). In humans, low-frequency, spontaneous correlations are detectable across the brain with fMRI and can be used to characterize the intrinsic architecture of large-scale brain systems, an approach often referred to as functional connectivity MRI (Biswal et al. 1995, Haughton & Biswal 1998; see Fox & Raichle 2007 for a recent review). Motor (Biswal et al. 1995), visual (Nir et al. 2006), auditory (Hunter et al. 2006), and attention (Fox et al. 2006) systems have been characterized using functional connectivity analysis (see also De Luca et al. 2006).

Greicius and colleagues (2003, 2004) used such an analysis to map the brain's default network (see also Fox et al. 2005, Fransson 2005, Damoiseaux et al. 2006, Vincent et al. 2006). Functional connectivity analysis is particularly informative because it provides a means to assess locations of interacting brain regions within the default network in a manner that is independent of task-induced deactivation. In their initial studies, Greicius et al. measured spontaneous activity from the posterior cingulate cortex, a core region in the default network, and showed that activity levels in the remaining distributed regions of the system are all correlated together. Their map of the default network, based on intrinsic functional correlations, is remarkably similar to that originally generated by Shulman et al. (1997) based on PET deactivations.

An important further observation from analyses of intrinsic activity is that the default network includes the hippocampus and adjacent areas in the medial temporal lobe that are associated with episodic memory function (Greicius et al. 2004). In fact, many of the major neocortical regions constituting the default network can be revealed by placing a seed region in the hippocampal formation and mapping those cortical regions that show spontaneous correlation (Vincent et al. 2006). FIGURE 3 shows a map of the default network as generated from intrinsic functional correlations with the hippocampal formation in four independent data sets.

Convergence across Approaches for Defining the Default Network

Is there convergence between the three distinct approaches for defining the anatomy of the default network described above? To answer this question, the overlap among the multiple methods for defining default network anatomy is displayed on the bottom panel of FIGURE 3. The convergence reveals that the default network comprises a distributed set of regions that includes association cortex and spares sensory and motor cortex. In particular, medial prefrontal cortex (MPFC), posterior cingulate cortex/retrosplenial cortex (PCC/Rsp), and the inferior parietal lobule (IPL) show nearly complete convergence across the 18 data sets.

Several more specific observations are apparent from this analysis of overlap. First, the hippocampal formation (HF) is shown to be involved in the default network regardless of which approach is used (task-induced deactivation or functional connectivity analysis) but, relative to the robust posterior midline and prefrontal regions, the HF is less prominent using the approach of task-induced deactivations.

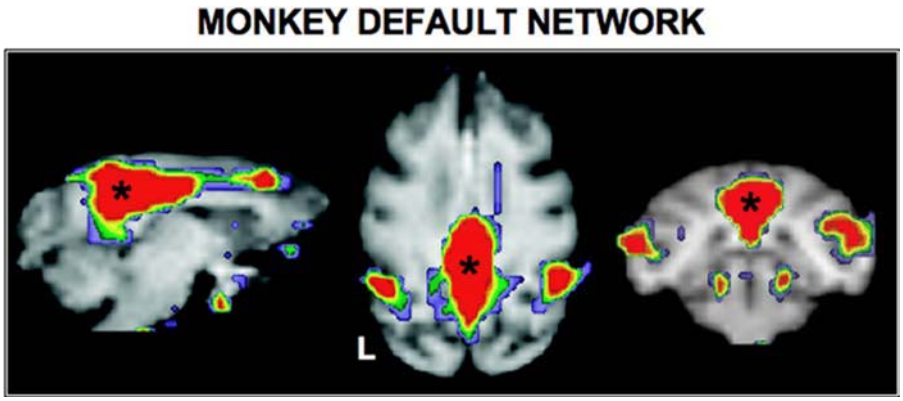


FIGURE 4. The default network in the monkey defined using functional connectivity analysis. A seed was placed in the posterior midline (indicated by asterisk) and the regions showing correlated activity were mapped. The left image shows the medial surface, the middle image a transverse section through parietal cortex, and the right image a coronal section through the hippocampal formation. Left is plotted on the left. Adapted from Vincent et al. (2007a).

Second, multiple default network regions are functionally correlated with the HF, reinforcing the notion that the medial temporal lobe is included in the network. Overlap is not perfect, however, with some indications of more extensive recruitment during passive cognitive states, including both in posterior parietal cortex and in prefrontal cortex. These details will be shown to be informative when subsystems within the default network are discussed. Third, lateral temporal cortex (LTC) extending into the temporal pole is consistently observed across approaches but, like the HF, is less robust. Together these observations tentatively define the core anatomical components of the default network (TABLE 1).

Insights from Comparative Anatomy

Important insights into the organization of human brain systems have been provided by comparative studies in the monkey. Vincent et al. (2007a) recently used functional connectivity analysis to show that the major default network regions in posterior cortex have putative monkey homologues including PCC/Rsp, IPL, and the HF (FIG. 4, see also Rilling et al. 2007). In addition, architectonic maps reveal many similarities between human and monkey anatomy in the vicinity of the default network (e.g., Petrides & Pandya 1994, Morris et al. 2000, Öngür & Price 2000, Vogt et al. 2001). Motivated by these recent observations, we provide here a detailed analysis of the architectonics and connectional anatomy of the default network, while recognizing that there may be fundamental differences in humans. As a means to simplify our analysis, we focus on areas that fall within PCC/Rsp and MPFC and their anatomic relationships with other cortical regions and the HF. Potentially important subcortical connections, such as to the striatal reward pathway and the amygdala, are not covered. Even with this simplification, the details of the anatomy are complex and one is immediately confronted with the observation that each of the activated regions, as defined based on human functional neuroimaging data, extends across multiple brain areas that have distinct architecture and connectivity. Progress will require significantly more detailed analysis of the anatomic extent and locations of default network regions in humans. Nonetheless, using available data we provide an initial analysis of the anatomy recognizing that it is provisional and incomplete.

Posterior cingulate cortex (PCC) and restrosplenial cortex (Rsp) have been extensively studied in the macaque monkey and recently so with focus on direct comparison to human anatomy (e.g., Morris et al. 2000, Vogt et al. 2001). The PCC and Rsp fall along the posterior midline and exist within a region that contains at least three contiguous, but distinct, sets of areas: Rsp (areas 29/30), PCC (areas 23/31), and precuneus (area 7m). Rsp is just posterior to the corpus callosum and, in humans, extends along the ventral bank of the cingulate gyrus (Morris et al. 2000, Vogt et al. 2001). In macaques, Rsp is much smaller and does not encroach onto the cingulate gyrus (Morris et al. 1999, Kobayashi & Amaral 2000). Just posterior to Rsp, along the main portion of the cingulate gyrus, is PCC. The precuneus, a region often cited as being involved in the default network, comprises the posterior and dorsal portion of the medial parietal lobe and includes area 7m (Cavanna & Trimble 2006, Parvizi et al. 2006). As an ensemble, these three structures are sometimes referred to as "posteriomedial

cortex," and each structure is interconnected with the others (e.g., Parvizi et al. 2006, Kobayashi & Amaral 2003).

The predominant extrinsic connections to and from the posteriomedial cortex differ by area. Collectively, the connections are widespread and, much like other association areas, are consistent with a role in information integration. Specifically, Rsp is heavily interconnected with the HF and parahippocampal cortex, receiving nearly 40% of its extrinsic input from the medial temporal lobe (Kobayashi & Amaral 2003, see also Suzuki & Amaral 1994, Morris et al. 1999). Rsp also projects back to the medial temporal lobe as well as prominently to multiple prefrontal regions (Kobayashi & Amaral 2007, FIG. 5). PCC area 23 has reciprocal connections with the medial temporal lobe and robust connections with prefrontal cortex and parietal cortex area 7a—an area at or near the putative homologue of the human default network region IPL (Kobayashi & Amaral 2003, 2007, FIG. 5). The medial temporal lobe also has modest, but consistent, connections with area 7a (Suzuki & Amaral 1994, Clower et al. 2001, Lavenex et al. 2002). Thus, PCC/Rsp provides a key hub for overlapping connections between themselves, the medial temporal lobe, and IPL—three of the distributed regions that constitute the major posterior extent of the default network.

An unresolved issue is whether the lateral projection zone of PCC/Rsp is restricted to area 7a in humans or extends to areas 39/40. Macaque PCC has reciprocal projections to superior temporal sulcus (STS) and the superior temporal gyrus (STG; see also Kobayashi & Amaral 2003). Analysis of the default network in macaques provides indication that the network's lateral extent includes STG (Vincent et al. 2007a). Complicating the picture, IPL is greatly expanded in humans, including areas 39/40 (Culham & Kanwisher 2001, Simon et al. 2002, Orban et al. 2006) that are closely localized to the lateral parietal region identified by human neuroimaging as being within the default network (see Caspers et al. 2006). A recent analysis of cortical expansion between the macaque and human brain based on mapping of 23 presumed homologies revealed that IPL is among the regions of greatest increase (Van Essen & Dieker 2007). Thus, these lateral parietal and temporo-parietal areas, which are not as well characterized as PCC/Rsp, are extremely interesting in light of their anatomic connections, involvement in the default network, and potential evolutionary expansion in humans.

The connectional anatomy of area 7m in the precuneus is difficult to understand in relation to the default network even though it is often included in the default network. One possibility is that area 7m is simply not a component of the default network. References to precuneus in the neuroimaging literature are often used loosely to label the general region that includes PCC area 29/30. Precuneus area 7m predominantly connects with occipital and parietal areas linked to visual processing and frontal areas associated with motor planning (Cavada & Goldman-Rakic 1989, Leichnetz 2001). Moreover, medial temporal lobe regions that have extensive projections to PCC and Rsp show minimal connections to area 7m. Connections do exist between area 7m and the PCC, which may be the basis for the extensive activation patterns sometimes observed along the posterior midline, but we suspect that area 7m is not a core component of the network.

Reinforcing this impression, close examination of the many maps that define the human default network in this review shows that the posterior medial extent of the network usually does not encroach on the edge of the parietal midline (where area 7m is located, Scheperjans et al. 2007). This boundary is labeled explicitly in FIGURE 7 by an asterisk. The middle panel of FIGURE 18 shows a particularly clear example of the separation between task-induced deactivation of PCC and its dissociation from the region at or near area 7m. Another example of dissociation between the default network and area 7m can be found in Vogeley et al. (2004; their Figure 2A versus 2B). For all these reasons, we provisionally conclude that area 7m in precuneus is not part of the default network.

The second hub of the default network, MPFC, encompasses a set of areas that lie along the frontal midline (Petrides & Pandya 1994, Öngür & Price 2000). Human MPFC is greatly expanded relative to the monkey (Öngür et al. 2003, FIG. 6). Two differences are notable. First, macaque area 32 is pushed ventrally and rostrally in humans to below the corpus callosum (labeled by Öngür et al. as area 32pl in the human based on Brodmann's original labeling of this area in monkey as the "prelimbic area"). Human area 32ac corresponds to Brodmann's dorsal "anterior cingulate" area. Second, human area 10 is quite large and follows the rostral path of anterior cingulate areas 24 and 32ac much like typical activation of MPFC in the default network. This is relevant because commonly referenced maps based on classic architectonic analyses restrict this area to frontalpolar cortex (e.g., Petrides & Pandya 1994). Some evidence suggests that area 10 is disproportionately expanded in humans even when contrasted to great apes, suggesting specialization during recent hominid evolution (Semendeferi et al. 2001).

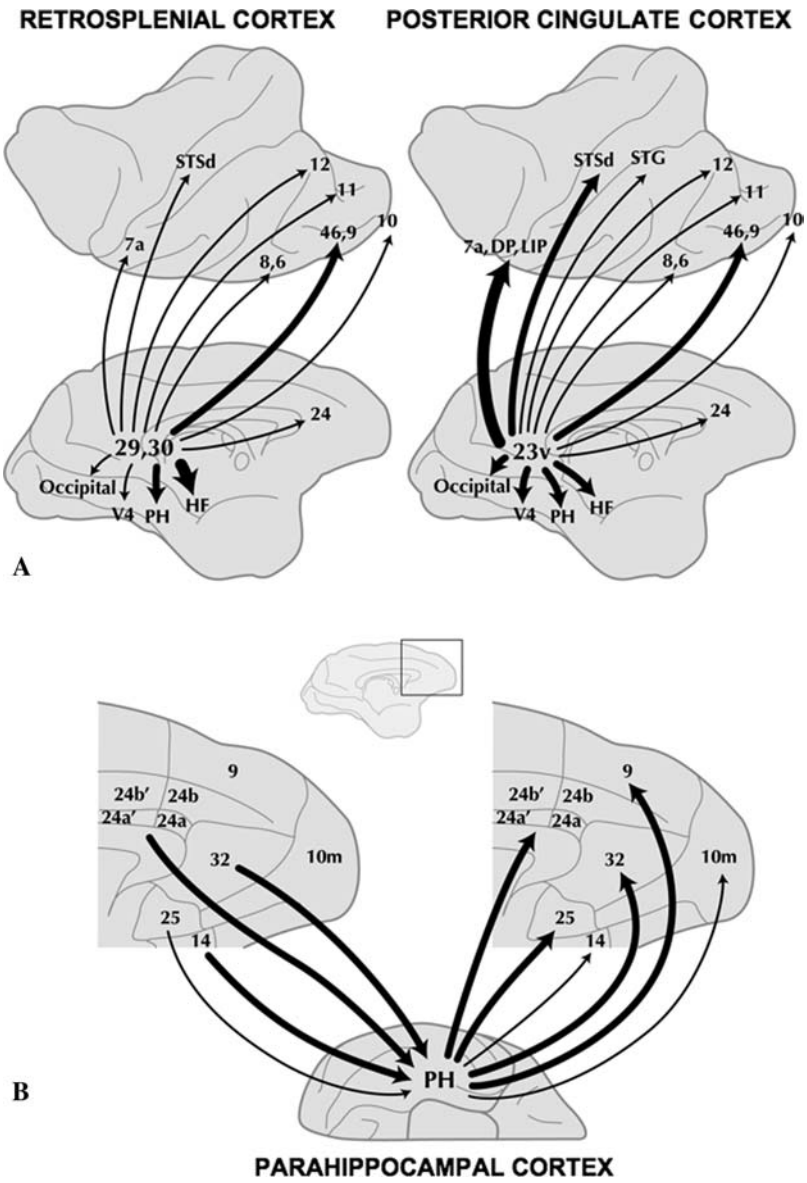


FIGURE 5. Monkey anatomy suggests that the default network includes multiple, distinct association areas, each of which is connected to other areas within the network. Illustrated are two examples of output (efferent) and input (afferent) connections for posterior cingulate/retrosplenial cortex (PCC/Rsp) and parahippocampal cortex (PH). **(A)** Output connections from Rsp (areas 29 and 30) and PCC (area 23) are displayed. Lines show connections to distributed areas; thickness represents the connection strength. Rsp and PCC are heavily connected with the medial temporal lobe (HF, hippocampal formation; PH, parahippocampal cortex), the inferior parietal lobule (IPL) extending into superior temporal gyrus (STG), and prefrontal cortex (PFC). Numbers in the diagram indicate brain areas. Adapted from Kobayashi and Amaral (2007). **(B)** Input and output connections to and from PH to medial prefrontal cortex (MPFC) are displayed. Adapted from Kondo et al. (2005).

Given these details, MPFC activation within the default network is estimated to encompass human areas 10 (10 m, 10 r, and 10 p), anterior cingulate (area 24/32ac), and area 9 in prefrontal cortex. The closest homologues to these areas in the monkey—the medial prefrontal network—show reciprocal connections with the PCC, Rsp, STG, HF, and the perirhinal/parahippocampal cortex; sensory inputs are nearly absent (Barbas et al. 1999, Price 2007). These connectivity patterns closely

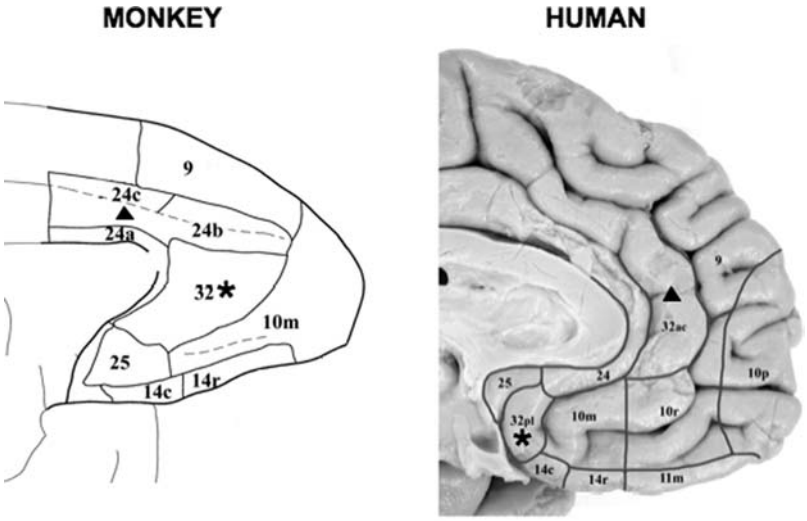


FIGURE 6. Architectonic areas within medial prefrontal cortex (MPFC) are illustrated for the monkey and human. The human MPFC is greatly expanded relative to the macaque monkey. This expansion is depicted by the triangle and asterisk that plot putative homologous areas between species based on Öngür et al. (2003). Area 32 in the macaque is homologous with area 32pl in the human. Area 24c is expanded and homologous to the caudal part of area 32ac in human. The MPFC region activated within the human default network likely corresponds to frontalpolar cortex and its rostral expansion (areas 10m, 10r, and 10p), anterior cingulate (areas 24 and 32ac), and the rostral portion of prefrontal area 9. Because of differences in functional properties, we sometimes differentiate in this review between dorsal and ventral portions of MPFC (dMPFC and vMPFC). Adapted with permission from Öngür et al. (2003).

parallel areas implicated as components of the default network.

At the broadest level, an important principle emerges from considering these anatomic details: the default network is not made up of a single monosynaptically connected brain system. Rather, the architecture reveals a series of interconnected subsystems that converge on key "hubs," in particular the PCC, that are connected with the medial temporal lobe memory system. In the next section, we explore evidence for these subsystems from functional connectivity analysis in humans.

The Default Network Comprises Interacting Subsystems

The default network comprises a set of brain regions that are coactivated during passive task states, show intrinsic functional correlation with one another, and are connected via direct and indirect anatomic projections as estimated from comparison to monkey anatomy. However, there is also clear evidence that the brain regions within the default network contribute specialized functions that are organized into subsystems that converge on hubs.

One way to gain further insight into the organization of the default network is through detailed analysis of the functional correlations between regions. FIGURE 7 plots maps of the intrinsic correlations associated with three separate seed regions within the default network in humans: the hippocampal formation including a portion of parahippocampal cortex (HF+), dMPFC, and vMPFC. The hubs—PCC/Rsp, vMPFC, and IPL—are revealed as the regions showing complete overlap across the maps. HF+ forms a subsystem that is distinct from other major components of default network including the dMPFC: both are strongly linked to the core hubs of the default network but not to each other. We suspect further analyses will reveal more subtle organizational properties. Of note, the map of the default network's hubs and subsystems shown in FIGURE 7 bears a striking resemblance to the original map of Shulman et al. (1997, FIG. 2) and updates the description of the network to show that it comprises at least two interacting subsystems.

Normative estimates of the correlation strengths between regions within the default network are provided in FIGURE 8. The bottom panel of FIGURE 8 is a graph analytic visualization of the correlation strengths using a spring-embedding algorithm to cluster strongly correlated regions near each other and position weakly correlated regions away from each other. This graphical representation illustrates the separation

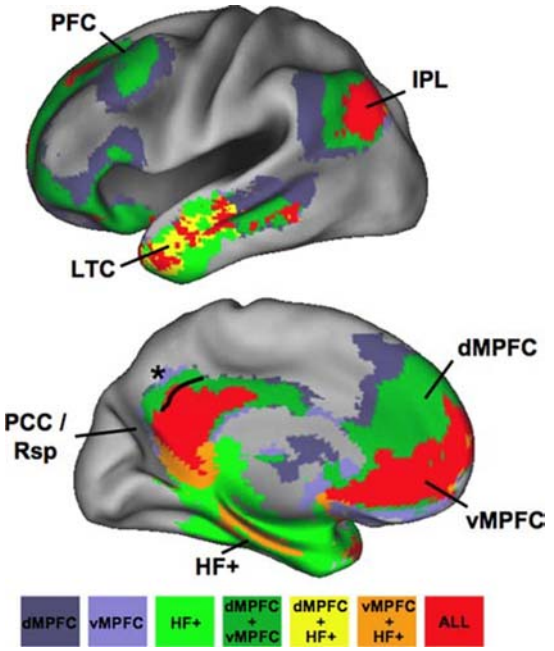


FIGURE 7. Hubs and subsystems within the default network are mapped using functional connectivity analysis. This map was produced by seeding three separate regions (dMPFC, vMPFC, HF+) and plotting the overlap of the functional correlations across the three regions (legend is at bottom; threshold for each map is $r = .07$). Data are high-resolution rest data (2mm voxels) from 40 participants (mean age = 22 years; 16 male) collected at 3-Tesla using a 12-channel head coil (data from Andrews-Hanna et al. 2007b). Three observations are notable. First, the combined map is remarkably similar to the original estimate of the default network from PET task-induced deactivation (see FIG. 2). Second, PCC/Rsp, IPL, and vMPFC represent anatomic hubs in the default network to which all other regions are correlated. Third, dMPFC and HF+, which are both strongly correlated with the hub regions, are not correlated with each other, indicating that they are part of distinct subsystems. A further interesting feature is that area 7m within the precuneus (indicated by asterisk) is not part of the default network. The black line near the asterisk represents the approximate boundary between areas 7m and 23/31 (estimated boundary based on Vogt & Laureys 2005).

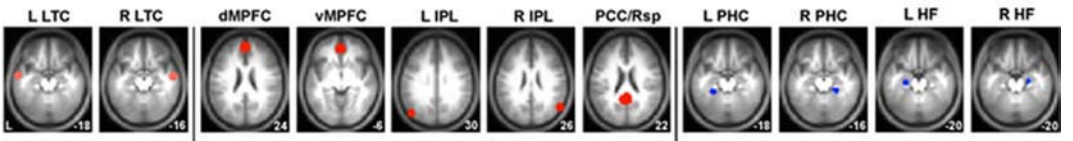
of the medial temporal lobe subsystem. The analysis also reveals that the medial temporal subsystem is less strongly associated with the core of the default network that is centered on MPFC and PCC. However, it is important to note that the correlational strengths associated with the medial temporal lobe are generally weaker than those observed for the distributed neocortical regions. As shown in FIGURE 3, the most robust correlations linked to the medial temporal lobe overlap the default network. It is presently unclear how to interpret the quantitatively lower overall levels of correlations associated with the medial temporal lobe. Functional understanding of the default network should seek to explain both the distinct contributions of the interacting subsystems and the role of their close interaction. Of interest, infants do not show the structured interactions between the default network regions, suggesting that the network develops in toddlers or children (Fransson et al. 2007). At the other end of the age spectrum, it has recently been shown that advanced aging is associated with disrupted correlations across large-scale brain networks including the default network (Andrews-Hanna et al. 2007a, Damoiseaux et al. in press). Thus, the correlation strengths presented in FIGURE 8 are only representative of normal young adults. An interesting topic for future research will be to understand the developmental course of the default network as well as the functional implications of its late life disruption.

Vascular and Other Alternative Explanations for the Anatomy of the Default Network

Given the reproducibility of the specific anatomy of the default network, an important question to ask is whether the pattern can be accounted for by some alternative explanation that is not linked to neural architecture. One possibility is that the observed anatomy reflects a vascular pattern—either draining veins, a global form of "blood stealing" whereby active regions achieve blood flow increases at the expense of nearby regions, or some other poorly understood mechanism of vascular regulation. The methods that have revealed the default network are based on hemodynamic measures of blood flow that are indirectly linked to neural activity (Raichle 1987, Heeger & Ress 2002). This issue is particularly relevant for analyses based on intrinsic correlations because slow fluctuations in vascular properties track breathing as well as oscillations in intracranial pressure. Wise et al. (2004) recently measured fMRI correlations with the slow fluctuations in the partial pressure of end-tidal carbon dioxide that accompany breathing. Their results convincingly demonstrate correlated, spatially specific fMRI responses suggesting that fMRI patterns can reflect vascular responses to breathing (see also Birn et al. 2006). While the spatial patterns associated with respiration do not closely resemble the default network, the results of Wise and colleagues are a reminder that a vascular account should be explored further.

One reason to be skeptical of a vascular account is that the default network is also identified using measures of resting glucose metabolism. In a

INTRINSIC CORRELATIONS WITHIN THE DEFAULT NETWORK



	L LTC	R LTC	dMPFC	vMPFC	L IPL	R IPL	PCC/Rsp	L PHC	R PHC	L HF	R HF
L LTC	1.00	**0.41**	**0.16**	**0.12**	**0.14**	**0.12**	**0.12**	**0.11**	**0.06**	**0.18**	**0.14**
R LTC		1.00	**0.16**	**0.18**	**0.07**	**0.20**	**0.19**	**0.08**	**0.10**	**0.15**	**0.17**
dMPFC			1.00	**0.47**	**0.22**	**0.31**	**0.34**	**-0.06**	**-0.10**	**-0.01**	**-0.04**
vMPFC				1.00	**0.27**	**0.31**	**0.52**	**0.11**	**0.06**	**0.20**	**0.16**
L IPL					1.00	**0.47**	**0.49**	**0.25**	**0.10**	**0.11**	**0.06**
R IPL						1.00	**0.42**	**0.12**	**0.05**	**0.09**	**0.07**
pCC/Rsp							1.00	**0.23**	**0.16**	**0.26**	**0.21**
L PHC								1.00	**0.57**	**0.31**	**0.28**
R PHC									1.00	**0.28**	**0.28**
L HF										1.00	**0.61**
R HF											1.00

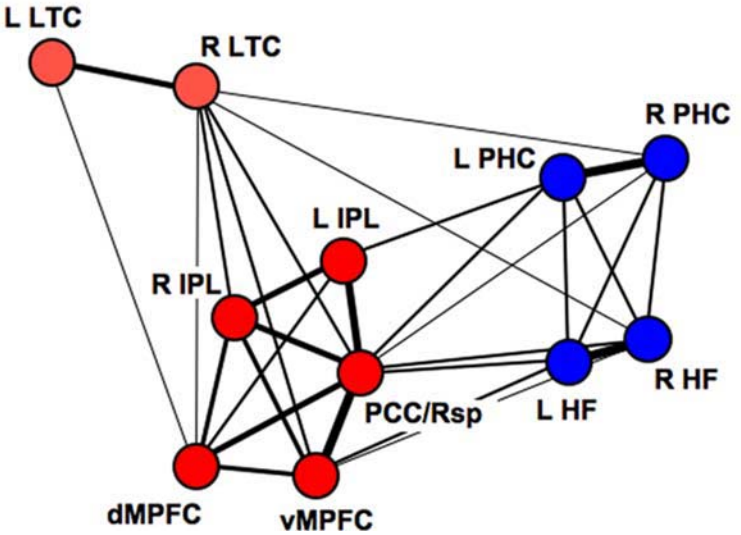


FIGURE 8. (top) Functional correlation strengths are listed for multiple regions within the default network. Each of the regions is displayed on top with the strengths of the region-to-region correlations indicated below (r-values were computed using procedures identical to Vincent et al. 2006). Regions are plotted on the averaged anatomy of the participant group (MNI/ICBM152 atlas with Z coordinates displayed). (bottom) The regions of the default network are graphically represented with lines depicting correlation strengths. The positioning of nodes is based on a spring-embedding algorithm that positions correlated nodes near each other. The structure of the default network has a core set of regions (red) that are all correlated with each other. LTC is distant because of its weaker correlation with the other structures. The medial temporal lobe subsystem (blue) includes both the hippocampal formation (HF) and parahippocampal cortex (PHC). This subsystem is correlated with key hubs of the default network including PCC/Rsp, vMPFC, and IPL. The dMPFC is negatively correlated with the medial temporal lobe subsystem suggesting functional dissociation. Graph analytic visualization provided by Alexander Cohen and Steven Petersen.

particularly informative study, Vogt and colleagues (2006) used [^{18}F]flourodeoxyglucose (FDG) PET to explore anatomy associated with the default network. Critically, FDG-PET measures neuronal activity through glucose metabolism independent of vascular coupling. Vogt et al. first defined regions within the PCC (ventral PCC and dorsal PCC) and Rsp in postmortem human tissue samples. They then measured resting state glucose metabolism in each of these regions across 163 healthy adults and correlated the

obtained values across the brain to yield metabolism-based maps of functional correlation. A quite remarkable pattern emerged: ventral PCC showed correlation with the main components of the default network including vMPFC and IPL (see their Figure 7, panel B). Moreover, this pattern was preferential to ventral PCC, suggesting that the posterior hub of the default network may be even more circumscribed than the fMRI data suggest, which have implicated the broader region including dorsal PCC and Rsp. Directly relevant to the question of whether a vascular explanation can account for the default network's anatomy, these results were obtained without relying on vascular coupling.

Glucose Metabolism and the Oxygen Extraction Fraction

Metabolic properties of the default network also set the network apart from other brain systems (Raichle et al. 2001). In particular, regions within the default network show disproportionately high resting glucose metabolism relative to other brain regions as measured using FDG-PET (e.g., Minoshima et al. 1997, Gusnard & Raichle 2001, see FIG. 17) as well as high regional blood flow (Raichle et al. 2001). For example, Minoshima et al. (1997, see their Figure 1) mapped resting glucose metabolism in healthy older adults referenced to the pons, allowing visualization of regional variation across the cortex. Along the midline, normalized glucose metabolism in PCC was about 20% higher than in most other brain regions. However, high glucose metabolism was not selective only to the default network—a region at or near primary visual cortex also showed high resting metabolism. To our knowledge, there has been no systematic investigation of resting glucose metabolism within default network regions as contrasted to regions outside the network; however, all reported exploratory maps of glucose metabolism converge on the observation that the posterior midline near PCC is a region of disproportionately high metabolism (e.g., Minoshima et al. 1997, Figure 1, Gusnard & Raichle 2001, Figure 1). Intriguingly, the regions within the default network that show high resting metabolism are also those affected in Alzheimer's disease, something that will be discussed extensively in the final section of this review. To foreshadow this final discussion, the possibility will be raised that high levels of baseline activity and metabolism (glycolysis) in the default network are conducive to the formation of pathology associated with Alzheimer's disease (Buckner et al. 2005).

A second metabolic property that has been explored in connection with the default network is regional oxygen utilization. In their seminal paper that drew attention to the default network, Raichle et al. (2001) mapped the ratio of oxygen used locally to oxygen delivered by blood flow. This ratio, referred to as the oxygen extraction fraction (OEF), decreases during heightened neural activity because the increased flow of blood into a region exceeds oxygen use (see Raichle & Mintun 2006). Raichle and colleagues (2001) hypothesized that an absolute physiological baseline could be shown to exist if OEF remained constant during passive (rest) task states, suggesting that task-induced deactivations within the default network are physiologically dissimilar from other forms of transient neuronal activity increase. While an intriguing possibility, there are several observations that suggest OEF within the default network does change at rest. First, OEF decreases were noted by Raichle et al. (2001) in several default network regions at rest when each was tested individually at the $p < 0.05$ level of statistical significance. Second, regional variation in OEF across the default network was correlated from one data set to the next ($r = .89$) indicating systematic modulation; a constant OEF across regions would show zero correlation from one data set to the next. The modulation was quantitatively small, however, with OEF values of most regions falling within 5 to 10% of the other regions. Further exploration will be required to determine if there is an absolute metabolic state that defines a baseline within the default network or whether there are meaningful variations across regions. In the next section, we will specifically explore the possibility that the special properties that arise in the default network associate with its role in spontaneous cognition during freethinking.

III. Spontaneous Cognition

> Human beings spend nearly all of their time in some kind of mental activity, and much of the time their activity consists not of ordered thought but of bits and snatches of inner experience: daydreams, reveries, wandering interior monologues, vivid imagery, and dreams. These desultory concoctions, sometimes unobtrusive but often moving, contribute a great deal to the style and flavor of being human. Their very humanness lends them great intrinsic interest; but beyond that, surely so prominent a set of activities cannot be functionless. (Klinger 1971 p. 347)

A shared human experience is our active internal mental life. Left without an immediate task that demands full attention, our minds wander jumping from one passing thought to next—what William James (1890) called the "stream of consciousness." We muse about past happenings, envision possible future events, and lapse into ideations about worlds that are far from

our immediate surroundings. In lay terms, these are the mental processes that make up fantasy, imagination, daydreams, and thought. A central issue for our present purposes is to understand to what degree, if any, the default network mediates these forms of spontaneous cognition. The observation that the default network is most active during passive cognitive states, when thought is directed toward internal channels, encourages serious consideration of the possibility that the default network *is* the core brain system associated with spontaneous cognition, and further that people have a strong tendency to engage the default network during moments when they are not otherwise occupied by external tasks. In considering the relationship between the default network and spontaneous cognition, it is worth beginning with a short review of spontaneous cognition itself.

Descriptions of human nature have alluded to the prominence of private mental experience since the classical period. In a whimsical description, Plato portrayed Socrates as "capable of standing all day in the market place lost in thought and oblivious of the external world," leading Aristophanes to coin the phrase "his head is in the clouds" (Singer 1966). Experimental study of internal mental life originated within the psychological movement of introspection in the late 19th century. Developed by Wilhelm Wundt and continued by the American psychologist Edward Titchener, introspective methods required participants to describe the contents of their internal mental experience. The premise of introspection was that conscious elements and attributes are sufficient to describe the mind. The focus on behaviorism during much of the 20th century, which emphasized measurement of the external factors that control behavior, caused a marked decline in the study of thought in mainstream science. The behaviorists rejected the methods of introspection because they relied on subjective report leading to a global "moratorium on the study of inner experience" (Klinger 1971).

The dark ages of spontaneous cognition ended in 1966 with a seminal publication by Jerome Singer that described an extensive empirical research program on the topic of daydreaming (see also Antrobus et al. 1970, Klinger 1971, Singer 1974). Several important advances emerged from this work. First, behavioral instruments were developed for the measurement of spontaneous cognition that correlated with such factors as individual differences in cognition, physiological measures and eye movements, and were also predictive of response patterns on varied tasks (e.g., Singer & Schonbar 1961, Singer et al. 1963, Antrobus et al. 1966, Antrobus 1968, Antrobus et al. 1970). Second, spontaneous cognition was observed to be quite common: 96% of individuals report daydreaming daily. Moreover, the contents of daydreams were found to include everything from mundane recounts of recent happenings to plans and expectations about the future. Finally, this work emphasized that spontaneous cognition is healthy and adaptive, and not simply a set of distracting processes or fantasies. Singer (1966), Antrobus et al. (1966) and later Klinger (1971) specifically suggested that internal mental activity is important for anticipating and planning the future. We will return to this important idea later.

In the past decade, the study of spontaneous cognition has built upon these foundations and introduced novel experimental approaches to explore the content of people's internal mental states (see Smallwood & Schooler 2006 for review). Critical to understanding the relationship between the default network and spontaneous cognition, measures of sampled thoughts track default network activity. Moreover, individual differences in tendencies to engage spontaneous cognitive processes parallel differences in default network activity. In the following section, we review these findings and discuss their implications.

Stimulus-Independent Thoughts

A number of brain imaging studies have explored stimulus-independent thoughts (SITs).[c] SITs are operationally defined as thoughts about something other than events originating from the environment; they are covert and not directed toward performance of the task at hand. The most common method for measuring SITs involves periodically probing trained participants to indicate whether they are experiencing a SIT. Care is taken to minimize the intrusiveness of the probe, although a limitation of this approach is that the probe nonetheless does interfere with the SIT, most typically to terminate its occurrence (Giambra 1995). Antrobus and colleagues (1966, 1968, 1970) showed that SITs occur quite pervasively—during both resting epochs and also during the performance of concurrent tasks. Even under heavy loads of external information, most individuals still report the presence of some SITs although the number of SITs correlates inversely with the demands of the external task.

[c]Various labels have been used in the reviewed papers to describe self-reported thought content including task-irrelevant thoughts (Antrobus et al. 1966), stimulus-independent thoughts (SITs, Antrobus et al. 1970, Teasdale et al. 1995), task-unrelated thoughts (TUTs, Giambra 1989), and task-unrelated images and thoughts (TUITs, Giambra 1995). For simplicity, we use the term "stimulus-independent thoughts" or SITs throughout the text.

Extending from these behavioral observations, several imaging studies have correlated the number of reported SITs with brain activity. In an early study, McGuire et al. (1996) demonstrated that the frequency of SITs estimated following various PET scans correlated with MPFC activity. Following a similar approach, Binder and colleagues (Binder et al. 1999, McKiernan et al. 2003, 2006) conducted two fMRI studies that explored the relationship between SITs and brain activity. In both studies they measured brain activity during rest and various tasks using typical fMRI procedures. Then, within a mock scanning environment, they had participants perform the same tasks while periodically probing for the presence of SITs. This procedure allowed them to sort the fMRI tasks based on their propensity to elicit SITs. The first study (Binder et al. 1999) revealed that rest, as compared to an externally oriented tone detection task, was associated with both increased default network activity, and nearly six times more SITs. The second study parametrically varied task difficulty across six separate tasks such that the easiest task (easy to detect target, slow presentation rate) produced about twice as many SITs as the most difficult task (McKiernan et al. 2003, 2006). Referenced to rest, there was a strong correlation between SITs and activity within the default network.

Mason et al. (2007) recently extended these approaches to study individual differences. Like the earlier work, they measured the propensity of rest and task states to elicit SITs. Task demands were manipulated using practice: a practiced variant of the task (low demands, many SITs) was compared with a novel variant (high demands, few SITs). The researchers replicated the work of Binder and colleagues by showing that default network regions, including MPFC and PCC/Rsp, tracked the different task states in proportion to the numbers of produced SITs. To ascertain who among their group was more likely to produce SITs, they administered a daydreaming questionnaire adopted from Singer and Antrobus (1972) that assessed general tendencies to engage in internal cognition (e.g., Do you daydream at work? When you have time on your hands do you daydream?). There was a strong correlation in regional default network activity with the participant's daydreaming tendencies (FIG. 9). Those individuals who showed the greatest default network activity during the practiced task condition were self-described daydreamers.

Taken collectively, these findings converge to suggest that task contexts that encourage SIT production show the greatest default network activity; furthermore, individuals who daydream most show increased default network activity, at least when placed in a conducive experimental setting.

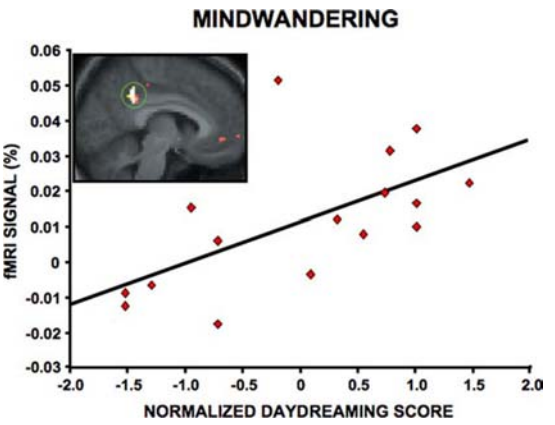


FIGURE 9. The default network is most active in individuals who report frequent mindwandering, suggesting a functional role in spontaneous cognition. Activity estimates are plotted for 16 subjects from PCC/Rsp (region shown in insert) from a task contrast conducive to encouraging mindwandering. The activity within this region is significantly correlated with individual self-reports of daydreaming obtained outside the scanner. Adapted from data published in Mason et al. (2007).

Momentary Lapses in Attention

An idea that emerges repeatedly in the study of internal mental activity is that there is competition between resources for internal modes of cognition and focus on the external world (Antrobus et al. 1966, 1970, Teasdale et al. 1995). In discussing forms of attention, William James (1890) wrote "When absorbed in intellectual attention we become so inattentive to outer things as to be 'absent-minded,' 'abstracted,' or 'distraits.' All revery or concentrated meditation is apt to throw us into this state" (pp. 418–419). In any given task context, there must be assignment of priorities for attending to external or internal channels of information, which in turn will have consequences for task performance (Singer 1966, Smallwood & Schooler 2006). When an external task is performed, focus on internal mental content will likely lead to mistakes or slowed performance on the immediate task at hand. Several studies have explored interactions between external attention and activity within the default network.

In one investigation, Greicius and Menon (2004) studied the dynamics of activity within the default network while people were presented blocks of external visual and auditory stimuli. They first showed that spontaneous activity correlations across regions within the default network continued during the stimulus blocks. The implication of this observation is that

spontaneous activity within the default network persists through both experimental and rest epochs. They further observed evidence for competition between sensory processing and spontaneous default network fluctuations: sensory-evoked responses were attenuated in those individuals who showed the strongest spontaneous activity correlations within the default network.

Momentary lapses in external attention were explored directly by Weissman and colleagues (2006) during a demanding perceptual task. Lapses in attention were defined as occurring when participants were slow to respond. Two observations were made. First, just prior to a lapse in attention, activity within brain regions associated with control of attention was diminished, including dorsal anterior cingulate and prefrontal cortex. Second, during the lapse of attention itself, activity within the default network was increased prominently in the PCC/Rsp. These findings suggest that transient lapses in the control of attention may lead to a shift in attention from the external world to internal mentation.

A related observation was made in the context of memory encoding by Otten and Rugg (2001). Brain activity was measured in two studies during the incidental encoding of words. The researchers found that increased activity in the posterior midline near PCC/Rsp and lateral parietal regions near IPL, among other regions, predicted which words would be later forgotten. This observation is consistent with the possibility that transient activity increases in the default network mark those trials on which the memorizers were distracted from their primary task, perhaps lapsing into private channels of thought.

Recently Li et al. (2007) tackled this possibility across two studies using a go/no-go paradigm. In their task, cues signaling participants to make speeded responses were intermixed with infrequent stop signals that mandated the responses should be withheld. Errors occurred when participants responded to stop signals. Exploring brain activity on the trials that preceded errors revealed that regions within the default network (MPFC and PCC/Rsp, but not IPL) augmented activity just prior to errors, an effect replicated in a second study. While again correlational, these data suggest that when the default network is active, lapses in focused external attention occur in ways that affect task performance.

However not all studies have found such relationships. Hahn et al. (2007), for example, noted that fast responses in a target-detection task were associated with increased default network activity (see Figure 3 in Hahn et al. 2007). Gilbert et al. (2006, 2007) hypothesized that the default network is associated with a broadly tuned form of outward attention ("watchfulness"). This idea, as will be discussed more extensively in the upcoming section, is reminiscent of Shulman and colleagues' (1997) suggestion that the default network participates in monitoring the external environment. While difficult to reconcile with the studies discussed earlier, the hypothesis put forward by Gilbert and colleagues is a reminder that evidence to date is limited and correlational, and further that opposing possibilities should be carefully explored. Thus, while an accumulating set of observations suggest that mindwandering is linked to increased activity in regions within the default network, further exploration is warranted to determine if the system is directly supporting the processes underlying the stimulus-independent thoughts that accompany mindwandering.

Spontaneous Activity Dynamics

The default network spontaneously exhibits slow waxing and waning of activity during rest that is correlated across its distributed regions (Greicius et al. 2003, Fox et al. 2005, Fransson 2005, Damoiseaux et al. 2006, Vincent et al. 2006). FIGURE 10 illustrates this robust phenomenon for a 5-minute epoch during which a young adult passively viewed a small fixation crosshair. As can be seen, activity within MPFC and PCC/Rsp—two of the most prominent components of the default network—spontaneously modulates over time. Critically, these two regions, which are anatomically distant from one another and supplied by separate vascular territories, show strong correlation, thereby indicating that the fMRI-measured activity swings arise from coordinated neural activity and not from measurement noise. The presence of fluctuations at rest—when SITs are at their peak—raises the question of whether these unprompted modulations reflect individual thoughts and musings (e.g., Greicius & Menon 2004, Fox et al. 2005, Fransson 2006). In a particularly thoughtful approach to this question, Fransson (2006) showed that correlated spontaneous activity within the default network attenuates when people perform a concurrent demanding cognitive task (see also Shannon et al. 2006). Such forms of tasks are known to reduce the frequency of SITs as discussed above (Antrobus et al. 1966, 1970).

While these observations are intriguing, there are several reasons to be cautious of presuming a simple relationship between spontaneous low-frequency activity modulations and cognitive processes (see Vincent et al. 2006, Fox & Raichle 2007). First,

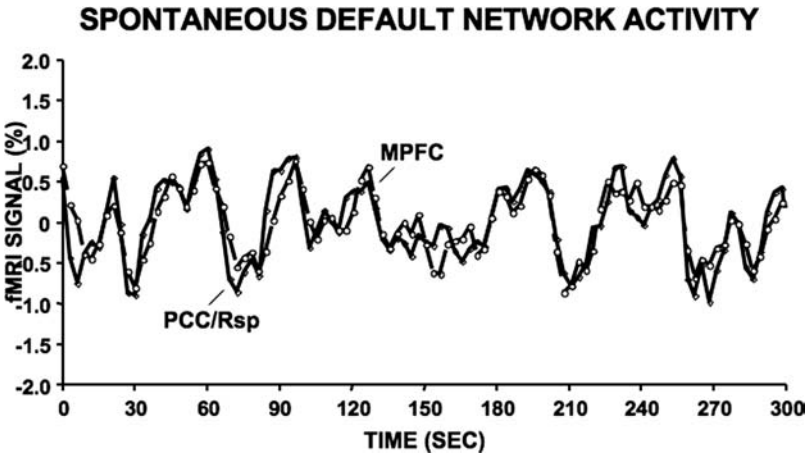


FIGURE 10. Regions within the default network spontaneously increase and decrease activity in a correlated manner. This is illustrated by plotting fMRI signal for two of the regions within the default network (PCC/Rsp and MPFC) as an individual rests in an awake state. Note that the activity slowly drifts about 2% and also that these intrinsic fluctuations are strongly correlated between the two regions. However, similar spontaneous correlations are observed between regions in other brain systems bringing into question whether this particular phenomenon is linked selectively to functional properties of the default network, such as spontaneous cognition. Adapted from data published in Fox et al. (2005).

spontaneous activity simultaneously exists in numerous brain systems including primary sensory and motor systems. It is not selectively observed in higher-order brain systems. Rather, spontaneous activity is pervasive (e.g., see De Luca et al. 2006). Second, spontaneous activity persists during sleep (Fukunaga et al. 2006, Horovitz et al. 2007) and under deep anesthesia verified by concurrently acquired burst-suppression electroencephalographic (EEG) patterns (Vincent et al. 2007a). Third, spontaneous activity is associated with extremely slow fluctuations that are slower than would be expected for cognitive events—less than one cycle every 10 seconds (Cordes et al. 2001, De Luca et al. 2006). Thus, while a considerable amount of data converges on the possibility that default network activity is associated with various forms of thought, the specific phenomenon of intrinsic low-frequency fluctuations may be incidentally related to immediate spontaneous thoughts (Vincent et al. 2006, Raichle 2006, Buckner & Vincent 2007). An intermediate possibility is that spontaneous activity fluctuations measured during rest may reflect *both* intrinsic low-level physiological processes that persist unrelated to conscious mental activity and also spontaneous cognitive events that come to dominate mental content when people are awake and disengaged from their external environments. An interesting future pursuit will be to disentangle these phenomena that are typically concurrent in awake states.

IV. Functions of the Default Network

A unique challenge for understanding the functions of the brain's default network is that the system is most active in passive settings and during tasks that direct attention away from external stimuli. This property informs us that contributions of the default network are suspended or reduced during commonly used active tasks but, unfortunately, tells us little about what the system does do. Two sources of data currently provide information about function. First, while most directed tasks cause task-induced deactivation within the network, there are an accumulating number of tasks that have been shown to elicit increased activity within the default network relative to other tasks. The properties that are common across these tasks provide some insight into function. Second, the specific anatomy of the default network constrains functional possibilities. For example, the default network does not include primary sensory or motor areas but does include areas associated with the medial temporal lobe memory system.

In this section, we explore two possible functions of the network, while recognizing that it is too soon to rule out various alternatives. One possibility is that the default network directly supports internal mentation that is largely detached from the external world. Within this possibility, the default network plays a role in constructing dynamic mental simulations based on personal past experiences such as used during remembering,

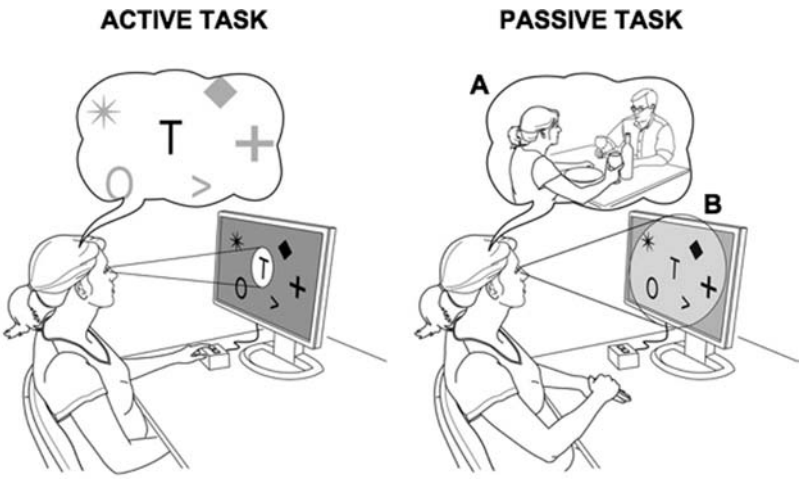


FIGURE 11. The functions of the default network have been difficult to unravel because passive tasks, which engage the default network, differ from active tasks on multiple dimensions. As one goes from an active task demanding focused attention (left panel) to a passive task (right panel), there is both a change in mental content **(A)** and level of attention to the external world **(B)**. Spontaneous thoughts unrelated to the external world increase **(A)**. There is also a shift from focused attention to a diffuse low-level of attention **(B)**. Hypotheses about the functions of the default network have variably focused on one or the other of these two distinct correlates of internally directed cognition.

thinking about the future, and generally when imagining alternative perspectives and scenarios to the present. This possibility is consistent with a growing number of studies that activate components of the default network during diverse forms of self-relevant mentalizing as well as with the anatomic observation that the default network is coupled to memory systems and not sensory systems. Another possibility is that the default network functions to support exploratory monitoring of the external environment when focused attention is relaxed. This alternative possibility is consistent with more traditional ideas of posterior parietal function but does not explain other aspects of the data such as the default network's association with memory structures. It is important to recognize that the correlational nature of available data makes it difficult to differentiate between possibilities, especially because focus on internal channels of thought is almost always correlated with a change in external attention (Fig. 11). We also explore in this section an intriguing functional property of the default network: the default network operates in opposition to other brain systems that are used for focused external attention and sensory processing. When the default network is most active, the external attention system is attenuated and vice versa.

Monitoring the External Environment: The Sentinel Hypothesis

One possibility is that the default network plays a role in monitoring the external environment (Ghatan et al. 1995, Shulman et al. 1997, Gusnard & Raichle 2001, Gilbert et al. 2007, Hahn et al. 2007). The hypothesis is that the critical difference between directed task conditions, which suspend activity within the default network, and passive conditions, which augment activity, is the form of their attentional focus on the external world. Active tasks typically require focused attention on foveal stimuli or on another type of predictable cue. By contrast, passive conditions release the participant to broadly monitor the external environment—what has been termed variably an "exploratory state" (Shulman et al. 1997) or "watchfulness" (Gilbert et al. 2007). Within this possibility, the default network is hypothesized to support a broad low-level focus of attention when one—like a sentinel—monitors the external world for unexpected events.

Hahn and colleagues (2007) specifically suggest that activity at rest "may reflect, among other functions, the continuous provision of resources for spontaneous, broad, and exogenously driven information gathering." By this view, task states represent the exceptional instances when focused attention is harnessed to respond to a specific, predictable event at the expense of broadly monitoring the environment. A variation of this idea is that external monitoring is more passive: the default network may mark a state of awareness of the external environment but should not be conceived of as supporting an active exploration. Rather, the default network may support low levels of attention that are

maintained in an unfocused manner while other, internally directed cognitive acts are engaged.

The sentinel hypothesis is consistent with certain properties of the default network as well as attentional deficits following bilateral posterior lesions. First, preliminary evidence suggests that task-induced deactivation in the default network is most pronounced during tasks that involve foveal as compared to parafoveal or peripheral stimuli (Shulman et al. 1997). Second, under some circumstances, performance on sensory processing tasks correlates positively with default network activity. Hahn et al. (2007), for example, observed that the default network was linked to high levels of performance on a target-detection task but only for a diffuse attention condition where targets appeared randomly at multiple possible locations. By contrast, performance was not associated with default network activity when attention was cued to a specific location. Finally, bilateral lesions that extend across precuneus and cuneus can induce Balint's syndrome (Mesulam 2000a). Balint's syndrome is characterized by a form of tunnel vision. Patients can only perceive a small portion of the visual world at one time and often fail to notice the appearance of objects outside the immediate focus of attention (Mesulam 2000a). This deficit is consistent with what might be expected if a brain system that supported global (as opposed to focused) attention were disrupted.

Constructing Alternative Perspectives: The Internal Mentation Hypothesis

An alternative hypothesis about the function of the default network is that it contributes directly to internal mentation. Self-reflective thought and judgments that depend on inferred social and emotional content robustly activate MPFC regions within the default network (e.g., Gusnard et al. 2001, Kelley et al. 2002, Mitchell et al. 2006). The default network also includes connections with the HF and overlaps with regions active during episodic remembering (e.g., Greicius et al. 2004, Buckner et al. 2005, Vincent et al. 2006). These later observations are particularly intriguing because we rely so heavily on memory when imagining social scenarios and other constructed mental simulations. Schacter and colleagues (2008), in this volume, explore the nature of cognitive processes linked to mental simulation (see also Tulving 2005, Gilbert 2006, Buckner & Carroll 2007, Schacter & Addis 2007, Schacter et al. 2007, Hassabis & Maguire 2007, Bar 2007, Gilbert & Wilson 2007). Here we discuss the possibility that the default network underlies these abilities. By mental simulation we mean here imaginative constructions of hypothetical events or scenarios.

Evidence that the default network participates in self-relevant mental simulation arises from the nature of the paradigms that have consistently activated the network. Particularly informative have been those that target autobiographical remembering, theory-of-mind, and envisioning the future (FIG. 12). During autobiographical memory tasks, individuals are encouraged to vividly recall past episodes from their own experiences. Such personal reminiscences are typically experienced as rich, mental simulations of the past event. Andreasen et al. (1995) were the first to note correspondence between autobiographical memory and the default network. In their study, autobiographical memory retrieval (as compared to a word fluency task) activated the major extent of the default network. Svoboda and colleagues (2006) recently conducted a thorough meta-analysis that included 24 separate PET and fMRI studies of autobiographical memory (see also reviews by Maguire 2001, Cabeza & St. Jacques 2007). In all the included studies, participants recalled experiences from their personal pasts. The aggregated plot across these studies highlights a set of regions remarkably similar to the default network including vMPFC, dMPFC, PCC/Rsp, IPL, LTC, and the HF (FIGS. 12 and 13).

Studies of theory of mind also reliably activate components of the default network. Theory of mind—also sometimes called "mentalizing"—refers to thinking about the beliefs and intentions of other people. In a typical test of theory of mind, a story is presented that requires the understanding of another person's perspective. Amodio and Frith (2006) provide the following example introduced by Wimmer and Perner (1983):

> Max eats half his chocolate bar and puts the rest away in the kitchen cupboard. He then goes out to play in the sun. Meanwhile, Max's mother comes into the kitchen, opens the cupboard and sees the chocolate bar. She puts it in the fridge. When Max comes back into the kitchen, where does he look for his chocolate bar: in the cupboard, or in the fridge?

To answer this question one must infer what Max is thinking—an inference that is adaptive and common to many social settings. Awareness of the mental states of people around us is important for anticipating behaviors and successfully navigating social interactions.

Commencing with the study of Fletcher et al. (1995), neuroimaging studies of theory of mind consistently reveal activity overlapping the default network (see Saxe et al. 2004, Amodio & Frith 2006 for recent reviews). FIGURE 12 shows an example using the task of Saxe and Kanwisher (2003, data from Andrews-Hanna et al. 2007b). In both the target and reference tasks,

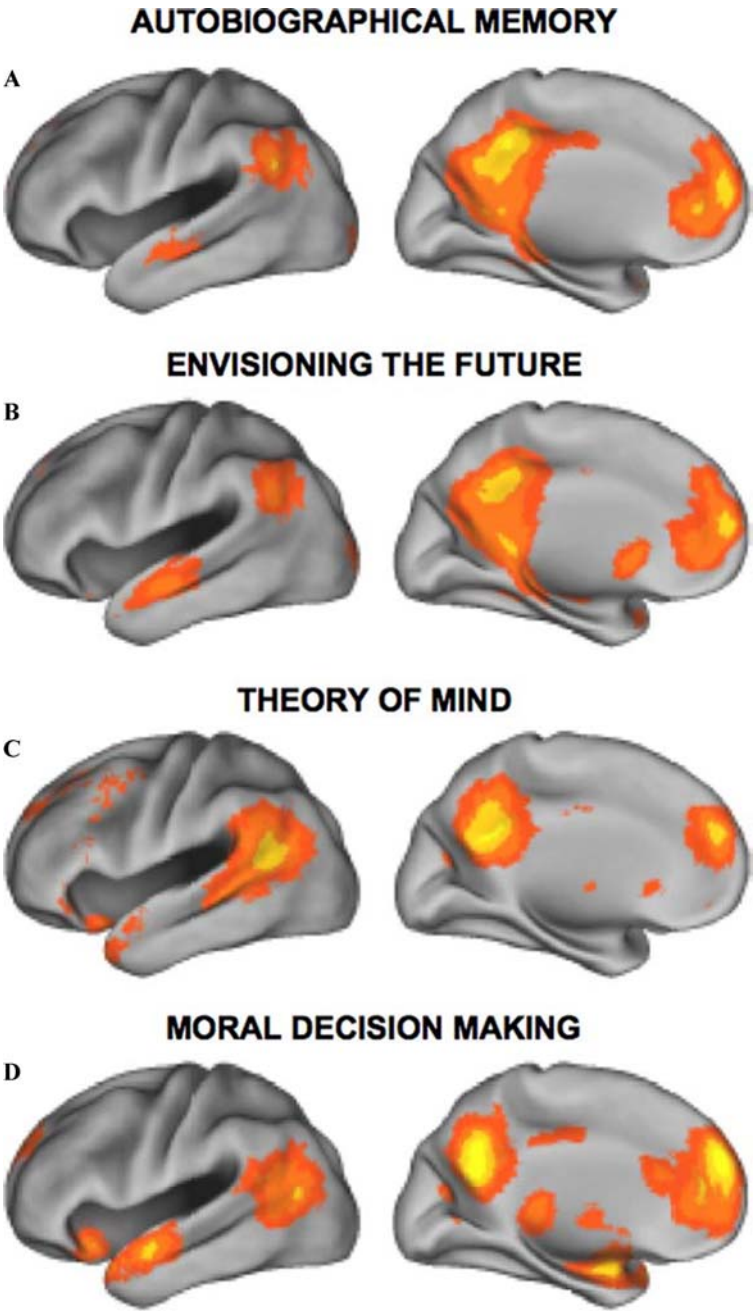


FIGURE 12. The default network is activated by diverse forms of tasks that require mental simulation of alternative perspectives or imagined scenes. Four such examples from the literature illustrate the generality. **(A)** Autobiographical memory: subjects recount a specific, past event from memory. **(B)** Envisioning the future: cued with an item (e.g., dress), subjects imagine a specific future event involving that item. **(C)** Theory of mind: subjects answer questions that require them to conceive of the perspective (belief) of another person. **(D)** Moral decision making: subjects decide upon a personal moral dilemma. Data come from prior studies and are here displayed using procedures similar to FIGURE 2. Data in A and B are from Addis et al. (2007). Data in C uses the paradigm of Saxe and Kanwisher (2003). Data in D is from Greene et al. (2001). Note that all the studies activate strongly PCC/Rsp and dMPFC. Active regions also include those close to IPL and LTC, although further research will be required to determine the exact degree of anatomic overlap. It seems likely that these maps represent multiple, interacting subsystems.

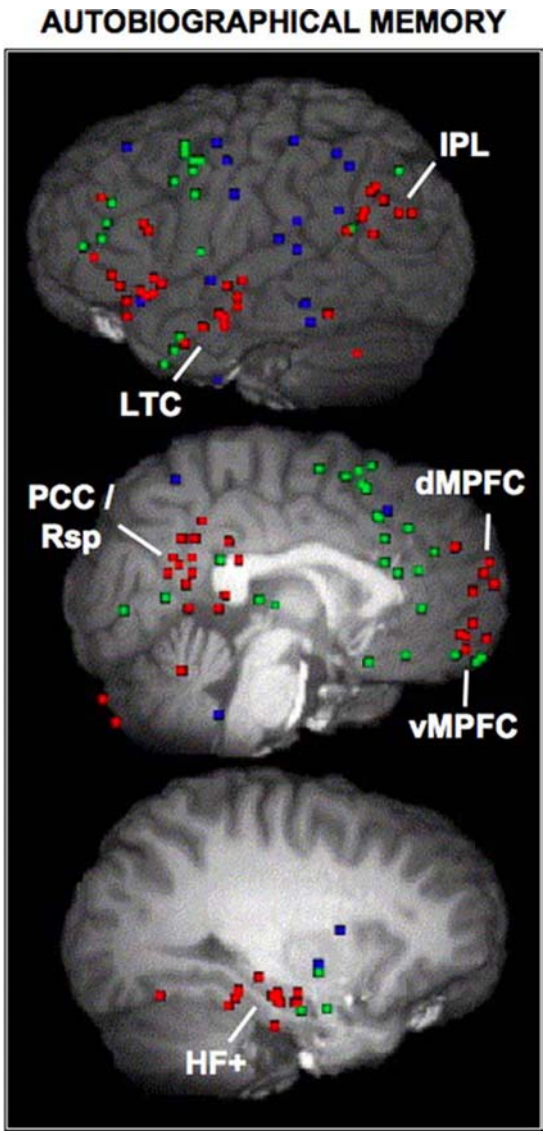


FIGURE 13. Meta-analysis of autobiographical memory tasks. Locations of activation during recall from autobiographical memory are plotted for 24 PET and fMRI studies on the lateral (top) and medial (middle) surfaces. A sagittal cut illustrates the plane of the hippocampal formation (bottom). Colors indicate whether the region contains high (red), medium (green), or low (blue) convergence across studies. Note the clear convergence with the core regions of the default network. Adapted from Svoboda et al. (2006).

subjects read stories that required conceiving a situation like the one above about Max. In one instance, the story was framed in relation to a person's beliefs; in another instance the question was about an inanimate object. For example, a story on what a person believed about an event was compared to a similar story about what a camera captured in a photograph. As can be seen in FIGURE 12, this contrast activates multiple regions within the default network, including prominently dMPFC, PCC/Rsp, and a region near IPL close to the temporo-parietal junction. In a follow-up study, Saxe and Powell (2006) showed that certain regions in the default network, including PCC, did not differentially activate to stories about people's bodily sensations (being hungry, cold) or stories that contained descriptions of people's appearances. PCC was only differentially responsive when stories required conceiving another person's thoughts.

Rilling and colleagues (2004) provide another example of default network activity during interpersonal interactions that depend on inferences about other people's thoughts. In their study, the participants were introduced to 10 living individuals just prior to going into the scanner. While in the scanner, they played a series of game trials where, on each trial, they either chose to cooperate or work against one of the other people. The outcome on each trial was determined both by the participant's decision and also the choice of a putative human playing partner. For example, the playing partner could appear to work against the participant. As a control, the participants performed a rewarded control task that did not involve playing the game. In reality, the participants were always playing a computer but believed fully they were playing real people. Brain activity in the default network differed markedly when the individuals believed they were playing other people as compared to the control task. Moreover, the activity modulation occurred when they received feedback about what the other players chose, suggesting a role in making inferences about other's minds.

The third class of task involves envisioning the future. Schacter et al. (2007, 2008) discuss in detail findings from such paradigms, so we only briefly mention them here. In the prototypical paradigm, participants are given a cue and instructed to imagine a future situation related to that cue. For example, cued with the word "dress," a participant in Addis et al. (2007) reported an imagined scene that included the following: "My sister will be finishing her undergraduate education. . . And I can see myself sitting in some kind of sundress, like yellow, and under some trees." Behavioral studies show that individuals are quite adept at conceiving plausible future scenarios that contain considerable detail and emotional content (D'Argembeau & Van der Linden 2006). Several such studies have been reported using PET and fMRI (Partiot et al. 1995, Okuda et al. 2003, Szpunar et al. 2007, Addis et al. 2007, Sharot et al. 2007, Botzung et al. 2008, D'Argembeau et al. in press). All these studies activated regions within the default

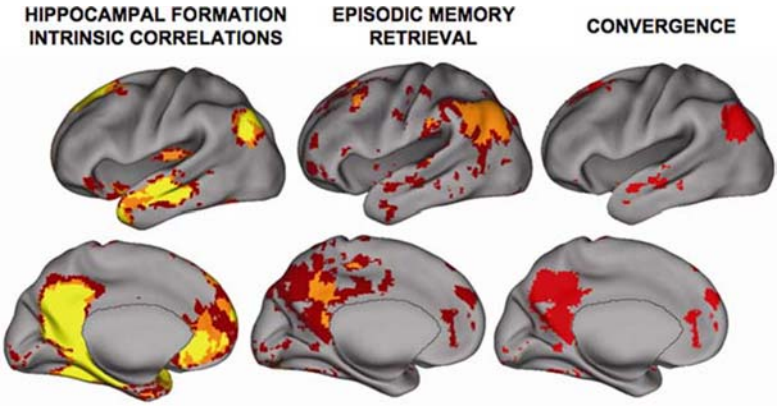


FIGURE 14. Posterior regions within the default network overlap regions that are active during successful episodic memory retrieval. (left) Image of the default network subsystem correlated with the hippocampal formation. These data represent the surface projection of data from FIGURE 3B. Adapted from Vincent et al. (2006). (middle) Image of successful episodic memory retrieval. This image shows regions with high levels of activity during episodic recollection as compared to familiarity-based recognition. Adapted from Wagner et al. (2005). (right) Regions of convergence across the two maps extend to the PCC/Rsp, IPL, and portions of MPFC.

network. Data from Addis et al. (2007) are plotted in FIGURE 12 to illustrate the similarity of the activated region to that of the default network.

An immediate question that arises based on the above observations is: What does this generality mean? While remembering, envisioning the future, and conceiving the mental states of others are different on several dimensions including temporal focus (e.g., past versus present) and personal perspective (e.g., self versus another person), they all converge on similar core processes (Buckner & Carroll 2007, FIGURE 12). In each instance, one is required to simulate an alternative perspective to the present. These abilities, which are most often studied as distinct, rely on a common set of processes by which mental simulations are used adaptively to imagine events beyond those that emerge from the immediate environment.

By this hypothesis, a defining property of the default network is its flexibility. The tasks that activate the default network share core processes in common but differ in terms of the content and goal to which these processes are applied. As a further example that illustrates the breadth of domains that activate the default network, Greene and colleagues (2001) explored brain regions supporting moral decisions. Their paradigms required individuals to evaluate whether a hypothetical action was moral or immoral (Greene & Haidt 2002). They observed that certain forms of moral judgment activated default network regions (Greene et al. 2001, FIG. 12). In particular, the default network was most active when evaluations included personal moral dilemmas (e.g., Consider whether it would be morally acceptable for you to push one person off a sinking boat to save five others). Solving moral dilemmas may be exactly the kind of situation where people simulate alternative events in the service of evaluating them (see Moll et al. 2005 for related discussion). While not explored to date, one wonders whether many reflective cognitive experiences—such as pride, shame, and guilt—are built upon the capacity of the default network to enable contrasts among imagined social scenarios and settings.

The possibility that the default network contributes to internal channels of thought is consistent with the subsystems that comprise its anatomy. The medial temporal lobe subsystem is associated with mnemonic processes and is activated during successful retrieval of old information from memory (see Wagner et al. 2005 for a review). FIGURE 14 illustrates this functional aspect of the medial temporal lobe subsystem by comparing regions intrinsically correlated with the HF to regions responding in traditional memory paradigms. There is considerable overlap between the two approaches, especially for PCC/Rsp and IPL. Furthermore, activity within the medial temporal lobe subsystem increases during retrieval of strong memory traces that include remembered associations and content details (Henson et al. 1999, Eldridge et al. 2000, Wheeler & Buckner 2004, Yonelinas et al. 2005). Taken together, these observations suggest that this subsystem contributes associations and relational information from memory perhaps to provide the critical building blocks of mental exploration (see also Bar 2007, Addis & Schacter 2008).

The second subsystem is linked to the MPFC, specifically dMPFC. dMPFC is activated by many task situations that require participants to make self-referential judgments and engage in other forms of self-relevant mental exploration (e.g., Gusnard et al. 2001, Kelley et al. 2002, Mitchell et al. 2006, see Adolphs 2003, Ramnani & Owen 2004, Amodio & Frith 2006 for relevant reviews). All the task forms noted above that activate the complete, or near complete, default network share in common that the imagined perspectives are self-referenced. Moreover, several findings suggest that reference to the self causes selective and preferential activity within the MPFC subsystem. For example, Szpunar et al. (2007) noted that MPFC was strongly activated by envisioning oneself in the past or future but not so for considering a personally unfamiliar public figure in a future setting. Saxe and Kanwisher (2003) showed greater dMPFC activity for making decisions about conceived perspectives of people as compared to inanimate objects (e.g., a camera). Güroğlu et al. (2008) demonstrated increased activity in the dMPFC and throughout the default network when individuals made judgments about whether to approach familiar peers versus celebrities in an imagined social setting. Mitchell and colleagues (2006) provided a particularly clear example of modulation along the "self" dimension. In their study, individuals made judgments about a fictitious person who was described as being either quite similar in sociopolitical views to the participant or quite different. Judgments made about similar others activated dMPFC to about the same degree as making a judgment about oneself. In contrast, judgments about people perceived as being politically different did not activate dMPFC.[d]

Thus, while it is admittedly difficult to define what is self or self-like, dMPFC is activated when the content of an imagined setting involves social agents that are being considered as such. Note that a subtle distinction is being drawn here: the common element that activates dMPFC does not appear to simply be reference to a person or oneself, which can occur devoid of elaborated context. The common element appears to align more with *thinking* about the complex interactions among people that are conceived of as being social, interactive, and emotive like oneself.

Within this hypothesis, the default network thus comprises at least two distinct interacting subsystems—one subsystem functions to provide information from memory; the second participates to derive self-relevant mental simulations. The adaptive function may be to provide a "life simulator"—a set of interacting subsystems that can use past experiences to explore and anticipate social and event scenarios (Gilbert 2006, Gilbert & Wilson 2007). This idea is similar to a recent hypothesis from Bar (2007) that the HF subsystem serves to supply associations and analogies from past experience to make predictions about upcoming events. An open question is when mental simulation depends on the interactions between both subsystems. As the functional analysis reveals, the dMPFC and medial temporal lobe are not intrinsically correlated with one another, suggesting some level of functional separation (FIG. 8). Certain situations draw heavily on both subsystems such as elicited during autobiographical memory tasks and when thinking about the future. Theory-of-mind tasks, while utilizing the dMPFC subsystem, activate the medial temporal lobe minimally. One possibility is that the dMPFC subsystem interacts with the medial temporal lobe subsystem to the degree that past episodic information is an important constraint on the mental simulation being derived. The convergence of the two subsystems on common hubs, in particular PCC, may serve to prepare the system for these critical interactions.

Competitive Functional Interactions

When initially considering the possibility of a brain system for internal mentation, Ingvar (1979) proposed that such a system might work in opposition to those specialized for sensory processing, which he termed "sensory-gnostic." He noted that

> the low flow/activity in postcentral sensory-gnostic regions appears to agree with a low general awareness of the sensory input from the immediate surroundings, when one is left to oneself, undisturbed, resting awake. Possibly the lower postcentral [flow] signals that the resting consciousness implies an active global inhibition of a sensory input, as if the brain filtered out trivial information in order to let the mind be busy with its own consciousness (p. 20).

The idea that the brain's default network may work in direct opposition to other systems has received recent support from the observation of strong negative activity correlations between the default network and other systems—coined variably "dynamic equilibrium" and "anticorrelations" (Greicius et al. 2003, Fransson 2005, Fox et al. 2005, Golland et al. 2007, Tian et al. 2007). For simplicity, we use the term "anticorrelation" as proposed by Fox et al. (2005).

[d] Dorsal and ventral are relative terms and are used variably depending on which regions are being compared. This paper defines dMPFC and vMPFC differently than did Mitchell et al. (2006). The region labeled here as dMPFC is the region Mitchell et al. describe as being ventral.

FIGURE 15 illustrates the phenomenon of anticorrelation. As shown earlier, the distributed regions within the default network show spontaneous correlations with one another (see FIG. 7). These intrinsic correlations also exist in other brain systems including those dedicated to external attention (as described by Corbetta & Shulman 2002). The phenomenon of anticorrelation refers to the additional observation that these distinct brain systems show strong negative correlations with one another: as activity within the default network increases, normalized activity in the external attention system show activity decreases.[e] This finding suggests that the brain may shift between two distinct modes of information processing. One mode, marked by activity within the default network, is detached from focused attention on the external environment and is characterized by mental explorations based on past memories. The second mode is associated with focused information extraction from sensory channels. These systems may be opposed to one another and thus represent functionally competing brain systems.

The possibility of competition raises important questions for future research—how is this competition regulated? Is there a separate control system, perhaps mediated by frontal cortex, that in some manner directs which of these two brain systems is active? Or, are the two systems in direct competition with one another in a way that local competitive interactions between them and input systems define their levels of activity? While minimal data exist to inform this question, Vincent and colleagues (2007b) have recently reported preliminary evidence for a frontal-parietal brain system that is anatomically juxtaposed between the default network and systems associated with external attention, providing a candidate for controlling the functional interactions between the two anticorrelated brain networks.

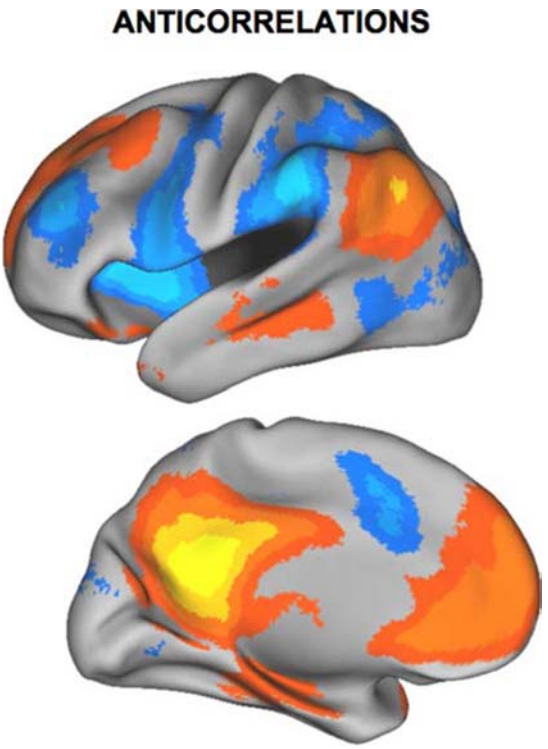


FIGURE 15. Intrinsic activity suggests that the default network is negatively correlated (anticorrelated) with brain systems that are used for focused external visual attention. Anticorrelated networks are displayed by plotting those regions that negatively correlate with the default network (shown in blue) in addition to those that positively correlate (shown in red). These two anticorrrelated networks may participate in distinct functions that compete with one another for control of information processing within the brain. Data are the same as analyzed for FIGURE 7.

V. Relevance to Brain Disease

To this point, extensive data have been considered that suggest humans possess a set of closely interacting subsystems known as the default network. One hypothesis is that, using memories and associations from past experiences as its building blocks, the default network participates in constructing self-relevant mental simulations that are exploited by a wide range of functions including remembering, thinking about the future, and inferring the perspectives and thoughts of other people. When left undisturbed, this is the network people engage by default. The focus of the present section is to explore the relationship of the default network to mental disorders including autism, schizophrenia, and Alzheimer's disease (TABLE 2). Each of these three clinical conditions is associated with cognitive dysfunction in domains that are linked to the default network. Other disorders for which important links are being made to the default network but are beyond the scope of this review include depression, obsessional disorders, attention-deficit/hyperactivity disorder, and post-traumatic stress disorder.

[e] A difficult technical issue associated with spontaneous negative correlations arises because the activity levels are normalized to remove global activity variation. Without such normalization, whole-brain signal fluctuations dominate the local regional correlations. This form of normalization causes the correlation strengths to be distributed around zero (Vincent et al. 2006) forcing negative correlations to emerge. Further research will be required to understand the contributions of normalization to negative correlations in spontaneous activity.

TABLE 2. Selected papers on cognitive disorders associated with the default network

	DATA TYPE
Autism Spectrum Disorders	
Castelli et al. (2002)	Activity–TID
Waiter et al. (2004)	Structure
Kennedy et al. (2006)	Activity–TID
Cherkassky et al. (2006)	Activity–fcMRI
Kennedy & Courchesna (2008)	Activity–fcMRI
Schizophrenia	
Harrison et al. (2007)	Activity–TID
Bluhm et al. (2007)	Activity–fcMRI
Garrity et al. (2007)	Activity–TID/fcMRI
Zhou et al. (2007)	Activity–fcMRI
Alzheimer's Disease	
Reiman et al. (1996)	Metabolism
Minoshima et al. (1997)	Metabolism
Herholtz et al. (2002)	Metabolism
Buckner et al. (2005)	PIB-PET, Structure
Scahill et al. (2002)	Structure
Thompson et al. (2003)	Structure
Lustig et al. (2003)	Activity–TID
Celone et al. (2006)	Activity–TID
Greicius et al. (2004)	Activity–fcMRI
Rombouts et al. (2005)	Activity–fcMRI
Wang et al. (2007)	Activity–fcMRI
Sorg et al. (2007)	Activity–fcMRI, Structure

Notes: Listed are example references that link disruption of the default network with disease. Type refers to the primary form of support in the paper for the association: Activity–TID, Task-induced deactivation data from either PET or fMRI; Activity–fcMRI, functional connectivity analysis from fMRI; Structure, Structural data from MRI; Metabolism, Resting glucose metabolism from PET; PIB-PET, amyloid binding as measured by PET. This list is not comprehensive, especially for metabolism studies that have a long history.

Autism Spectrum Disorders

The autism spectrum disorders (ASD) are developmental disorders characterized by impaired social interactions and communication. Symptoms emerge by early childhood and include stereotyped (repetitive) behaviors. Baron-Cohen and colleagues (1985) proposed that a core deficit in many children with ASD is the failure to represent the mental states of others, as needed to solve theory-of-mind tasks. Based on an extensive review of the functional anatomy that supports theory-of-mind and social interaction skills, Mundy (2003) proposed that the MPFC may be central for understanding the disturbances in ASD. Given the convergent evidence presented here that suggests the default network contributes to such functions, it is natural to explore whether the default network is disrupted in ASD.

Developmental disruption of the default network, in particular disruption linked to the MPFC, might result in a mind that is environmentally focused and absent a conception of other people's thoughts. The inability to interact with others in social contexts would be an expected behavioral consequence. It is important to also note that such disruptions, if identified, may not be linked to the originating developmental events that cause ASD but rather reflect a developmental endpoint. That is, dysfunction of the default network and associated symptoms may emerge as an indirect consequence of early developmental events that begin outside the network.

Many studies have explored whether ASD is associated with morphological differences in brain structure. The general conclusion from this literature is that the brain changes are complex, reflecting differences in growth rates and attenuation of growth (see Brambilla et al. 2003 for review). At certain developmental stages these differences are manifest as overgrowth and at later stages as undergrowth. Early observations have implicated the cerebellum. A further consistent observation has been that the amygdala is increased in volume in children with ASD (e.g., Abell et al. 1999, Schumann et al. 2004), perhaps as a reflection of abnormal regulation of brain growth (Courchesne et al. 2001). While not discussed earlier because of our focus on cortical regions, the amygdala is known to contribute to social cognition (Brothers 1990, Adolphs 2001, Phelps 2006) and interacts with regions within the default network. The amygdala has extensive projections to orbital frontal cortex (OFC) and vMPFC (Carmichael & Price 1995).

Of perhaps more direct relevance to the default network, dMPFC has shown volume reduction in several studies of ASD that used survey methods to explore regional differences in brain volume (Abell et al. 1999, McAlonan et al. 2005). The effects are subtle and will require further exploration, but it is noteworthy that, of those studies that have looked, several have noted dMPFC volume reductions in ASD. Of interest, a study using voxel-based morphometry to investigate grey matter differences in male adolescents with ASD noted that several regions within the default network exhibited a relative increase in grey matter volume compared to the control population (Waiter et al. 2004). Because this observation has generally not been replicated in adult ASD groups, future studies should investigate whether complex patterns of overgrowth and undergrowth of the regions within the default network exist in ASD and, if so, whether they track behavioral improvement on tests of social function (see also Carper & Courchesne 2005).

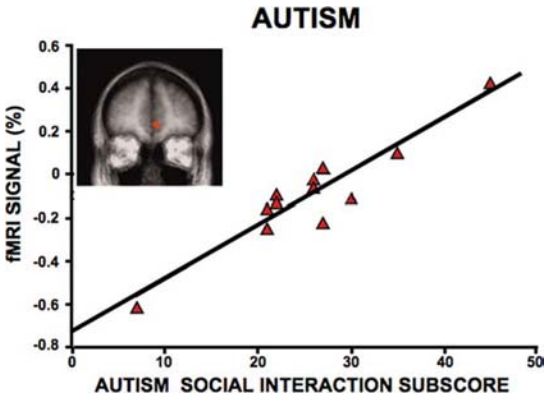


FIGURE 16. Default network activity tracks the severity of social dysfunction in autism. An exploratory correlational analysis by Kennedy et al. (2006) found that activity within MPFC (region shown in inset) was correlated with social impairment as measured by the Autism Diagnostic Interview–Revised. Individuals with autism spectrum disorder who showed less task-induced deactivation had lower social impairment scores. Adapted from Kennedy et al. (2006).

Kennedy and colleagues (2006) recently used fMRI to directly explore the functional integrity of the default network in ASD. In their study, young adults with ASD and age-matched individuals without ASD were imaged during passive tasks and demanding active tasks that elicit strong activity differences in the default network. While the control participants showed the typical pattern of activity in the default network during the passive tasks, such activity was absent in the individuals with ASD. Direct comparison between the groups revealed differences in vMPFC and PCC. Moreover, in an exploratory analysis of individual differences within the ASD group, those individuals with the greatest social impairment (measured using a standardized diagnostic inventory) were those with the most atypical vMPFC activity levels (Fig. 16). An intriguing possibility suggested by the authors of the study and extended by Iacoboni (2006) is that the failure to modulate the default network in ASD is driven by differential cognitive mentation during rest, specifically a lack of self-referential processing.

Another recent study using analysis of intrinsic functional correlations showed that the default network correlations were weaker in ASD (Cherkassky et al. 2006). Of note, the individuals with ASD showed differences in a fronto-parietal network that has been recently hypothesized to control interactions between the default network and brain systems linked to external attention (Vincent et al. 2007b). These data in ASD suggest an interesting possibility: the default network may be largely intact in ASD but under utilized perhaps because of a dysfunction in control systems that regulate its use.

Schizophrenia

Schizophrenia is a mental illness characterized by altered perceptions of reality. Auditory hallucinations, paranoid and bizarre delusions, and disorganized speech are common positive clinical symptoms (Liddle 1987). Cognitive tests also reveal negative symptoms, including impaired memory and attention (Kuperberg & Heckers 2000). These symptoms lead to questions about their relationship to the default network for a few reasons. The first reason surrounds the association of the default network with internal mentation. Many symptoms of schizophrenia stem from misattributions of thought and therefore raise the question of an association with the default network because of its functional connection with mental simulation. A second related reason has to do with the broader context of control of the default network. While still poorly understood, there appears to be dynamic competition between the default network and brain systems supporting focused external attention (Fransson 2005, Fox et al. 2005, Golland et al. 2007, Tian et al. 2007, see also Williamson 2007). Frontal-parietal systems are candidates for controlling these interactions (Vincent et al. 2007b). The complex symptoms of schizophrenia could arise from a disruption in this control system resulting in an overactive (or inappropriately active) default network. The normally strongly defined boundary between perceptions arising from imagined scenarios and those from the external world might become blurry, including the boundary between self and other (similar to that proposed by Frith 1996).

Three studies have provided preliminary data supporting the possibility that the default network is functionally overactive. Garrity and colleagues (2007) recently reported an analysis of correlations among default network regions in patients with schizophrenia. Studying a sizable data sample (21 patients and 22 controls), they explored task-associated activity modulations within the default network and identified largely similar correlations among default network regions in patients and controls. Differences were noted in specific subregions, as were differences in the dynamics of activity as measured from the timecourses of the fMRI signal. Of particular interest, they noted that within the patient group, the positive symptoms of the disease (e.g., hallucinations, delusions, and thought confusions) were correlated with increased default network activity during the passive epochs, including MPFC and PCC/Rsp. In a related analysis, Harrison et al. (2007) noted accentuated default network activity during

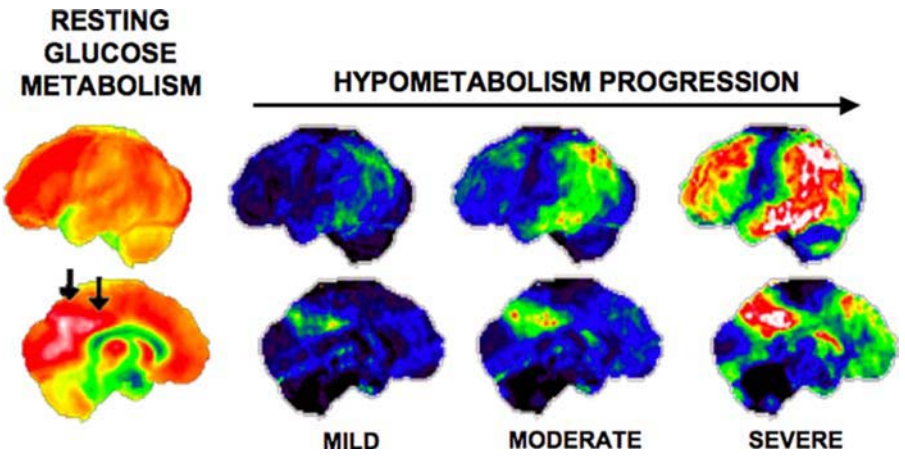


FIGURE 17. Glucose metabolism within the default network is reduced in Alzheimer's disease. Normal resting glucose metabolism shows a disproportionately high level of metabolism in healthy individuals as measured by FDG-PET (left). Arrows indicate high metabolism near PCC/Rsp. Alzheimer's disease is consistently associated with progressive reduction in glucose metabolism (hypometabolism) in specific regions that overlap the default network (right). These data map the glucose metabolism reduction from a cross-sectional sample of older adults across the range of mild (Mini-Mental Status Examination score, MMSE = 30), moderate (MMSE = 20), and severe (MMSE = 0) Alzheimer's disease. Adapted from Minoshima et al. (1997).

passive task epochs in patients with schizophrenia as contrasted to controls, again suggesting an overactive default network. Moreover, within the patient group, poor performance was again correlated with MPFC activation during the passive as compared to the active tasks. Finally, Zhou and colleagues (2007) found that regions constituting the default network were functionally correlated with each other to a significantly higher degree in patients than in control participants. Thus, while the data are limited, these studies converge to suggest that patients with schizophrenia have an overactive default network, as would be expected if the boundary between imagination and reality were disrupted. Overactivity within the network correlates with task performance (Harrison et al. 2007) and clinical symptoms (Garrity et al. 2007).

Alzheimer's Disease

The most compelling link between clinical disease and disruption of the default network occurs in Alzheimer's disease (AD). AD is a progressive dementia typically occurring after the age of 70 and affecting approximately half of older adults above 85. Initial symptoms are memory difficulties, but sensitive tests often reveal disturbances of executive function as well (e.g., Balota & Faust 2001). AD has been extensively studied in living individuals using multiple imaging approaches including measurement of glucose metabolism, measurement of structural atrophy, and measurement of intrinsic and task-evoked brain activity (TABLE 2). All approaches converge to suggest that the default network is disrupted.

The earliest evidence that the default network is disrupted in AD comes from studies of resting glucose metabolism. Patients with AD show a specific anatomic pattern of reduced metabolism relative to age-matched healthy peers (Benson et al. 1983, Kumar et al. 1991, Herholz 1995, Minoshima et al. 1997, de Leon et al. 2001, Alexander et al. 2002, FIG. 17). The pattern of hypometabolism bears a striking resemblance to the regions comprising the posterior components of the default network including PCC/Rsp, IPL, and LTC (Buckner et al. 2005). Hypometabolism in AD progresses with the disease and correlates with mental status (e.g., Minoshima et al. 1997, Herholz et al. 2002). Patients at genetic risk for AD also show similar metabolism differences, implying the disturbances occur early in the course of the disease (Reiman et al. 1996).

Methods that survey atrophy across the brain in AD have also all converged to show disruption in the default network prominently including the medial temporal lobe (Scahill et al. 2002, Thompson et al. 2003, Buckner et al. 2005). Accelerated atrophy is present in PCC/Rsp and the medial temporal lobe at the preclinical stages of the disease, again implying the default network is disrupted early as the disease progresses (Buckner et al. 2005). Recently, functional changes in the default network have been explored in AD using both analysis of task-induced deactivation (Lustig

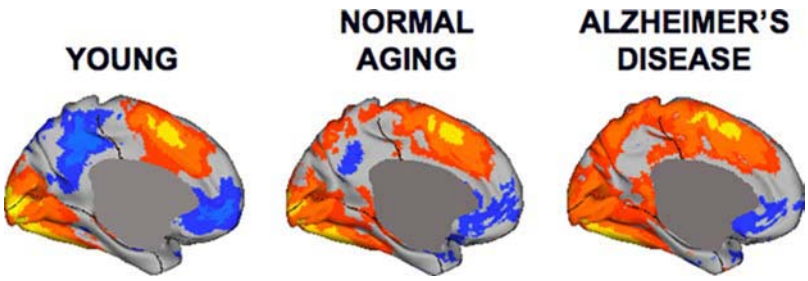


FIGURE 18. Activity within the default network is disrupted in Alzheimer's disease. Task increases (red) and decreases (blue) from a simple word classification task referenced to a passive baseline task are plotted for young adults (left panel), normal older adults (middle panel), and demented older adults with AD (right panel). The young adults show the classic pattern of task-induced deactivation within PCC/Rsp and MPFC. The effect attenuates significantly in AD. Adapted from Lustig et al. (2003, see also Greicius et al. 2004).

et al. 2003, Celone et al. 2006) and analysis of intrinsic activity correlations (Greicius et al. 2004, Rombouts et al. 2005, Celone et al. 2006, Wang et al. 2006). Again, in all instances, disruption has been noted consistent with the metabolic and structural changes. FIGURE 18 shows data from Lustig et al. (2003).

Thus, by all measures the default network appears disrupted in AD, including prominently the medial temporal lobe susbsystem. Recently, molecular imaging methods able to measure AD pathology (Klunk et al. 2004) have revealed an even more surprising link to the default network: pathology preferentially accumulates in the default network even before symptoms emerge. In the next section, we will explore the possibility that metabolic properties or activity patterns within the default network directly relate to—or even cause—the pathology of AD (Buckner et al. 2005).

Default Network Activity May Set the Stage for Alzheimer's Disease: The Metabolism Hypothesis

AD pathology forms preferentially throughout the default network, suggesting the unexpected possibility that activity within the network may facilitate disease processes (Buckner et al. 2005). The leading hypothesis about the cause of AD proposes that toxic forms of the amyloid ß protein (Aß) initiate a cascade of events ending in synaptic dysfunction and cell death (Walsh & Selkoe 2004, Mattson 2004). "Plaques" and "tangles" are the residues of this pathological process. Consistent with the clinical observation that initial symptoms of the disease include memory impairment, the medial temporal lobe and cortical structures linked to memory are affected early in the disease. Several theories have offered explanations for why memory structures are particularly vulnerable to the disease, including ideas based on anatomy (Hyman et al. 1990) and also the possibility that memory structures are sensitive to toxicity because of their role in plasticity (Mesulam 2000b). Early pathological studies also implicated distributed cortical regions as vulnerable to AD (e.g., Brun & Gustafson 1976) leading to a call to explore further systems-level causes of the disease (Saper et al. 1987). The discovery of the default network and the observation that it is active during rest states suggests a novel hypothesis regarding the origins of AD.

The basic idea is that the default network's continuous activity augments an activity-dependent or metabolism-dependent cascade that is conducive to the formation of AD pathology. Buckner and colleagues (2005) referred to this idea as the "metabolism hypothesis." Maps of Aß plaques in living individuals provide the key evidence (Klunk et al. 2004), as images of Aß plaques taken at the earliest stages of AD show a distribution that is remarkably similar to the anatomy of the default network (Buckner et al. 2005, FIG. 19). About 10% of nondemented older individuals also show this pattern, presumably reflecting the preclinical stage of the disease (Buckner et al. 2005, Mintun et al. 2006a). The preferential use of the default network throughout life may be conducive to increased accumulation of Aß and its pathological sequelae. By this view, memory systems may be preferentially affected by the disease because these systems play a central role in resting brain activity as part of the default network.

Several recent observations lend support to the metabolism hypothesis, although it should still be considered highly speculative. Of particular interest is the discovery of a plausible biological link between neural activity and upregulation of Aß. In a technically innovative study, Cirrito and colleagues (2005) showed that Aß levels increased following stimulation of the brain

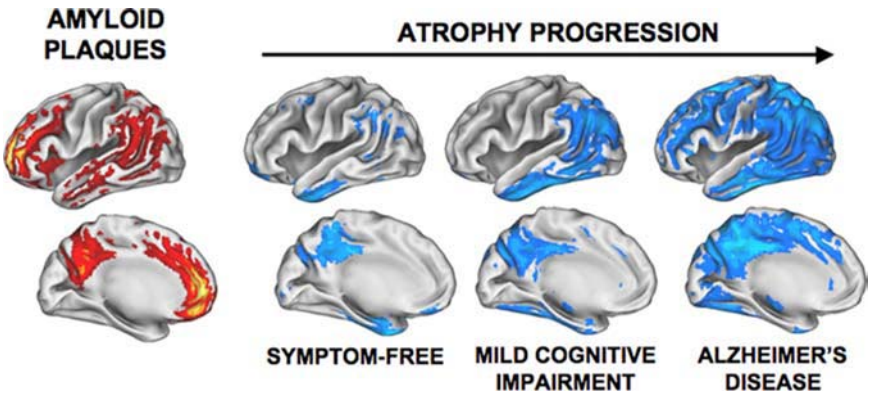


FIGURE 19. Alzheimer's disease may be causally related to default network activity. Regions manifesting default activity in young adults (e.g., FIGS. 2 and 7) are highly similar to those that show pathology in early stages of the disease as measured by molecular imaging of amyloid plaques using PET (left). These regions, in turn, appear affected by structural atrophy as measured by longitudinal MRI (right). One possibility is that activity within the default network augments an activity-dependent or metabolism-dependent cascade that leads to the formation of Alzheimer's disease pathology. Adapted from Buckner et al. (2005).

in living genetically engineered mice expressing human proteins that form the building blocks of Aß. This observation suggests that synaptic activity can increase the presence of extracellular Aß (see also Selkoe 2006). A further supporting observation comes from a new PET method to map glycolysis based on measuring the ratio of oxygen to glucose consumption. Glycolysis is the process by which glucose is metabolized into cellular energy. The map of rest-state glycolysis correlates remarkably well with the distribution of amyloid plaques (Mintun et al. 2006a). The metabolism hypothesis might also explain certain risk factors for AD. Specifically, a genetic risk factor was recently discovered that links to the enzyme GAPDH involved in glycolysis (Li et al. 2004). If AD takes foothold earliest in regions of high glycolytic metabolism within the default network, it is possible that the explanation for this genetic risk factor may lie in differences in metabolic efficiency across individuals (Buckner et al. 2005).

At the most global level, the possibility that brain activity states can influence a disease process has implications for intervention and understanding of disease. We so often think about how aberrant molecular and cellular processes affect brain circuits and cognitive processes. The present hypothesis highlights a potential influence in the opposite direction: brain activity patterns may directly modulate the molecular cascades that are relevant to disease. In the case of AD, rest-state activity may accelerate the formation of pathology. Intervention may take the form of a therapy that modifies glycolysis or other aspect of brain metabolism.

VI. Conclusions

The brain's default network is a recently described brain system that has been identified using neuroimaging methods. The reviewed findings suggest properties of the network that set it apart from other brain systems. In particular, the default network is the most active brain system when individuals are left to think to themselves undisturbed. The default network also increases activity during mental explorations referenced to oneself including remembering, considering hypothetical social interactions, and thinking about one's own future. These properties suggest that the default network functions to allow flexible mental explorations—simulations—that provide a means to prepare for upcoming, self-relevant events before they happen.

Analysis of connectional anatomy in the monkey and intrinsic functional correlations between regions in the human suggest that the default network is organized around a set of interacting subsystems that comprise distributed association areas of the brain (TABLE 2, FIGS. 7 and 8). The main hubs of the default network are within the MPFC cortex and along the posterior midline including PCC. A particularly important direction for future research will involve the study of behavioral deficits following damage to regions within the network and also the study of nonhuman primate models that allow causal inferences about function to be explored.

Characterization of the default network, unlike study of other brain systems, arose almost entirely from correlational imaging approaches. The study of most

other brain systems has been initiated by a neurological syndrome and then probed further using animal models and neuroimaging approaches. On the one hand, the discovery of the brain's default network represents a unique contribution of neuroimaging to cognitive neuroscience. On the other hand, there have been no lesion studies that motivate their behavioral probes based on the recent characterization of the network, leaving a large number of questions unanswered. Providing some information, studies of patients with lesions to regions overlapping the default network are noted in the present review and also discussed in the companion paper of Schacter et al. (2008). However, considerably more work needs to be conducted.

A further open issue is how the default network interacts with the distributed brain systems that contribute content to the process of mental exploration. Studies of episodic memory retrieval have shown that visual cortex and auditory cortex are preferentially activated during the recollection of visual objects and sounds (e.g., Nyberg et al. 2000, Wheeler et al. 2000). Imagining the personal future, which activates the default network under many contexts, has also been demonstrated to additionally recruit the anterior temporal cortex (Partiot et al. 1995) and the amygdala (Sharot et al. 2007, see also Güroğlu et al. 2008) when strong emotional context is a component of the upcoming episode. Judgments about inferred emotions have been linked to regions within the default network (e.g., Ochsner et al. 2004, see also Maddock 1999). One possibility is that the regions within the default network transiently interact with sensory, motor, and emotional systems to represent the content of the imagined event.

Germane to this possibility, Hassabis and Maguire (2007) recently proposed that interactions among regions within the default network may "facilitate the retrieval and integration of relevant informational components, stored in their modality-specific cortical areas, the product of which has a coherent spatial context, and can then later be manipulated and visualized." They refer to this process as "scene construction," a term emphasizing that mental simulation often unfolds in one's mind as an imagined scene with rich visual and spatial content (see also Hassabis et al. 2007). Vogeley and colleagues (2004) have also noted that regions within the default network are differentially active depending on the perspective taken when imaging a scene. The default network is most active when one takes a first-person perspective centered upon one's own body as opposed to a third-person perspective.

Perhaps the most intriguing avenue for future exploration surrounds the implication that specific brain systems are devoted to internal modes of cognition. To date, cognitive and systems neuroscience has concerned itself primarily with how information is extracted from sensory inputs and integrated over time to make decisions and plan actions. Knowledge that the default network exists reminds us that there may be specialized brain systems that underlie our abilities to mentally explore and anticipate future situations. Such constructive processes may be adaptive because they allow the brain to preexperience upcoming events and to derive prospectively useful forms of representation that are many steps removed from their originally encoded sources.

Relevant to this possibility, studies of neural activity in the rat hippocampus have recently revealed that future event sequences are the beginnings of journeys (Diba & Buzáki 2007) and choice points (Johhnson & Redish 2007) providing a candidate neural mechanism for evaluating the consequences of upcoming actions before they happen (see also Shapiro et al. 2006, Buckner & Carroll 2007). In a series of recent studies, Johnson and Redish (2007) focused on the behavior of rats at a critical choice point in a maze where they were confronted with a high-cost decision. The rats had to follow a path to the right or left, and the incorrect choice required an extended journey to obtain another chance for reward. By recording from ensembles of cells with place fields in the hippocampus, they were able to visualize the representation of space in the rat brain at these critical decision junctures. What emerged was quite remarkable: when the rats paused before their decision, the neurons fired in patterns that swept ahead of the location, first down one choice and then the other. This prospective coding occurred, on average, for about 10% of the time the rats were at the choice point. Moreover, on some trials where the rats made decision errors, the representations of space swept back toward the choice point and down the path of the correct journey. Although a direct causal link to the decision choice has yet to be uncovered, these findings suggest a candidate neural mechanism by which potential future choices can be simulated in the rat brain in the service of planning.

The default network's prominent use during passive epochs may contribute adaptive function by allowing event scenarios to be constructed, replayed, and explored to enrich the remnants of past events in order to derive expectations about the future. This functional role may explain why the default network increases its activity during passive moments when the demands for processing external information are minimal. Rather than let the moments pass with idle brain activity, we capitalize on them to consolidate past experience in ways that are adaptive for our future needs.

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Conflict of Interest

The authors declare no conflicts of interest.

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