Review

The serendipitous discovery of the brain's default network

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ABSTRACT

One of the most unexpected findings by functional neuroimaging has been the discovery of the brain's default network — a set of brain regions that is spontaneously active during passive moments. The default network's discovery was a fortunate accident that occurred due to the inclusion of rest control conditions in early PET and functional MRI studies. At first, the network was ignored. Later, its presence was shunned as evidence of an experimental confound. Finally, it emerged as a mainstream target of focused study. Here, I describe a personal perspective of the default network's serendipitous discovery.

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Contents

The brain's default network was a completely unexpected discovery arising from the early days of human neuroimaging. The default network is a set of brain regions that increase their activity when individuals lie at rest in a PET or MRI scanner. Activity modulation in the default network is often the largest effect in brain imaging studies, despite it rarely being the intended focus. One possibility is that the network underlies internally-directed cognitive processes. During passive moments, people think about recent events and social interactions, and muse about expected events that have yet to unfold. The default network's ubiquitous and robust appearance across studies suggests it plays a major role in human brain function. What has also drawn attention is the finding that the default network is disrupted in diseases of the mind including Alzheimer's, depression, schizophrenia, and autism.

Many articles summarize observations about the default network, discuss possible functions, and describe links to cognitive development and mental illness (e.g., Andrews-Hanna, 2011; Binder et al., 1999, 2009; Buckner and Caroll, 2007; Buckner et al., 2008; Callard and Margulies 2011; Christoff et al., 2004; Gusnard and Raichle, 2001; Mazoyer et al., 2001; Raichle et al., 2001; Shulman et al., 1997b; Spreng et al., 2009). I will not rehash the same materials here. Instead, in this paper I will tell the story of the discovery of the default network from my personal perspective.

What makes the discovery of the brain's default network so interesting to me is that it is a story of scientific serendipity. There was no eureka moment. In fact, early observations were largely ignored. But as time went on, accidental observations across many laboratories called for more and more attention to be focused on the network.

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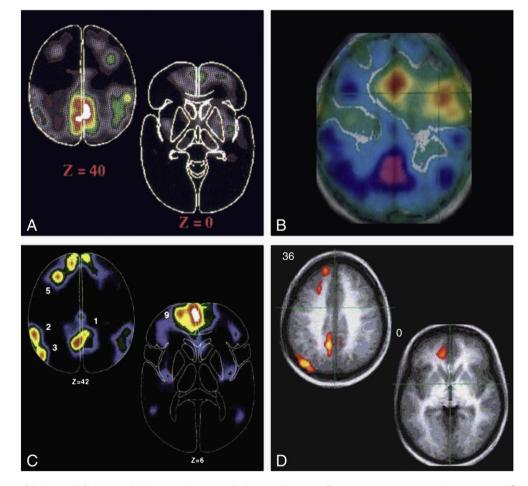*E-mail address:* randy_buckner@harvard.edu.

My own ideas about the default network have shifted over the past two decades. I was involved with its early description through my work as a graduate student with Steven Petersen and through a project led by Gordon Shulman. But then I failed to see its importance again until the papers of Marc Raichle, Debra Gusnard and colleagues in 2001 championed study of the network. Cindy Lustig uncovered connections to aging and Alzheimer's disease that shifted my laboratory's focus back onto the default network. I was stunned when the first images of amyloid deposition in Alzheimer's disease, presented by Bill Klunk, Chet Mathis, and colleagues in 2004, revealed that pathology preferentially targets the default network. All the while, in the background of these emerging observations was an in-field debate about what constitutes an appropriate control condition for a neuroimaging study. It was this debate that shaped my early encounters with the default network.

In search of the perfect baseline

Anyone conducting a human neuroimaging study that uses a passive baseline as a control will observe the default network if they look. The network emerges when one contrasts regions active in a passive task condition (such as fixating a cross-hair) with most externally focused tasks (such as reading a word or judging the movement direction of a dot array). The default network jumped out of the data in my first study as a graduate student (Fig. 1A). We documented its presence across four different contrasts but, having little grasp of its importance, only noted, "Although the fixation task was intended as a low-level control task, it nevertheless may require distinct processing resources" (Buckner et al., 1995). If my memory is accurate, my thinking at the time focused on the possibility that the default network supported some form of external attention related to the subjects fixating on the visual cross-hair. My bias was revealed in a paper published the next year. When we observed that certain regions active during memory retrieval overlapped the passive-task activations, we set them aside as not relevant to memory specifically because they showed activity increases during passive task states (Buckner et al., 1996).

Why did we (and everyone else!) initially place so little emphasis on these mysterious increases in activity in passive tasks? Part of the reason was that we didn't understand them. They fell victim to the always-present bias to ignore what is least understood. Another part of the reason is because they were not the focus of the experiments. We were targeting memory, or in other instances perception, attention, and language. These increases in activity were emerging during the control condition. And that leads to the most likely culprit for early neglect: the default network's presence made the use of passive control conditions as a baseline murky.

The early years of neuroimaging witnessed a contentious debate about how to design task contrasts. Without additional steps,

Fig. 1. Early descriptions of the brain's default network. (A) Two axial sections display an early report of brain regions increasing activity in a passive (fixation) condition as contrasted with an active word generation task. Posterior and anterior midline regions are present, as well as regions within the inferior parietal lobule. Adapted from Buckner et al. (2005). (B) Regions of passive-task activation are illustrated in blue from a paper by Andreasen et al. (1995) that discussed possible functions of what would later become known as the default network. Adapted from Andreasen et al. (1995). (C) Shulman et al. (1997b) conducted a meta-analysis across 10 studies to illustrate the consistently of regions active during passive task states. These data would be reanalyzed and reprinted in many future papers, and became the iconic description of the anatomy of the default network. Adapted from Shulman et al. (1997b). (D) Binder et al. (1999) were the first to experimentally target the default network for study. Their work revealed that the regions active in passive task states might reflect conceptually-driven as contrast to perceptually-driven processes. Adapted from Binder et al. (1999).

positron emission tomography (PET) blood flow images and MRI T2* images are images of anatomy. The changes in blood flow that accompany changes in neural activity are small compared to the variation that the anatomy induces. This is why one can recognize the blurred details of brain anatomy in raw PET and functional MRI (fMRI) images before they are subjected to additional processing steps that reveal the sought-after functional changes. For this reason, one must contrast different conditions to isolate changes in neural activity.

Disagreement about how best to design a study for neuroimaging reached its peak in the 1990s. Some leaders of the neuroimaging community argued against simple subtractions of low-level control conditions, because the subject's behavior is unknown, while others argued for the necessity of such controls to serve as a common reference because active tasks suppress competing systems. A transcribed debate from March of 1991 culminated with Richard Frackowiak instructing Marc Raichle that, "The best control state is a 'constrained state,' which differs from the active state only by the feature you are trying to map. 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" (p. 231, Ciba Foundation 1991). Even with these potential problems, many investigators saw the utility of low-level control states and they were included in numerous subsequent studies. The accumulating data allowed observations to emerge that bubbled above the debates of the time.

Turning points

An early paper by Andreasen et al. (1995) addressed both the debate about using passive states as a control and also how passive states reveal insight into the default state of brain function. To my knowledge, they were the first in the modern era of PET and fMRI to write about the functional importance of the default network.[1] Andreasen and colleagues reported on a PET study of autobiographical memory. They noted that the functional anatomy active during remembering was similar to that active during their rest control state, when both were compared to an active control condition (Fig. 1B). This led them to refer to "rest" with the intentionally ironic acronym "*R*andom *E*pisodic *S*ilent *T*hinking" and conclude that "free-ranging mental activity (random episodic memory) produces large activations in association cortex and may reflect both active retrieval of past experiences and planning of future experiences," and further that this circuitry may "permit human beings to experience identity, consciousness, and self-awareness" (p. 1576, Andreasen et al., 1995). They also commented specifically on the anatomy of the default network, noting that the network primarily comprises regions of association cortex that "are more highly developed (i.e., comprise a larger portion of the brain volume) in human beings than in nonhuman primates or other animals, have the most complex columnar cortical organization, and are the last to myelinate. Apparently, when the brain/mind thinks in a free and unencumbered fashion, it uses its most human and complex parts" (p. 1583).

Nancy wrote to Marc Raichle and me about her upcoming paper in August of 1995. In her letter to me, Nancy noted "[they] used 'rest' as [their] baseline condition, thereby selecting a control task that

probably involves a lot of memory retrieval…" It is interesting to look back at her letters and paper, which anticipate much of my own later work on the default network. I remember being perplexed by the notion that spontaneous remembering could make a major contribution to a passive task condition and didn't deeply consider the implications of Nancy's idea until many years later. In our first empirical analysis of the anatomy of the default network led by Gordon Shulman (described below) we did not mention Nancy's work. Gordon only learned about her paper after ours was published. I knew about Nancy's work but just hadn't made the connection. In fact, none of the papers on the default network between 1999 and 2001 cited this early and insightful paper. I suspect one reason for this omission is that Andreasen et al. were focused on the connection to memory systems, which would not become a widely entertained idea for another decade (an exception to this is Stark and Squire, 2001). Another reason is that their paper brought into question the use of passive states as a control condition, an unpopular notion with laboratories using rest as a control. What is clear is that Andreasen and colleagues contributed a tremendously thoughtful paper that highlighted components of the brain network that is now well known to the community as the default network.

Gordon Shulman led a major effort in our laboratory in St. Louis to analyze regions that increase activity during passive task states in relation to a wide range of active verbal and non-verbal tasks (Shulman et al., 1997b; see also Mazoyer et al., 2001).[2] Gordon's analysis was part of a series of studies that originally sought to explore whether there were common regions of increased activation (Shulman et al. 1997a, 1997c). Back then Gordon worked in Steve Petersen's laboratory and collaborated with Maurizio Corbetta on studies of attention. Julie Fiez and I were also in the mix. It was an exciting time, and I'm thankful to have worked with such a great group, and particularly thankful for Steve's mentorship. Steve encouraged us to each focus on different topics so, while Maurizio, Julie, and I shared an office, we worked on separate projects. The result was that lots of diverse data were piling up.

Gordon drew on data from studies on attention by Maurizio, an imagery study by Julie, my studies of memory, and a study on automaticity of language led by Marc Raichle. The project was a major undertaking as meta-analytic techniques had not yet been applied to PET data. What emerged from his herculean effort was a surprisingly consistent network of brain regions active during passive tasks. The network included regions across the posterior midline, medial prefrontal cortex, inferior parietal lobule, lateral temporal cortex, and specific subdivisions of the dorsolateral prefrontal cortex (Fig. 1C). Shulman et al. (1997b) proposed a number of ideas about what could give rise to the passive-task activations setting the stage for further explorations of its function.

Gordon's analysis was a landmark for the field because it made explicit the phenomenon of passive-task activation, demonstrated the details of the anatomy, and showed that the effect generalized across a wide range of contexts. It compellingly illustrated something that many researchers were observing but were not discussing; the paper also provided the iconic image of the default network. Fig. 1

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[1] David Ingvar wrote thoughtfully about the concept of a default network in the 1970s, in a series of papers that, at the time, did not attract much attention in the scientific mainstream (see Buckner et al., 2008 for review). But some investigators did take notice. There is, in fact, a direct lineage from Ingvar's work to the later work of Andreasen and colleagues. In the early 1980s Endel Tulving was beginning to formulate his own ideas about how memory might help individuals to envision the future (a theme first raised in Tulving, 1985 and expanded in Tulving, 2005). He and Ingvar were initially unaware of each other's work and, upon finding out about Ingvar's earlier publications, Endel initiated a friendship that would lead to some of the first brain images of episodic memory in 1988. Endel then later became a friend and colleague of Nancy Andreasen following her visit to Toronto in 1994 and his own visit to Iowa in 1995. Andreasen et al. (1995) opens by citing Tulving's and Ingvar's work.

[2] In our 1995 and 1997 papers, and several later papers, we referred to regions more active in passive task states as "decreases," "task-induced decreases," or "deactivations" because they were less active in the targeted experimental tasks when referenced to the passive control tasks. In Konishi et al. (2000) we awkwardly formulated the possibility that memory retrieval effects could be contaminants of deactivation as, "a 'deactivation' could be less deactivated for the easier trials," yielding the illusion of a contribution to memory retrieval. As the years have passed, I have found this terminology confusing, as you might also find from your own reading of the sentence above. The phrasing implies special status to the active task as contrast to the control state. All that can be inferred from the *typical* PET or fMRI contrast is a relative difference. It therefore seems simplest to describe the regions of the default network as more active in the passive task condition relative to the active task, rather than 'deactivated' by the task. For an alternative conceptualization, see Raichle et al. (2001) where they explore the possibility of an absolute metabolic baseline.
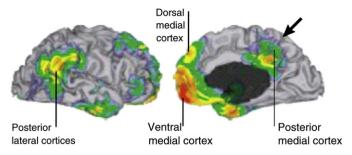
of Shulman et al. (1997b) has been modified and republished in many forms (e.g., Andrews-Hanna, 2011; Buckner et al., 2005, 2008; Gusnard and Raichle, 2001; Raichle et al., 2001).

The next major turning point came when Jeffrey Binder's laboratory began a systematic investigation of the default network's functions (Fig. 1D; Binder et al., 1999; McKiernan et al., 2006; see also Binder, this volume). They conducted a study directly aimed at exploring the default network; the earlier studies analyzed the network post hoc, based on studies conducted for other reasons but nonetheless that offered serendipitous insight. Binder et al. (1999) focused on the distinction between external (perceptual) and internal (conceptual) sources of information that can guide information processing. In typical perceptual tasks, such as those that attenuate activity in the default network, the task goals are substantially weighted toward extracting information from the external environment. In conceptual tasks, past knowledge is the dominant content of information processing. Binder et al. (1999) demonstrated that a challenging task, focused on conceptual knowledge, could activate the default network relative to a perceptual task, much like had been observed for passive tasks. This observation was a milestone for multiple reasons.

Binder et al. (1999) marked the first focused analysis of processing demands that activate the default network. Their work sought a general explanation for default network activity that accommodated its increased activity in passive states as well as directed task forms that activate the network. They connected the observation of default network activity to an earlier, rich behavioral literature on spontaneous thought (e.g., Antrobus, 1968), a theme expanded upon in McKiernan et al. (2006) and one that would become central to my own ideas (Buckner et al., 2008). In doing so, they converged on the same general hypothesis as Andreasen et al. (1995) by suggesting that regions of the default network are "active during conscious resting and are engaged in such processes as retrieval of information from long-term memory, information representation in conscious awareness in the form of mental images and thoughts, and manipulation of this information for problem-solving and planning" (p. 86, Binder et al., 1999). Critically, they pointed out that such processes are adaptive: "By storing, retrieving, and manipulating internal information, we organize what could not be organized during stimulus presentation, solve problems that require computation over long periods of time, and create effective plans governing behavior in the future. These capabilities have surely made no small contribution to human survival and the invention of technology." (p. 85, Binder et al., 1999).

A series of papers by Marc Raichle, Debra Gusnard, and colleagues represents the signal event that drew attention to the default network (Gusnard and Raichle, 2001; Gusnard et al., 2001; Raichle et al., 2001). Marc was already accumulating data on the default network by the time I began my graduate studies in 1991 — years before any PET papers mentioned the phenomenon. He had a folder affectionately labeled *MMPA* for "medial mystery parietal area" that contained examples of deactivation in the region that would eventually come to be known as the hub of the default network, but Marc would not publish directly on his own ideas for over a decade.[3] He spent the intervening time talking about the network, compiling converging evidence, and patiently gathering his thoughts in preparation for a trilogy of remarkable papers that published in 2001.

In the first paper by Raichle and colleagues in January of 2001, they explored what might define a default baseline state. Recall that the contentious debate of the time was whether passive states could be used as an appropriate control condition. The specific empirical focus of the paper was to define an absolute baseline based on the oxygen extraction fraction (OEF). In pursuing a means to measure an

Fig. 2. The emergence of the default network into the scientific mainstream. A trio of seminal papers by Raichle, Gusnard and colleagues drew attention to the default network and set a conceptual framework that has stimulated an extraordinary amount of future research. The figure above comes from Gusnard and Raichle (2001) and illustrates a surface projection of Shulman et al.'s (1997b) original data. By titling their first paper "A default mode of brain function," Raichle et al. (2001) gave the default network its name.

absolute baseline, Raichle et al. (2001) framed the study of basal activity as a topic that is broader than the local issue of how to define a control task for a neuroimaging study: baseline states are intimately important to brain function. The ideas of the paper, and its companion pieces, have had an enormous impact on the field both in the study of the default network and in setting the stage for exploring basal intrinsic activity.
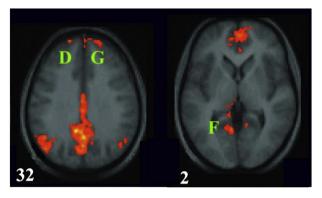
For example, a theme of Raichle et al. (2001) that has had lasting influence on the field, but is beyond the scope of the present article, is the exploration of basal metabolic states that connect to questions about the function of intrinsic oscillatory activity and related forms of intrinsic activity, what Marc Raichle has referred to as the "brain's dark energy" (Raichle, 2010). By using his inaugural article as a new member of the National Academy of Sciences to draw attention to the default network, Marc raised the status of the topic to prominence in a way that the earlier papers had not. The paper also gave the phenomenon a name that has since stuck when it referred to the resting state as the 'default mode'.[4]

Directly relevant to the study of the default network's function, Gusnard et al. (2001) and Gusnard and Raichle (2001) examined the kinds of active tasks that elicit activation of regions within the network. They highlighted that one of the prominent regions of the default network — the dorsal medial prefrontal cortex — was active during a range of active tasks that demanded self-referential mental activity, leading them to suggest that the region "is important for spontaneous and task-related self-referential or introspectively oriented mental activity" (Gusnard and Raichle, 2001).[5] Their emphasis on self-referential processing has had a lasting influence on the field.

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[3] Marc was deeply involved with Gordon Shulman's work and co-authored on Shulman et al. (1997).

[4] Raichle et al.'s 2001 paper titled "A default mode of brain function" gave the field a name for the network of regions most active in passive states, which is now referred to as either the "default network," or "default mode network." I have typically used "default network" to make clear I am referring to the specific set of brain regions active in passive states, as contrast to the "default mode" defined by Raichle and colleagues as the state characterized by a constant oxygen extraction fraction (OEF) profile across the brain. This distinction is no longer needed. Both terms are now typically used to refer to the brain network illustrated in Figs. 1, 2, and 3. Ironically, the term "default state" was used earlier in the context of the default network by Binder et al. (2000), in a manner consistent with how the term is most often used today (and even earlier in Giambra, 1995). But Binder's and Giambra's anticipations are not the origin of the name's common use; the paper by Raichle and colleagues brought the name into the scientific mainstream.

[5] An insightful, often overlooked, paper by McGuire et al. (1996) from the Hammersmith Hospital made a similar point. They noted that spontaneous thoughts were highest during rest as contrast to active tasks, and further that the frequency of spontaneous thoughts was correlated with medial prefrontal activity. In a table they noted that the medial prefrontal region linked to spontaneous cognition was active in other studies involving attributing mental states, judging other person's knowledge, and imaging events and feelings.

Fig. 3. Intrinsic connectivity networks reveal the default network. Greicius et al. (2003) demonstrated that regions of the default network are intrinsically coupled with one another, suggesting they are components of an anatomically- or functionally-coherent system. The images display axial sections with regions functionally correlated with the posterior cingulate shown in brighter colors. Adapted from Greicius et al. (2003).

Thus, while each group's work possessed different emphases, multiple papers were all raising the possibility that the default network might participate in the self-generated stream of thought that takes place when we are left undisturbed and our minds wander. To some experimentalists this possibility was uninteresting as it spoke to a confound of using rest-state scans as a control condition. But to others the discovery was of great interest because, unintentionally, the passive state epochs had possibly captured a central processing function of the human brain — the ability to spontaneously construct mental models of personally significant events.

Collision with intrinsic functional connectivity

At about the same time interest in the default network began to grow, Biswal et al. (1995) at the Medical College of Wisconsin described the presence of intrinsic connectivity networks. They showed that low-frequency intrinsic activity of motor cortex was functionally coupled to distributed regions of the motor system. Their discovery inspired widespread use of intrinsic functional connectivity to identify the architecture of brain systems, often referred to as resting-state or intrinsic connectivity networks (RSNs or ICNs; see Biswal, this volume for an historical account). It is tempting to equate the phenomenon observed by Biswal et al. as functionally related to the passive-state activations that are observed within the default network. After all, both can be observed in data collected in resting subjects. However, the phenomenon of intrinsic functional coupling is likely distinct from the observation that the default network increases activity at rest. Several prior discussions (e.g., Buckner et al., 2008; Callard and Margulies, 2011; Fox and Raichle 2007; Vincent et al., 2006) of the two phenomena have made their differences clear and early publications on the default network, including from the Medical College of Wisconsin (Binder et al., 1999), do not make connections to low-frequency intrinsic activity. Nonetheless, recent conflation of the two phenomena has led to quite a bit of confusion.

Intrinsic connectivity networks are *typically* identified from the correlated activity patterns observed at rest. However, the intrinsic activity fluctuations that give rise to "resting-state" networks are not specific to rest states nor to any particular brain system. The phenomenon is pervasive: it is present at rest, during sleep, and during continuous active tasks. Even at rest, their coupling modes are dynamic. Moreover, low-frequency functional coupling is simultaneously present in all brain systems. For these reasons, there is interest in the physiological basis of this form of intrinsic activity and understanding its functional significance (Raichle, 2011). But, it is unlikely

the same phenomenon that gives rise to the relative increase in activity in the default network observed in passive task conditions.[6]
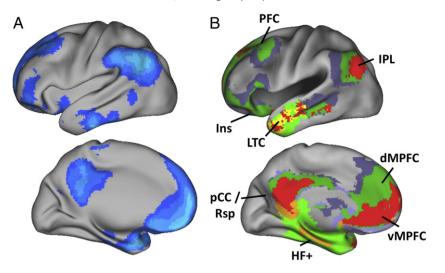
Why have the two phenomena become conflated? There are several reasons. First, analysis of intrinsic functional coupling was first conducted in resting data, giving the impression that a rest state is required to elicit the phenomenon. This is simply not the case. Intrinsic activity correlations are similar (but not identical) across task and arousal states suggesting that their origins lie in a general physiological mechanism that is not specific to a task or brain system. Second, many of the same researchers who were interested in the default network were also active investigators of intrinsic functional connectivity. That's probably because the same individuals who were open to exploring the default network were also open to exploring this other property of resting-state activity. Adding to the confusion, many articles have gone back and forth between the two phenomena implying functional similarity, and sometimes even directly stating equivalence. Finally, and most relevant here, Michael Greicius, Vinod Menon and colleagues at Stanford used intrinsic functional connectivity as a tool to make important observations about the default network.

Greicius et al. (2003) adopted an analysis strategy similar to Biswal et al.'s original work in 1995 but instead of focusing on the motor system they examined the network functionally coupled to the posterior cingulate. What emerged was a distributed set of regions that are prominent components of the default network: medial prefrontal cortex, inferior parietal lobule, and lateral temporal cortex. Their observation that functional connectivity MRI could be used to define the default network was important for technical and conceptual reasons. By illustrating that functional connectivity could reveal networks involving limbic and association cortex, they demonstrated the potential of the method for mapping diverse brain systems. I remember seeing the results from Stanford and recognizing the utility of the approach for studying brain systems involved in memory — something I failed to appreciate when observing the earlier results focused on sensory and motor systems. I suspect others were similarly inspired by Greicius et al.'s publication.

At a conceptual level, their observations suggested that the default network behaves as a coherent brain system, or set of coupled brain systems. Up until that point, a reasonable perspective was that the distributed regions comprising the default network were those that just happened to be active during passive states, potentially for different reasons. For example, Gusnard and Raichle's (2001) discussion of the potential functional contributions of default network regions hypothesized distinct roles for the frontal midline and parietal regions, with the leading hypotheses for the parietal regions involving attentional processes that occur during passive viewing states. By showing that the distributed regions across the default network were functionally coupled, Greicius et al. (2003) illustrated that they behave as a coherent brain system. Thus, this critical paper encouraged

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[6] There may be points of contact between the two phenomena. Some component of the low-frequency signal may be related to spontaneous cognition, but unlikely the majority, and almost certainly not the major component that is now the broad focus of the intrinsic connectivity literature (for discussion see Fox and Raichle, 2007; Buckner et al., 2008). The differences are important to emphasize because conflation has led to claims that may be incorrect. For example, it is not uncommon to read or hear that the presence of low-frequency coupling in the default network under anesthesia or during sleep implies something about its function, in particular that it is not used for high-level cognition. When I gave the plenary lecture at the annual Human Brain Mapping conference in Barcelona in 2010, I was asked what the presence of intrinsic activity in the default network during unconscious states says about its function and whether it undermines arguments about a role in awake cognition. I replied that such observations tell us little about its functions leading to several disgruntled follow-up e-mails. I still hold this opinion. Low-frequency functional coupling is pervasive and, in isolation, does not inform us about the specific functional domains of the systems in which it occurs. Just as functional coupling among visual regions in subjects resting with their eyes closed says little about the functional role of the visual system, similar forms of coupling in the default network inform us minimally about its function.

Fig. 4. Modern descriptions of the default network. (A) A surface projection of the default network is displayed from the Shulman et al. (1997b) data. The regions in blue represent those regions more active during passive task states than a variety of active tasks. (B) A near complete topography of the default network can be accounted for by exploring regions functionally coupled to the posterior cingulate, dorsal medial prefrontal cortex (dMPFC), and hippocampal formation (HF+). However, detailed analysis of the coupling properties reveals that the default network is not a single, coherent system but rather is made up of multiple, functionally interacting subsystems. Adapted from Buckner et al. (2008).

exploration of the default network as a functionally-coupled brain system — a perspective that has since been extended and refined (see Figs. 4 and 5 for recent extensions).
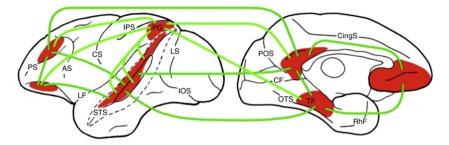
Beyond passive states

The field became aware of the brain's default network because it increases activity during passive task states as contrasted to a wide range of active, externally-focused tasks. The manner in which the default network was discovered was fortunate because it caused many of us to begin to wonder about the adaptive functions of spontaneous and intrinsic neural processes. A number of interesting ideas grew from this initial seed. However, discovering the network in this manner was also unfortunate. It lulled us into focusing on the default network's attenuation during most active tasks, and it took several years before ideas on the default network's role in active cognition were brought to the forefront. And that's when things got really interesting.

The hypothesis my group is currently exploring is that the default network enables construction of mental models or simulations that are adaptive and facilitate future behavior (Buckner and Caroll, 2007; Buckner et al., 2008). By this view, the default network's defining mode of operation is internally-focused cognition that relies on mnemonic systems. But that does not mean it lies dormant to be used only during passive moments. The default network may be used actively when decisions require imagining an alternative scenario from the one being experienced (Andrews-Hanna et al., 2010; Spreng et al., 2010). Variants of this idea have been put forth by other investigators, including in early work by Ingvar (1979, 1985) and later by Andreasen et al. (1995). Binder et al. (1999, 2009) have also thoughtfully pursued a related possibility (see Binder, this volume).

My own thinking on the functional role of the default network shifted as we learned more about the anatomy of brain systems supporting our ability to remember. In the late 1990s, study of memory retrieval was becoming more sophisticated through the use of event-related fMRI. Studies began to isolate moments of successful recognition (e.g., Eldridge et al., 2000; Henson et al., 1999; Konishi et al., 2000). What consistently emerged was activation of posterior midline and inferior parietal lobule regions that overlapped with the posterior components of the default network. Mark Wheeler, in his final study as a graduate student, observed that specific parietal

regions active during recollection were also those that were most active during passive epochs (Wheeler and Buckner, 2004). A meta-analysis of retrieval success effects from event-related fMRI studies revealed that overlap existed between the default network and posterior regions active during remembering (Buckner et al., 2005). Adding another piece to the puzzle, Vincent et al. (2006) observed that the parietal regions most selective to recollection were functionally-coupled to the medial temporal lobe memory system and likely homologs of the macaque area Opt that receives direct anatomic projections from parahippocampal cortex. Thus, it seemed no longer appropriate to consider the posterior components of the default network as task-irrelevant or involved in processes associated with external perception. Rather, converging findings began to suggest that posterior regions of the default network were involved, in some unspecified manner, with successful attempts to remember from one's past and could be actively engaged by targeted remembering.

Study of autobiographical remembering provided another critical insight.[7] In autobiographical remembering, a participant is presented a cue (e.g., the word 'dress') and asked to remember a specific episode from her past. Unlike recognition tasks, autobiographical remembering tasks are less constrained and allow the participant to vividly retrieve an extended, self-relevant memory of her own personal past. When asked to recall the episode, typical subjects will describe a detailed first-person perspective of the imagined event. Studies of autobiographical remembering activate a network almost indistinguishable from the full default network, which includes both the posterior components of the network as well as the frontal midline (e.g., Svoboda et al., 2006). Taken together, an interesting picture emerges: (1) constrained event-related studies of successful memory retrieval activate posterior components of the network, (2) self-referential processing tasks preferentially activate the frontal midline, and (3) autobiographical remembering tasks activate the entire

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[7] My own thinking on the functions of the default network began to shift when we observed responses in the network during constrained memory retrieval tasks. Only afterwards did I consider the autobiographical memory studies in detail. This is because autobiographical memory tasks are, in many ways, operationally similar to the passive tasks that activate the default network. Subjects are given extended epochs of time without needing to attend to external stimuli. It was thus important for me to see the responses in tightly constrained cognitive contrasts to be able to appreciate their functional relevance in the less constrained active task settings. Others, including Nancy Andreasen and colleagues, made the critical connection between the default network and mnemonic processes much earlier.
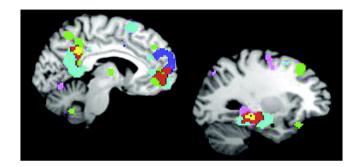
Fig. 5. Estimated anatomical pathways underlying the default network. Careful examination of the macaque anatomic literature shows that polysynaptic connections exist between the estimated homologues of the default network. The areas of the default network, while densely connected to one another and limbic structures, are minimally connected to sensory and motor areas. Of further interest, the areas are among those regions preferentially expanded in humans relative to the macaque (Van Essen and Dierker, 2007), are late to mylenate during development (see Fig. 3 of Catani and ffytche, 2005), and may be absent consistent forward and feedback laminar projection patterns typical of sensory-motor hierarchies (Yeo et al., 2011). All of these properties may underscore the default network's role in mental functions that are detached from the immediate external environment and preferentially expanded in the human brain. Figure adapted from Binder et al. (2009).

network. We had come full circle to the ideas raised by Andreasen and colleagues a decade before, but there were a few more critical connections that had yet to emerge.

To this point, we had been focused on the relationship between the default network and remembering. Two further results led to a much broader hypothesis about the functional role of the default network. The first observation came from the work of Donna Addis, a post-doctoral fellow working in the laboratory of my long-time collaborator Daniel Schacter. Donna and Dan conducted an influential study in which participants were asked to imagine an upcoming scenario, in addition to the conventional task of remembering past events. What they observed is that the same broad network, which overlapped with the default network, was active during both remembering and imagining the future (Addis et al., 2007). Thus, the default network's function was flexible and called upon when imagining future scenarios.

Rebecca Saxe contributed the second observation. Rebecca and Nancy Kanwisher had been studying theory-of-mind: the ability to shift one's perspective and conceive another person's viewpoint. In 2003 they published an important paper that described a network of regions active during theory-of-mind tasks and particularly emphasized a region in the inferior parietal lobule that they labeled the TPJ for temporo-parietal junction (Saxe and Kanwisher, 2003). In their paper, they noted that this region decreases activity during

Fig. 6. Convergence of remembering, prospection, navigation and theory-of-mind on the default network. Images from a recent meta-analysis of tasks that require individuals to mentally project themselves into an alternative setting. Red and yellow represent overlap of two or three forms of task. While there are important anatomic differences that are not captured by this display, the data illustrate that multiple forms of active task rely upon the default network. These active tasks share in common that individuals must represent a self-relevant mental scene to complete the task. Based on these observations, one current hypothesis is that the default network supports the ability to construct mental models of personally significant events (Andrews-Hanna, 2011; Buckner and Caroll, 2007; Buckner et al. 2008). Another hypothesis is that the default network overlaps association regions important to store and retrieve semantic knowledge (Binder et al., 2009). Figure adapted from Spreng et al. (2009).

certain forms of attention-demanding tasks and overlapped with the properties observed by Shulman et al. (1997b). Rebecca approached me after one of my talks on the default network that I presented at an MIT symposium in 2006. She suggested that there might be overlap between the default network I was discussing and the network she was observing during her theory-of-mind tasks. She was right (Fig. 6).

What could this convergence mean? Working with a talented undergraduate student Daniel Carroll, we spent the summer reading the literature on the separate domains of episodic memory, prospection (thinking about the future), and theory-of-mind. Others were also making such links. A great example can be found in Marsel Mesulam's work, where his observations of neurological patients inspired him to propose that diverse cognitive abilities depend on a common, core ability to shift one's vantage point to another perspective. He noted that in many forms of cognition "events tend to be assessed from an egocentric perspective so that the horizon of consciousness does not extend beyond the here-and-now and the self is the center around which other events revolve," but also that it is possible to expand one's perspective beyond this immediate, environmentally dependent mode. He continued, "One way to transcend the [environmentally dependent mode][8] would be to transpose the effective reference point from self to other, from here to there, and from now to then" (Mesulam, 2002, p. 22).

This idea resonated with us. A common function that remembering, thinking about the future, and thinking about another person's perspective depend upon is the ability to shift from perceiving the immediate environment to building a mental model, perhaps to be considered a simulation, of an alternative scenario. My colleague Daniel Gilbert, who studies such faculties from a cognitive perspective, equated this ability to having an "experience simulator." In his 2004 TED talk, he explained, "Pilots practice in flight simulators so that they don't make real mistakes in planes. Human beings have this marvelous adaptation that they can actually have experiences in their heads before they try them out in real life."

In searching for an explanation for the functions of the default network we stumbled upon a much bigger hypothesis than we had anticipated. A core network, expanded in humans relative to other primate species, is at work during a diverse array of tasks that require individuals to project themselves into alternative scenarios. The default network is active when people are directed to remember, encouraged to think about the future or other related abilities. Critically, people engage the network spontaneously when left without a demanding task in a PET or MRI scanner. Thus, while analysis of passive task states helped us to initially identify this network, its importance to

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[8] Ironically, Mesulam referred to the environmentally-driven mode as "the default mode" meaning the "straight and narrow path from stimulus to response." To avoid confusion, I've omitted his alternative use of the term "default mode" from the quote.

cognition is far from confined to quiet moments captured serendipitously during control conditions in neuroimaging experiments. People use this core network actively in many kinds of task context.

The connection to aging, Alzheimer's disease, and psychiatric illness

A surprising set of connections has been made between the default network and neuropsychiatric illness. These links can only be briefly touched upon here, so I will focus on one connection that I have been directly involved with — to Alzheimer's disease (AD). AD is a progressive dementia that affects a large number of people over the age of 75 and sometimes earlier. The ability to remember is one of the first faculties to deteriorate. Though theories have proposed that AD is transmitted through a contagious agent (e.g., a virus), there is presently consensus that AD arises from normal cellular function that leads to toxic byproducts as we age. This immediately raises the question of why some brain systems are more vulnerable to the disease than others.

Posterior cortical regions show reduced metabolism in AD as measured by FDG-PET (e.g., Friedland et al., 1983). The patterns of hypometabolism in AD look suspiciously similar to the posterior cortical regions of the default network. Gusnard and Raichle (2001) noted that regions of hypometabolism "coincide remarkably" with the regions identified as components of the default network. Cindy Lustig, then a talented post-doctoral fellow in my laboratory, was inspired by these connections. With help from Avi Snyder, a gifted and scientifically generous colleague, she began systematically exploring activity patterns in the default network in advanced aging and AD.[9] What Cindy and Avi found is that the typical task-induced deactivations that define the default network are absent in AD (Lustig et al., 2003).

Greicius and colleagues, in a milestone paper, further showed that functional coupling among default network regions was reduced in AD as compared to age-matched controls (Greicius et al., 2004). What was so striking about the Greicius et al. result is that it revealed the broader system was affected, not simply focal regions of passive-task activity. These collective observations suggested that AD preferentially disrupts the default network. But how?

In the summer of 2004, I presented our work on disruption of the default network at a small meeting in Bar Harbor, Maine that was also attended by Bill Klunk. Bill presented on his landmark work with Chester Mathis from the University of Pittsburgh that developed a safe PET method to image amyloid deposition in the living brain (Klunk et al., 2004). The fibril form of amyloid beta is found in plaques, one of the two pathological markers of AD. By developing a PET tracer that bound to fibrular amyloid beta, Klunk et al. (2004) provided a candidate test to identify individuals with pathology during the silent period of AD, long before clinical symptoms are present. This was a genuine breakthrough, so I was quite excited to hear Bill speak.

What emerged from Bill's talk was an unexpected link to the default network. Bill showed a movie that animated a transparent three-dimensional volume of amyloid deposition; the red and yellow colors gave the impression of a brain on fire. I was blown away: that image could have been mistaken for an image of the default network.[10] Regions of the brain most active at rest in healthy young

adults were also those showing early markers of AD pathology in older adults. Working with Bill Klunk, Chet Mathis, and my St. Louis colleagues Avi Snyder, John Morris, and Mark Mintun, we published on this surprising relation in 2005.

What could such a relation mean? While there is no clear answer, the association suggests something about the activity or metabolism of the default network is conducive to the formation of AD pathology (Bero et al., 2011; Buckner et al., 2005, 2008, 2009; Cirrito et al., 2005; Jagust and Mormino, 2011; Vlassenko et al., 2010). Such a possibility may explain why amyloid pathology targets these regions early during disease progression and also why higher-level cognition, including remembering, is preferentially disrupted. This is an insidious (and frankly scary) possibility. AD may be so devastating to higher cognitive function specifically because it targets brain systems expanded in the human brain and important to the default network, robbing the ability to remember and imagine. The clinical insight from this connection is that downstream consequences of normal basal activity and metabolism may facilitate AD pathology. Interventions should consider targeting early metabolic events.

Conclusion

The discovery of the brain's default network and the evolving ideas about its function are wonderful examples of serendipity in science. Perhaps the most critical innovation was that we began putting people in scanners and watching their brains at work. Our original reasons for conducting the studies gave way to a much broader observation — that there is a consistent set of brain regions that is active when people passively think to themselves. This simple observation set the stage for asking questions about how the network is used in other contexts, its specific anatomic underpinnings, and what its adaptive role for cognition is. The answers to these questions are incomplete, and I suspect that several of our dearly held ideas about the functions of the default network will turn out to miss the mark. I feel truly fortunate to have stumbled into such an exciting scientific adventure when I began as a graduate student twenty years ago.

Acknowledgments

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[9] It was not my idea to explore the default network in aging. Cindy Lustig, who led the project with help from Avi Snyder, took the initiative and explored whether the activity patterns in the passive (control) epochs were affected by aging and AD. In fact, I initially thought we should instead focus first on the task components of the data. I'm glad Cindy didn't take my advice. Cindy discovered that activity in the default network, particularly posterior components, was markedly different in patients with AD as compared to nondemented older adults.

[10] The first images of amyloid deposition were published in Klunk et al. (2004) and also shown earlier at the 2002 Stockholm International Conference on Alzheimer's Disease, but the particular images and sections displayed in the 2004 paper do not cause the similarity to the default network to jump out.

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