# THE YEAR IN COGNITIVE NEUROSCIENCE 2008

edited by

Alan Kingstone

Michael B. Miller

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*Edited by*
ALAN KINGSTONE AND MICHAEL B. MILLER

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# The Year in Cognitive Neuroscience 2008

# *Preface*

Welcome to the inaugural volume of *The Year in Cognitive Neuroscience!* It was in March 2007 that we first discussed the idea of editing this peer-reviewed annual review series. Our goal was simple and straightforward—to bring together each year the very best minds in cognitive neuroscience so that they could put forward and review the cutting-edge ideas and issues in the field. A new peer-reviewed volume will be published this time each year, and we expect that it will be a must-read annual review for new and established scientists in the field alike.

The birth of cognitive neuroscience has enabled scientists to come together in their shared enterprise to study the neural basis of cognition across a broad range of traditional domains of research, such as memory, attention, and executive control. As our field has grown, we have moved from studying issues that are specific to cognitive domains to investigating complex issues that cut across traditional domains and that are foundational to science and society. This new annual review, *The Year in Cognitive Neuroscience*, reflects this development within our exciting field. Each of the reviews in this first volume exemplifies an issue-based approach that now defines and fuels cognitive neuroscience, ranging from studies of the brain's default network (Randy Buckner), to investigations of the adolescent brain (B.J. Casey), to matters regarding awareness in the vegetative state (Adrian Owen).

As is always the case with any substantial enterprise, there are many people who have played critical roles in its success. Michael Gazzaniga strongly encouraged us to edit *The Year in Cognitive Neuroscience*. He and our editorial advisory board have contributed greatly to our vision for this series. Kirk Jensen, executive editor of the *Annals of the New York Academy of Sciences*, deserves our most sincere appreciation for his support of our venture. The willingness of these individuals to commit to this initiative is a great testimony to the fact that the time was right for an annual review in cognitive neuroscience. We are also grateful to the referees, who are listed in this publication, for providing their well-considered suggestions and peer commentaries. Finally, and most importantly, we would like to acknowledge the world-class authors who invested a great deal of time and effort to make this annual review an outstanding success.

*The Year in Cognitive Neuroscience* is published as part of the *Annals of the New York Academy of Sciences*, which is one of the oldest scientific series in the United States and among the most cited of multidisciplinary scientific serials. We are proud and excited to be editors of this new publication and trust that you will find its stimulating articles to be essential reading now and in the years to come.

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# The Year in Cognitive Neuroscience 2008

*Editors*
ALAN KINGSTONE AND MICHAEL B. MILLER

CONTENTS

# 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).

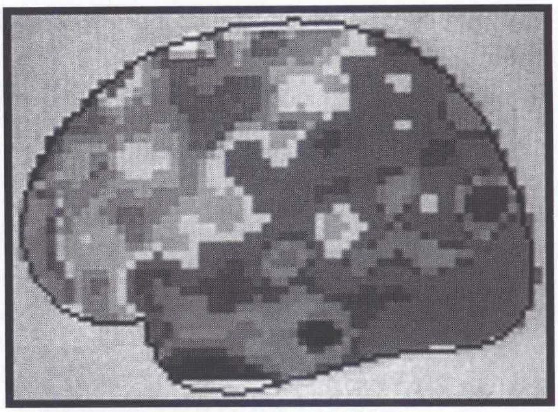

**FIGURE 1.** An early image of regional cerebral blood flow (rCBF) at rest made by David Ingvar and colleagues using the nitrous oxide technique. The image shows data averaged over eight individuals to reveal a "hyperfrontal" activity pattern that Ingvar proposed reflected "spontaneous, conscious mentation" (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.

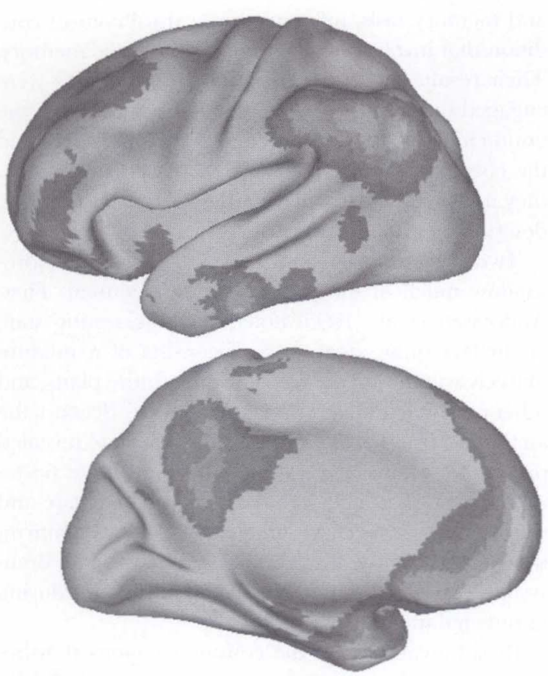

**FIGURE 2.** The brain's default network was originally identified in a meta-analysis that mapped brain regions more active in passive as compared to active tasks (often referred to as task-induced deactivation). The displayed positron emission tomography (PET) data include nine studies (132 participants) 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.

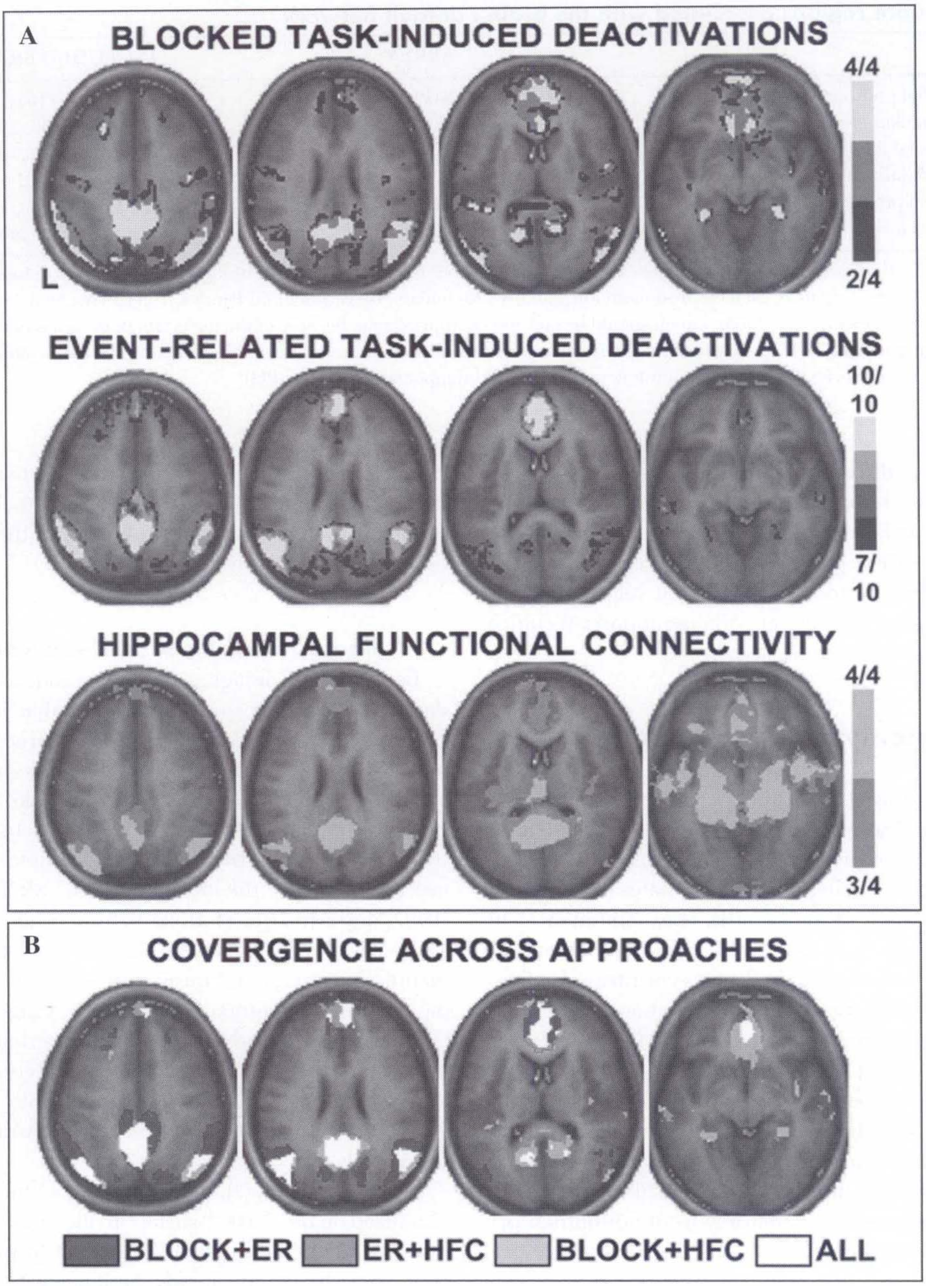


**FIGURE 3.** The brain's default network is converged upon by multiple, distinct fMRI approaches. **(A)** Each row of images shows a different fMRI approach for defining the default network: blocked task-induced deactivation (top row), event-related task-induced deactivation (middle row), and functional 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.