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Comments and Controversies

Unrest at rest: Default activity and spontaneous network correlations

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A series of recent empirical observations demonstrate structured activity patterns that exist during passive task states. One observation is that a network of regions, referred to as the default network, shows preferentially greater activity during passive task states as compared to a wide range of active tasks. The second observation is that distributed regions spontaneously increase and decrease their activity together within functional–anatomic networks, even under anesthesia. We believe these rest activity patterns may reflect neural functions that consolidate the past, stabilize brain ensembles, and prepare us for the future. Accumulating data further suggest that differences in rest activity may be relevant to understanding clinical conditions such as Alzheimer's disease and autism. Maps of spontaneous network correlations also provide tools for functional localization and study of comparative anatomy between primate species. For all of these reasons, we advocate the systematic exploration of rest activity.

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It is fitting that in the year following the 50th anniversary of Louis Sokoloff and Seymour Kety's report on cerebral circulation and metabolism, we return to the puzzle that they seeded so long ago. Using the Kety–Schmidt nitrous oxide method to measure cerebral blood flow (Kety and Schmidt, 1945, 1948), they explored the degree to which circulation and metabolism changed as one goes from a quiet rest state to an engaged period of mental concentration (solving arithmetical problems) (Sokoloff et al., 1955). Contrary to their expectations, global measures of brain circulation and metabolism were minimally changed. That is, the brain energy consumption at rest was considerable and increased minimally when a directed task was engaged. With minor modifications, the key aspects of their observations have held up to further investigation (Raichle and Mintun, 2006).

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Sokoloff and Kety's findings imply that a significant amount of brain activity persists in the absence of immediate task goals. In support of this possibility, Hans Berger, in his seminal work on human electroencephalography (EEG), observed structured activity patterns during awake rest states that he postulated reflected internal mental activity (Berger et al., 1930, 1931). In a classic series of studies using early imaging methods based on xenon inhalation, David Ingvar measured activity increases in cortical regions including frontal cortex during rest that he interpreted as reflecting "anticipatory simulation of behavior" and argued that rest-state activity has a functional role in human cognition (Ingvar 1979, 1985).

Exploration of passive (resting) states has recently received a major resurgence due to robust empirical observations from modern imaging techniques and also focus on the issue through a series of thought-provoking reviews by Marcus Raichle and colleagues (Raichle et al., 2001; Gusnard and Raichle, 2001). Analyses based on positron emission tomography (PET) have revealed a highly stereotypic pattern of brain regions that manifest greater activity during passive task states as compared to many forms of active task states (Shulman et al., 1997; Binder et al., 1999; Mazoyer et al., 2001). Functional MRI (fMRI) studies involving both blocked task paradigms and rapid event-related paradigms reproduce a rest-state network nearly identical to that initially characterized using PET (e.g., McKiernan et al., 2003). The network prominently includes frontal regions along the midline, lateral, and medial parietal regions extending into posterior cingulate and retrosplenial cortex, and the medial temporal lobes. The consistency of this activity pattern in undirected task states as well as its metabolic properties led Marcus Raichle and colleagues to designate the activity observed in rest states as reflecting a "default mode" of brain function (Raichle et al., 2001). For descriptive purposes, we extend the terminology of Raichle and refer to the network of regions active in rest states as the default network and to the activity within this network during rest states as default activity.

More recent analyses of the temporal dynamics of fMRI-measured activity during rest have further revealed that networks of regions spontaneously increase and decrease activity together in

a correlated manner, including within the default network (De Luca et al., 2002; Laufs et al., 2003; Greicius et al., 2003, 2004). Spontaneous network correlations, however, are not confined to regions within the default network. Complex, structured activity patterns emerge in many brain systems (e.g., Biswal et al., 1995; Lowe et al., 1998; Hampson et al., 2002; Vincent et al., 2006, in press; Fox et al., 2006). For example, a topographically distinct brain network supporting attention to the external environment also shows spontaneous correlations across its included regions, but with temporal dynamics that suggest that the externally directed network is independent or even opposed to the default network (Fransson, 2005, 2006; Fox et al., 2005). De Luca and colleagues (2006) have recently identified five resting state networks that include distinct sensory, motor, and cognitive brain systems. Collectively, these results demonstrate that the brain contains highly organized, spontaneous patterns of functional activity at rest.

In a recent commentary, Morcom and Fletcher (2007) question the utility of studying rest activity from a number of perspectives. In what follows, we describe several reasons why default activity in the rest state and spontaneous network correlations are important to study and, in doing so, use them to illustrate an alternative perspective.

Rest activity patterns may be central to understanding information processing

In considering findings from study of rest-state activity, David Ingvar (1979) speculated that “On the basis of previous experiences, represented in memories, the brain – one’s mind – is automatically busy with extrapolation of future events and, as it appears, constructing alternative hypothetical behavioral patterns to be ready for what may happen”. His hypothesis suggests that there may be important processing events that are relevant to behavior and cognition yet not directed towards responding to immediate task demands.

Morcom and Fletcher (2006) advocate that any kind of cognitive process that is spontaneously engaged could be (or perhaps should be!) studied by providing a constrained task to engage that process. Their perspective is quite understandable and proceeds from an implicit assumption that measured brain activity is functionally related directly to the immediate environment and soon-to-be-executed behaviors. To understand brain function, one must understand how brain areas extract information from perceptual inputs, integrate that information over time and sources, and make decisions and plan motor actions. For a particularly clear example of this approach see Shadlen and Newsome (2001). Despite its importance for understanding certain aspects of brain function, however, an exclusive focus on processing associated with immediate task events may be limited if critical brain processes persist, or only occur, independent of engaged task events. That is, rest-state activity may be relevant to information processing in ways that we have not conventionally considered. This idea needs some unpacking.

Cognitive science has alluded to processes that are absent immediate behaviors on many occasions such as in the concepts of memory consolidation and planning. Processing events that take place during sleep fall into this category. These kinds of process are likely to be functionally relevant to behavior but not necessarily directed at the immediate execution of behaviors. We believe that it is premature to assume that all brain processes and networks are dedicated to perceiving and responding to immediate environ-

mental events. The boundaries are already blurry. Just as everyone agrees that we should study activity events associated with immediate task demands, there is also comfort with studying brain activity events that persist over seconds between a stimulus and response during working memory, motor preparation, and attention paradigms. The queasiness emerges when one moves into the murkier realm of brain activity patterns that are distant from their originating event and not clearly under control from the immediate experimental environment and task demands. The structured activity patterns that emerge in rest activity scans may be examples of these phenomena.

A recent study by Foster and Wilson (2006) recording from the hippocampus in navigating rats illustrates this point (Fig. 1). In their study rats were trained to run back and forth in a simple maze. Using multi-unit neuronal recording methods, they observed the well-documented hippocampal place fields: as the rats ran back and forth within the maze, place-specific neurons fired. Of interest here is what happened during periods immediately following spatial navigation when the rats stopped. During stopped periods, cells with place fields spontaneously fired with structured patterns that echoed the sequential patterns that occurred when the rats were actively navigating, but much faster and in reverse order.

Foster and Wilson’s (2006) discovery of temporally compressed, reverse replay in rats during stopped periods is an example of a brain activity event that differs from that elicited during active performance. The spontaneous activity they observed is tied directly to the experience of the rat when engaged in the outside world and, although not established yet, is presumed to influence information processing and performance, perhaps as a mechanism of learning.

Critical to our point, the discovered activity patterns are revealed during the stopped periods and are quite distinct from the form observed during the active periods of navigation. We wonder if many forms of structured activity events will be discovered between the active moments of tasks or concurrent with directed activity but

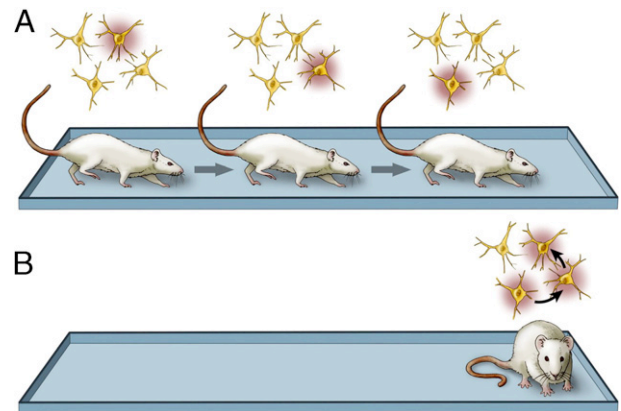


Fig. 1. Rest activity states contain complex, structured brain activity patterns that may support important brain functions. Functions may include both processes associated with conscious, cognitive events as well as spontaneous activity events that operate below our awareness to consolidate, stabilize, or otherwise set the context for future information processing. Illustrated is one such example adapted from Foster and Wilson (2006). (A) Hippocampal cells demonstrate place fields that fire sequentially as a rat runs on a linear track. (B) When the rat stops, the cells with place fields rapidly fire in reverse order to their original sequence. Reverse replay of immediately preceding episodes during stopped (rest) periods suggests a functional role for spontaneous activity in learning and memory.

detached from it. Default activity, for example, may relate to spontaneous cognition perhaps linked to planning and imagination as anticipated by Ingvar (1979, 1985) and Andreasen et al. (1995), and expanded upon this past year by Fransson (2006) and Esposito et al. (2006). We have recently noted that the default network engaged during passive task states is suspiciously similar to the core brain network engaged when people imagine themselves in alternative perspectives to the present, such as when remembering the past or envisioning the future (Buckner and Carroll, 2007; see also Addis et al., 2007). Other forms of rest activity may reflect spontaneous activity events that operate below our awareness and serve to consolidate, stabilize, or otherwise set the context for future information processing (Raichle, 2006). Vincent et al. (in press) report that spontaneous network correlations can persist under anesthesia suggesting the existence of spontaneous, structured activity events that may be quite distinct from that associated with rest-state cognition. Exclusive focus on task-evoked brain activity events may miss these potentially important neural processes.

Alzheimer's disease and other disorders are linked to rest activity patterns

Study of rest activity patterns may be central for understanding diseases of the mind. Morcom and Fletcher (2006) do not dispute the importance of using rest states to understand the physiology of disease. We raise this important topic, however, because it speaks to their most general assertion where they “question the value, and indeed the interpretability, of the study of the resting state and suggest that observations made under resting conditions have no privileged status as a fundamental metric of brain functioning”.

Recent studies of disease illustrate the importance of studying rest conditions in the context of clinical exploration. Several studies have demonstrated that clinical diagnosis of Alzheimer's disease correlates with differences in default network activity (e.g., Lustig et al., 2003; Greicius et al., 2004; Rombouts et al., 2005; Wang et al., 2006). Recent data have further revealed differences in rest-state activity in autism (Kennedy et al., 2006), depression (Anand et al., 2005), multiple sclerosis (Lowe et al., 2002), and attention deficit hyperactivity disorder (Tian et al., 2006). These data suggest that analysis of resting state activity patterns may inform the understanding of disease and aid diagnosis.

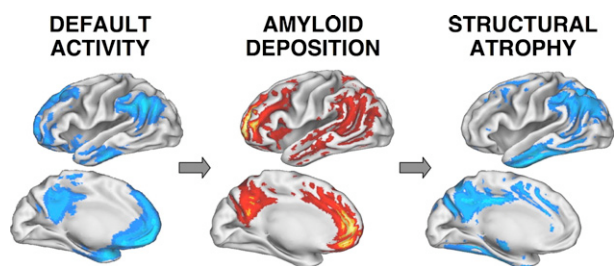


Fig. 2. Alzheimer's disease may be causally related to default network activity. (left) Regions manifesting default activity in young adults are highly similar to (middle) those that show Alzheimer's pathology in early stages of the disease as measured by molecular imaging of amyloid plaques using positron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

Even more provocative is the recent unexpected possibility that default network activity may directly, or indirectly through resultant metabolism (e.g., glycolysis), play a causal role in Alzheimer's disease pathology associated with amyloid plaques. Fig. 2 illustrates data supporting this possibility. The pattern of default network activity commonly observed in young adults is remarkably similar to where amyloid plaques are detected using molecular imaging methods in early-stage Alzheimer's disease (Buckner et al., 2005). The cortical regions affected by pathology show atrophy as the disease progresses (Buckner et al., 2005; Schill et al., 2002). A speculative possibility is that lifelong default network activity patterns may augment an activity- or metabolism-dependent cascade that leads to the formation of Alzheimer pathology and the eventual symptoms of the disease (Buckner et al., 2005; see also Cirrito et al., 2005; Selkoe, 2006).

Rest activity maps provide methods for functional localization, exploration of individual differences, and study of comparative anatomy between primate species

One of the reasons for the growing interest in rest activity patterns, in particular the spontaneous low-frequency network correlations, is how robust they are (e.g., Biswal et al., 1995; Greicius et al., 2003, 2004; Fransson, 2005, 2006; Fox et al., 2005; Vincent et al., 2006). As one illustration, Fig. 3 shows maps from two individual subjects constructed using analysis of spontaneous network correlations in rest scans (see also Damoiseaux et al., 2006). These data were acquired in about 20 min and show the regions spontaneously correlated with the hippocampal formation. Greicius et al. (2004) further pointed out that rest activity measures are more easily obtained than traditional task paradigms in patient groups because the task requirements to elicit them, by definition, are minimal. In monkeys, structured spontaneous network correlations persist even under anesthesia (Vincent et al., in press) suggesting a way to map functional brain regions in non-compliant subjects, such as might be useful for presurgical planning in cognitively impaired individuals. For example, it may be possible to determine the intrinsic lateralization of language pathways without having patients perform a language task. The simplicity and power of spontaneous activity analysis make it amenable as a localization and mapping tool. Three specific uses are (1) functional localization, (2) study of individual differences, and (3) exploration of comparative functional anatomy between primate species.

Functional localization

A common approach to data analysis has been to define functional regions using task-based localizers (e.g., Tootell et al., 1995; Kanwisher et al., 1997). Functional correlation analysis is similarly able to meaningfully define functional regions based on spontaneous activity during rest states. A recent example can be seen in our work where we used rest activity correlations with the hippocampal formation to define functional regions, in particular within parietal cortex and posterior midline regions, that were then revealed to be selectively responsive to memory processes (Vincent et al., 2006). In concept, this approach can be modified to survey the cortex broadly by using the complex topography of rest scan correlations to functionally segment the entire cortex (e.g., De Luca et al., 2006). Parcellations based on spontaneous activity patterns may be useful for defining multiple functional regions or as constraints for functional (as opposed to only anatomical)

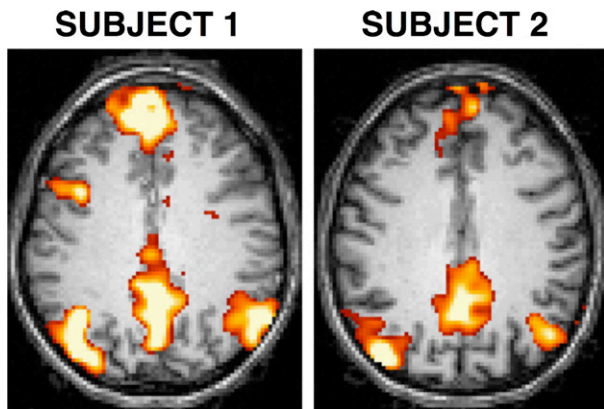


Fig. 3. Analyses based on rest activity provide powerful tools for mapping brain systems. As an example, the maps depict cortical regions spontaneously correlated with the hippocampus measured during rest in two separate subjects. Note the similarity between the two subjects and the potential for mapping individual participant anatomy. Measurement of functional brain networks using correlation techniques during rest fMRI provides a powerful tool for comparing functional anatomy between individuals and primate species, for registering functional anatomy such as required for atlas transformations, and for presurgical planning without the need for task compliance. Adapted from Vincent et al., 2006.

between-subject spatial registration. For example, the spatial organization derived from spontaneous functional correlations that are embedded in most fMRI studies may be useful as the primary information used for between-subject spatial registration.

Individual differences

While a few recently published studies have found broad similarities between subjects (Damoiseaux et al., 2006; Vincent et al., 2006), we suspect that differences will also emerge. It seems entirely possible that differences in rest-state activity may be important to understanding individual differences in functional anatomy, cognition, and risk for disease (e.g., Alzheimer's disease). A potentially rich area for future exploration is to explicitly use variance in spontaneous activity patterns as the basis for exploring functional differences among individuals (see Hampson et al., 2006 for a related approach).

Comparative functional anatomy

Extending from the same general principle discussed above in the context of exploring individual differences, analysis of rest activity may provide a unique window to explore comparative functional anatomy between species. Historically, functional comparisons between species were difficult because the methodologies differ (single cell/local field potential recordings vs. fMRI). Study of task-evoked fMRI in monkeys and humans has facilitated functional comparisons between species using similar techniques (Orban et al., 2004, 2006; Grefkes and Fink, 2005; Koyama et al., 2004; for a recent review see Nakahara et al., 2007). However, monkeys must undergo extensive training to perform complex tasks in the MRI scanner. Great apes because of their size and strength have not been trained to behave in the MRI environment. Furthermore, it is always possible that monkeys and humans use different strategies to complete the task that could make comparisons ambiguous.

The study of the network organization of correlated spontaneous activity using fMRI has great potential for exploring functional homologies between monkeys, great apes, and humans. Recently, it has been shown that spatial organizations revealed from spontaneous correlations in anesthetized animals are similar to those which have been extensively explored using traditional tract tracing methods, electrophysiology, and task-related fMRI (Vincent et al., in press). This result establishes a novel method of examining functional localization and network organization without the cost of training the animal. We believe that parallel study of spontaneous activity patterns using fMRI in humans and a broad range of species including non-human primates will greatly expedite our understanding of functional homology and provide targets for physiological study.

Agreements and open issues

Although our perspective differs from Morcom and Fletcher's on the fundamental merit of studying data from rest states, there are several specifics on which we generally agree. Perhaps most substantively, we agree with the caveats associated with *exclusively* using rest states as baseline conditions in neuroimaging studies. The debate about how useful rest states are as reference tasks in neuroimaging has been going on since the methods were established. A discussion between Richard Frackowiak and Marcus Raichle during a 1991 symposium held by the Ciba Foundation captured this long-standing debate (from Chadwick and Whelen, 1991 p. 231):

The best control state is the '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 (Frackowiak, 1991).

We seem to be polarizing this issue of control states when it doesn't need to be polarized. We in St. Louis do as many complex subtractions as you do, but we have also found it useful, in evaluating the data at the outset, to compare these various states against, say, a fixation point, because it gives you the entire picture. It's a means of gaining a perspective as you look through the data (Raichle, 1991).

One of us has previously discussed the empirical merits of using low-level control conditions *in addition to* targeted contrasts in some detail (e.g., Buckner, 1996). We do not repeat the arguments here.

We also agree that "there are problems with the assumption that the resting state is a baseline to which others states should be referred". References to rest baseline states have been informative in many contexts but principally when used in conjunction with manipulations of task conditions. Moreover, rest baselines, used exclusively, may be misleading as pointed out in the study of hippocampal function by Stark and Squire (2001). Spontaneous, structured activity patterns in some systems may attenuate during task conditions (Fransson, 2006; see also Arfanakis et al., 2000), which may be one of the reasons why rest states are unequal partners when contrasted to active task conditions. We did not fully appreciate this complexity in the past. Now we do.

An area where we are agnostic concerns definition of a baseline state through analysis of the relative amount of oxygen utilized to the amount of oxygen delivered to a region—referred to as the oxygen extraction fraction (OEF). At the core of Raichle and colleagues' (2001) definition of a default mode, is their interpretation that the rest state has uniform OEF (at least insofar as default mode regions are concerned). We find this possibility interesting but believe further exploration of the phenomenon is warranted, in particular in relation to the discovery of spontaneous fluctuations in default network regions. Spontaneous fluctuations imply OEF may be less static than initially believed. For all of the reasons articulated earlier, we nonetheless believe that rest activity is important to study.

Conclusions

Morcom and Fletcher's commentary articulates a perspective many share concerning all of the reasons to avoid study of rest activity states. Their points are well taken. Some cautions surround a conception that rest-state activity arises from unconstrained cognition and therefore brain function can best be understood by devising appropriate tasks that target specific mental processes. Put simply, why let a free-wheeling state dictate the experimental course when we can direct the path using constrained tasks? They imply in their discussion that understanding a brain region's processing function in solving directed tasks is sufficient to understand its processing functions in general. Given that assumption they arise at a reasonable conclusion "It is our belief that, given the unconstrained nature of 'resting' states ... the best approach is likely to be to determine what controllable experimental manipulations affect the level of activity in these regions and the dynamics of their interactions". Despite its appeal, we suspect this conclusion is ultimately flawed.

Our fundamental departure from Morcom and Fletcher's perspective is this: considerable aspects of brain activity may be functional, adaptive, and process specific information but may not be directed toward immediate behavior. Studying the activity of brain regions only during active tasks assumes that all neural functions related to cognition can be captured in the moment of the cognitive event. However, some functional processes may have evolved to occur over longer time scales rather than to support immediate task goals. A radical perspective is that such future-oriented processes are the majority of the brain's function. Perhaps our recent evolutionary adaptations, having largely solved surviving the moment, now include a great deal of neural resources dedicated to surviving future moments. That is, while we spend critical moments engaging the environment to solve immediate tasks, we spend most of our time directed away from the environment in processing modes that consolidate the past, stabilize brain ensembles, and prepare us for the future. Activity events supporting these functions may be structured in ways fundamentally different from those we have gleaned by studying input–output relations under immediate experimental control. Within this speculative view, baseline activity patterns during rest may be our first glimpse into these processes.

We are beginning to look directly at the spontaneous neural patterns that emerge during the intervening periods that punctuate externally directed mental acts. Initial studies, including our own, are frustratingly descriptive and focus on gross properties of the activity patterns that emerge. Ultimately, such explorations will only be informative if we can link rest activity patterns to functional consequences. Making the endeavor difficult is the

expectation that the functional consequences may be revealed in distant behaviors or as processing modifications that accumulate gradually over time. We are in uncharted territory.

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