

Target Article

Does the brain have a baseline? Why we should be resisting a rest

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In the last few years, the notion that the brain has a default or intrinsic mode of functioning has received increasing attention. The idea derives from observations that a consistent network of brain regions shows high levels of activity when no explicit task is performed and participants are asked simply to rest. The importance of this putative “default mode” is asserted on the basis of the substantial energy demand associated with such a resting state and of the suggestion that rest entails a finely tuned balance between metabolic demand and regionally regulated blood supply. These observations, together with the fact that the default network is more active at rest than it is in a range of explicit tasks, have led some to suggest that it reflects an absolute baseline, one that must be understood and used if we are to develop a comprehensive picture of brain functioning. Here, we examine the assumptions that are generally made in accepting the importance of the “default mode”. We 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. In doing so, we challenge the utility of studies of the resting state in a number of important domains of research.

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“Absence of occupation is not rest,
A mind quite vacant is a mind distress’d.”
Retirement—William Cowper

In recent years, there has been increasing interest in functional neuroimaging studies of the brain in a state of ‘rest’. This interest

Abbreviations: fMRI, functional magnetic resonance imaging; PET, positron emission tomography; BOLD, blood oxygenation level dependent; OEF, oxygen extraction fraction; rCBF, regional cerebral blood flow; PCO₂, partial pressure of carbon dioxide; gCBF, global cerebral blood flow; TID, task-independent decrease.

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has been kindled by claims that brain activity in this state represents an intrinsic baseline that is qualitatively different from the states evoked by goal-oriented activity. Specifically, it is said that it reflects a ‘default mode’, one from which the brain moves when external demands are made and one to which it returns when those demands cease. To quote the leading proponents of this view, in order to understand the basis of behavior “...we must focus not only on changes evoked in brain systems during various behaviors, but also on the ongoing and very costly intrinsic activity within these systems” (Raichle and Gusnard, 2005). In this article, we examine the theoretical and empirical foundations of this view. We question the utility and meaning of the idea of a ‘default mode’ and of the study of the resting state. We conclude that these have a limited role to play in understanding the ways in which the activity of neural systems contributes to behavior.

The case for a default mode comprises three related ideas. The first is that the resting state constitutes an absolute baseline, and is therefore a fixed point relative to which all cognitive and physiological states can and should be considered (Gusnard and Raichle, 2001). Second is the notion that the level of neural activity in this resting state is substantial and therefore functionally important, with changes produced by task demands representing just the “tip of an iceberg” (Raichle et al., 2001). Finally, relative to a wide range of tasks the resting state is said to be associated with higher levels of activity in a consistent set of brain regions. This has led to the idea that, at rest, we return to a ‘default mode’, which plays a critical role in the ‘intrinsic’ functioning of the brain (Shulman et al., 1997; Gusnard and Raichle, 2001). We believe that these three claims, and their synthesis, should be evaluated critically for theoretical and practical reasons. If they are valid, then the resting state is indeed a context in which to study brain processes that are fundamental and important relative to the small flickers of activity produced by task demands. It would follow that cognitively driven fluctuations cannot be interpreted except in the context of the default system.

We suggest that the case for a default mode does not survive this critical evaluation. We first explain and evaluate the claim that ‘rest’ is a baseline state for the human brain, summarizing the support for this, and the ways in which a baseline might or might not be necessary in functional neuroimaging. We conclude that despite the interesting characteristics of rest as baseline in terms of

oxygen balance, these are not relevant to studies that seek to understand how neural activity underpins cognitive processing. Secondly, while we accept that a high level of energy expenditure of the brain at ‘rest’ indicates that the resting state is active, we do not agree that this activity has a special status compared with that in any other task, or that the brain’s energy budget is informative about the nature of a ‘default mode’. Thirdly, with respect to the idea that patterns of brain activity found at ‘rest’ are consistent, we point out that the evidence for this is inconclusive. Furthermore, we would question what conclusion could be drawn from such a consistency, if it is ultimately demonstrated. Finally, we note that the idea of a default mode is based not only on three separate claims but upon their synthesis. We scrutinize this synthesis with regard to the support that it gives to rest/default mode as a state that is qualitatively different from any other mental and neural state. We conclude that even if there is empirical consistency in the patterns of activity observed at rest, and a subjective appeal to the notion that when we rest we are in a default state because there is no explicit task to perform, these are insufficient grounds for affording the resting state a privileged status in accounts of human behavior. We further suggest that, in most situations, the aims of cognitive neuroscience are best served by the study of specific task manipulations, rather than of ‘rest’.

The search for a baseline

Raichle, Gusnard and coworkers argue that we should reconsider the importance of a baseline in neuroimaging (Raichle et al., 2001; Gusnard and Raichle, 2001). As is well known, both direct (PET) and indirect (BOLD fMRI) functional neuroimaging techniques are based on a particular characteristic of cerebrovascular autoregulation: when a region increases its level of neural activity, this is reflected in a disproportionate increase in blood flow, and concomitant reduction in the proportion of oxygen used (oxygen extraction fraction; OEF; Fox and Raichle, 1986; Ogawa et al., 1990a,b; Shulman and Rothman, 1998). This change is traditionally referred to as an ‘activation’ (for review see Raichle and Gusnard, 2002).

In functional neuroimaging studies, the level of the regional BOLD signal or blood flow is thus taken as a measure of the underlying neural activity (henceforth referred to as ‘activity’). To investigate how this activity relates to cognition, subtractions are often made among activity measurements during different tasks. This ‘cognitive subtraction’ is performed because experimenters are interested in the neural correlate of a particular cognitive function and seek to isolate this by identifying differences in activity between tasks that differ only in terms of that function. Of course, not all neuroimaging studies employ a simple subtraction design, and the merits, flaws and fallacies of subtraction have been debated elsewhere (e.g., Friston et al., 1996; Sartori and Umiltà, 2000). However, our discussion regarding a baseline is pertinent to any approach that analyzes the neural correlates of a process or processes in one task or physiological context and then seeks to generalize them to another context (e.g., Friston et al., 1996; Price and Friston, 1997). We thus take a simple subtraction study as an illustrative example, and Fig. 1 illustrates possible patterns of differential activity that may be observed between two task conditions. In such a case, as Gusnard and Raichle (2001) point out, a finding that task T1 elicits greater activity than task T2 may be associated with qualitatively different patterns when these tasks are also compared to ‘rest’. Both may show activity increases

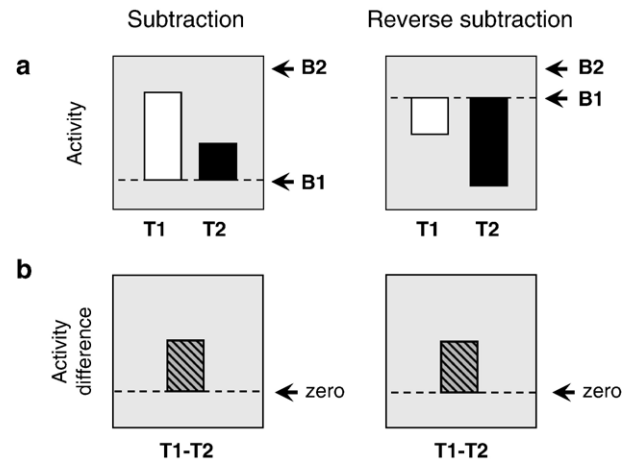


Fig. 1. A schematic representation of findings of a neuroimaging study with a simple subtraction design and two tasks, T1 and T2. In panel a, the y-axis represents activity associated with tasks T1 and T2 measured against some kind of a baseline, possibly rest (indicated by black arrows). A subtraction is shown on the left and a reverse subtraction on the right, where the baseline is B1. See text for comment on the alternative baseline, B2. In panel b, the y-axis represents the directional difference in activity between T1 and T2.

(greater for T1 than for T2), or both may show activity decreases (greater for T2 than for T1, a ‘reverse subtraction’; see also Gusnard and Raichle, 2001, Box 2).¹ In many cognitive neuroimaging studies, these possibilities are not tested and, critically, are not thought to be important since the degree to which the process of interest is active under resting conditions is unknown.

Raichle et al., however, noting that comparisons of tasks with rest can yield relative decreases in activity during the tasks, ask “...whether these unexplained decreases merely arise from unrecognized increases (i.e., activation...) present only in the ‘control state’... (On) this argument, any control state, no matter how carefully it is selected, is just another task state with its own unique areas of activation. Unfortunately, in most instances there is insufficient information about the control state to judge whether the observed decrease arose in this manner” (Raichle et al., 2001). In another paper, Gusnard and Raichle state that “without the knowledge of such a reference point or baseline, it is impossible to exclude the possibility that such decreases merely represent the product of a reverse subtraction. Providing a definition of a physiological baseline should facilitate a greater understanding of all changes in activity, both decreases and increases, that are encountered” (Gusnard and Raichle, 2001). But in what way might

¹ We should note at this point a possible source of confusion that relates to analytic methods. Gusnard and Raichle’s (2001) distinction between a subtraction and a reverse subtraction is made alongside a distinction between both of these and a case where condition A (i.e., T1) shows a decrease from baseline and condition B (i.e., T2) an increase (Gusnard and Raichle, 2001, Box 2, e). Their claim is that the increase in activity for A relative to B will be underestimated, and this would surely be the case were it not possible to create contrasts of A compared to B which take the direction of the changes into account. In the analytic software with which we are most familiar (<http://www.fil.ion.ucl.ac.uk/spm>), although statistical tests are one-sided, the contrasts used to create them are not and so this would not be a problem. That said, it is clearly important for researchers to understand the analytic methods we employ and to ensure that, where relevant, such a case is not neglected.

knowing whether a relative difference $T1 > T2$ is a ‘real’ increase or the result of a reverse subtraction be fundamental to its interpretation in processing terms? In what follows, we deliberately avoid discussion of possible differences between *task-related* increases ($T1 > T2$, where $T2$ is the control task and $T1$ is hypothesized to engage additional processes), and decreases ($T2 > T1$): it is well-established that the engagement of additional neural processing can produce systematic and regionally specific decreases in activity (Frith and Friston, 1996). This distinction is of some importance but, we feel, is a separate theoretical issue (see Otten and Rugg, 2001; Wagner and Davachi, 2001; for discussion in the context of episodic memory). Instead, we focus on the issues associated with the possible impact of a baseline on such between-task comparisons.

It seems to us that there are problems with the assumption that the resting state is a baseline to which other states should be referred, a notion entailed by the call for a distinction between a subtraction and a ‘reverse subtraction’. If, as we believe, such a distinction is irrelevant in cognitive neuroimaging studies, the utility of the term ‘baseline’ in this context must also be called into question. In considering these problems, we need to distinguish between two views: one that the resting task constitutes a processing baseline and one that it serves as a physiological baseline that does not relate directly to processing. In so doing, we highlight the fact that the notion of a ‘default mode’ rests in part on a relationship between the physiological and processing aspects of ‘rest’. We conclude that although rest may be, subjectively, a ‘default’ state (in the sense that it is what we are doing when we are not doing anything else), it is of no utility as a processing baseline. We find that the suggested link between the processing taking place at rest and its physiology is one that can have no direct relevance for neuroimaging. That said, we do accept that it may be helpful in some contexts to regard rest as a physiological baseline.

A processing baseline?

One possibility is that every region has a cognitive or processing baseline, and that if we knew what this was, our interpretation of a difference in activity between two cognitive tasks would be richer and better informed. But what neutral cognitive state would this entail, and is there a sense in which ‘rest’ (henceforth taken to mean lying quietly in a scanner with one’s eyes closed) is a processing baseline for all brain regions? Here, there are two questions to be considered: first, does a cognitive subtraction require a reference point? Second, is rest the state of choice for such a reference task?

A strong response to the first of these questions is that such baseline information is indeed *essential* for a proper understanding of a difference in the activity associated with two tasks, $T1$ and $T2$. If this is the case, the meaning of a subtraction and a reverse subtraction are different. One might regard the former case as ‘additional activity during task $T1$ ’ because the task difference is driven mainly by an increase for $T1$ compared to baseline, and the latter case by similar reasoning as ‘reduced activity during task $T2$ ’ (see Fig. 1a). The presumption is that this is telling us more than the simple statement, true equally of both cases, that $T1$ is associated with additional activity *compared to $T2$* (see Fig. 1b). However, this presumption depends on knowing already the significance of the level of baseline activity $B1$ in a region. If one took an alternative state, $B2$, as a baseline, this might be associated with a higher level of activity than $T1$, $T2$ and $B1$, and thus the

subtraction and the reverse subtraction relative to $B1$ would both become reverse subtractions relative to $B2$ (see Fig. 1a). In other words, a subtraction and a reverse subtraction are in principle interchangeable.

The fact that a comparison between $T1$ and $T2$ does not *require* a baseline does not prevent meaningful information being derived from separate comparisons of them both with a reference task. If there is a state B whose processing demands are known, and in which we already know the associated level of activity in region X , then the relationship between that level of activity and the activity found during $T1$ and $T2$ can certainly inform our interpretation of the difference between $T1$ and $T2$ in the manner just described. Another example of the utility of such a reference condition is in support of between-region functional dissociations, as Henson (2005) has pointed out. Typically the finding of a ‘crossover’ interaction between activity changes in regions X and Y , with $T1 > T2$ in the first region, and $T2 > T1$ in the second, is interpreted as indicating that X and Y subserved distinct kinds of processing (e.g., Rugg, 1999). However, it is possible that the direction of changes in activity is always reciprocal between certain regions, regardless of the task. In other words, when region X shows a relative increase, Y may always show a relative decrease. A functional dissociation can be confirmed if it can be shown that the relative directions of changes in X and Y elicited by $T1$ and/or $T2$ are the same relative to a third task, this does imply a functional dissociation (see Henson, 2006, Fig. 1f). Critically, however, none of the foregoing implies that $T1$ and $T2$ can *only* be interpreted in the presence of B , nor that any one ‘baseline’ task B is more informative than another.

We have argued that the observation of a difference between a subtraction and a reverse subtraction is not evidence for the importance of the baseline; on the contrary, it is itself based on an a priori choice of the baseline used to distinguish these two cases. What independent considerations might motivate such an a priori choice? An obvious candidate for an absolute baseline would be a state in which a given region is carrying out no processing at all. We dismiss this notion for present purposes as it seems clear to us that proponents of the ‘default mode’ are not suggesting that ‘rest’ is a baseline of this kind—in fact, as we will see, quite the contrary. They imply instead that the habitual state of the system provides a useful processing baseline. In the resting state, blood supply and energy demand are approximately matched, the local OEF being roughly constant across the brain (Raichle et al., 2001). Raichle et al. argue that this metabolic calibration may have evolved precisely because rest, in processing terms, has been our habitual state, associated with ‘a long-term modal level of activity’ in each region. It is possible that this regional modal level of metabolic activity might also have implications for regional sensitivity to certain kinds of pathology or insult (Raichle et al., 2001; Buckner et al., 2005). The physiological characteristics of this metabolic baseline may also have implications, and we discuss these in the next section. However, from a processing point of view, the relevance of some habitual level of processing to inferences about a region’s role in a specific experiment remains obscure. Given that the nature of the processes engaged by the resting task are largely unknown, it is hard to see the value of rest as a processing baseline.

A physiological baseline?

The uniformity of the OEF across the resting brain occurs despite widely varying levels of oxygen consumption, and is the

main basis of Raichle et al.'s (2001) definition of rest as a baseline: "...we identify a baseline state of the normal adult human brain in terms of the brain oxygen extraction fraction or OEF" (see also Gusnard and Raichle, 2001; Shulman et al., 2004). This uniformity implies a consistent and regulated relationship between varying local blood flow and varying local energy consumption, whereby, in the resting state, supply and demand are approximately in equilibrium. But why should this matter when studying neuronal activity, and do we need to refer our cognitive interpretations of evoked brain responses to a physiological baseline state? One possibility is that the nature of this equilibrium affects the *measurements* we make of changes in brain activity (i.e., the mapping from neuronal activity to hemodynamic response). This is an important possibility to consider since we have argued that a 'subtraction' and a 'reverse subtraction', are equivalent in terms of the underlying neural activity: such an assertion rests on an assumption that the change in neuronal activity evoked by a given change in processing demand is independent of the level of baseline measurement in a region. The requisite linear relationship between neuronal activity and measured signal is illustrated in Fig. 2a. In this context, if tasks T1 and T2 demand more of a given process than their baseline tasks B1 and B2, the differential signals measured for T1-B1, and T2-B2 will be of the same magnitude, because although the baseline is different, the change in signal elicited by the same differential neuronal activity is the same. On the other hand, if the measured signal depends on absolute neuronal activity, then we may find baseline dependency, for example, a smaller signal increase at high relative to lower baseline levels, for the same change in neuronal activity (i.e., a ceiling effect; see Fig. 2b). In short, the quantitative interpretation of activations from different baselines in terms of neuronal responses requires a linear relationship between neuronal activity and hemodynamic signal. If this assumption of *additivity* is violated, then there may be an absolute baseline to which every activity change should be referred.

However, any violation of additivity in the mapping of neuronal to hemodynamic response *has no effect* on the validity of cognitive subtraction *per se* (although it may influence its sensitivity). This is because a simple subtraction involves no quantitative comparison

of activations, because there is only one activation, or difference; one is simply inferring that the difference is not zero. All that is required is that the relationship between neuronal activity and hemodynamics is monotonic, even if it is highly nonlinear. Having said this, the quantitative comparison of activations in two different contexts (e.g., using two baselines) does rest on an assumption of additivity. This means that the notion of an absolute reference may be important for their interpretation. This is a common consideration in psychology, where trivial explanations for interactions, such as floor or ceiling effects, speak to the notion of some absolute baseline that falls within the dynamic range of experimentally inducible responses. Having established that the notion of an absolute baseline may be important for the interpretation of (and only of) interactions measured hemodynamically, we now consider evidence for a nonlinear relationship between neuronal and measured responses. As noted above, such a nonlinearity would mean that a hemodynamic response depends on the baseline from which it is elicited.

The assumption of additivity in this context entails that the hemodynamic response to a fixed change in neural activity does not vary with the absolute value of the signal in that region at the time the change occurs. A substantial body of empirical work has addressed these questions in both BOLD fMRI and PET. It is generally accepted that, within the normal physiological range, there is very little evidence for an interaction between baseline and evoked activations. This was examined in the early days of PET and more recently in fMRI. The first study to look at this issue (Ramsay et al., 1993) showed that: "the effect of the activation on the rCBF was apparently 'additive' to the rise of rCBF associated with PCO₂-related gCBF increase. The results... provide support for the use of an 'additive' model."

More recent evidence supports a similar conclusion under most circumstances for the more complex case of BOLD fMRI. When the baseline blood flow is manipulated without altering neural activity, as in hyperventilation studies, the same stimulus evokes the same increment in activity from baseline, but the *absolute* level of this evoked activity varies (Hyder et al., 2002; Smith et al., 2002). In other words, when the regional blood flow changes without the neural activity changing, both baseline and evoked activity change by the same amount. Here, the neural baseline is unchanged, but the vascular baseline has been altered. This is clearly in keeping with the additivity assumption outlined above. This is important, because it suggests that although the resting state may be unique in terms of its uniform OEF across the brain, the magnitude of the differential BOLD response between tasks will not depend on how much the OEF changes between these tasks and rest. In other words, from the point of view of neurovascular coupling at least, relative and absolute increases and decreases in the BOLD signal appear to be independent.

Of course, the picture is very different when the *neural* baseline is manipulated, for example using a general anesthetic. In such situations, the absolute level of BOLD activity evoked by a given stimulus is constant and is coupled to the pyramidal cell spike rate (Shulman et al., 1999; Hyder et al., 2002; Smith et al., 2002). However, because the neural baseline has been altered, the relative *increment* from that baseline changes—starting from a lower level of neural activity, under deeper anesthesia, the eventual level of evoked neural activity is the same, and thus the increment between this new baseline and the task is bigger. In short, "the incremental signals depend on, among other things, the starting resting brain

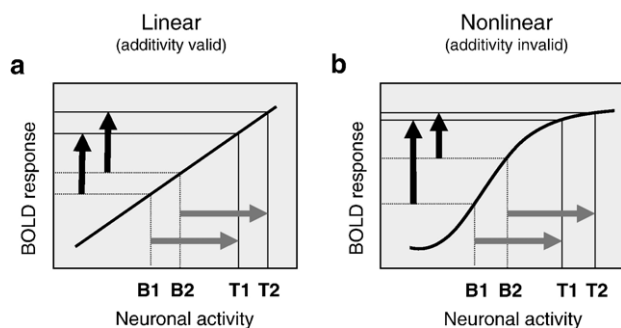


Fig. 2. Illustration of the difference between (a) a linear and (b) a nonlinear neuronal to BOLD mapping: only the nonlinear mapping induces the need for an absolute baseline. The black arrows show the evoked BOLD responses for comparisons of two tasks (T1 and T2), with two baselines (B1 and B2). The evoked neuronal responses are identical in magnitude for T1-B1 and T2-B2, and so are the evoked BOLD responses when the mapping is linear. However, this is not the case when the mapping is nonlinear. In the latter case, there is an apparent interaction in the hemodynamic response, and an implicit baseline dependency.

activity itself” (Hyder et al., 2002). This makes perfect sense and is an example of an interaction (at the neuronal level), which is the focus of most modern factorial neuroimaging designs. In this case, we are looking at an interaction between anesthesia-induced change in basal neuronal activity and stimulus-related effects.

There are a range of other data to support a linear relationship between neural activity and cerebral blood flow and the peak BOLD signal, at least under normal physiological conditions (e.g., Mathiesen et al., 1998; Martindale et al., 2003; Martin et al., 2006). Despite this, drugs and other factors may potentially disrupt the assumptions on which subtraction rests. General anesthetics may not be a good model for neural changes in awake animals, as they can induce nonlinearities in both neural responses and neurovascular coupling, at least when sensory stimulation extends into a high intensity range (Hewson-Stoate et al., 2005; Martin et al., 2006). Likewise, the possibility cannot be ruled out of ‘physiological but not cognitive’ changes in neural activity that are different in kind from those associated with a change in the task. We will return to this point in the next section.

Critically, we find no support for the notion that the physiological characteristics of the resting state mean that it is an absolute baseline against which the signals measured during other tasks must be compared in order to be interpretable. A task-related reduction (or increase) in a region can be interpreted as a task-related reduction (or increase) in neural activity in just the same way regardless of whether this change is measured relative to rest or relative to some other condition. Thus, so far as we can determine, a ‘reverse subtraction’ is equivalent to a subtraction, in physiological as well as in processing terms. As we have stated, we readily admit that the assumption of additivity is likely to have its limits; however, there is no evidence that these can or must be defined in relation to the resting task. Thus any notion of a ‘default mode’ based on the metabolic equilibrium at rest appears irrelevant to investigations of how neural activity supports cognition.

The tip of the iceberg?

The second key observation that draws attention to the resting task, and to the linked idea of a default mode, is the high level of energy expenditure of the brain at rest (Shulman and Rothman, 1998; Shulman et al., 1999, 2004; Raichle et al., 2001). Before considering this in detail, we note that although the detailed relationship between brain physiology and cognitive processing is beyond the scope of our discussion, we assume that the latter is embodied in the former. However, we remain agnostic about the extent to which neuronal activity sustains purely ‘physiological,’ as opposed to cognitive, processes. Rather, our concern is with what impact, if any, the physiological changes have on the study of the cognitive processing. It has been observed that the change in energy consumption ‘evoked’ by task manipulations is a small fraction of that due to ongoing ‘intrinsic’ activity (Raichle and Gusnard, 2002; Sokoloff et al., 1955). Various metabolic and EEG studies suggest that this ‘intrinsic’ energy consumption is predominantly due to neuronal signaling (see Shulman et al., 2004 for review). This, together with the metabolic considerations outlined in the previous section, has led to the quantitative component of the claim that brain activation “can be distinguished both qualitatively and quantitatively from resting metabolic activity” (Raichle et al., 2001; see also Shulman and Rothman, 1998). The use of the ‘tip of the iceberg’ metaphor, and the emphasis on this quantitative difference,

explicitly suggests that this high energy consumption in the resting task is important for brain function as a whole.

Before considering the extent to which it is important, we suggest that the quantitative argument can be challenged. Although neural processing may contribute substantially to the brain's energy consumption, the figure of ~80% attributed to “ongoing neuronal activity” (Raichle and Gusnard, 2002; see Shulman et al., 2004 for review) includes a large indirect contribution from neurotransmitter cycling. More importantly, the regional BOLD signal may not depend on this overall regional energy consumption, but instead may be linked rather more directly to neuronal activity itself (Attwell and Iadecola, 2002). Thus the brain's overall ‘energy budget’ is likely to have limited direct relevance for investigations of neural processing (see also Logothetis and Pfeuffer, 2004). Furthermore, with regard to the qualitative importance of rest, energy consumption and even neural signaling are likely also to be high in other states, for example during the performance of specified experimental tasks. This follows from the low figures for task-related differences in energy consumption (Sokoloff et al., 1955). It is therefore not clear to us why the resting task is deserving of special consideration in this context, or what implications the brain's high energy consumption in a range of tasks might have for a ‘default mode’ which has any cognitive or processing specificity.

That said, we do not dispute that the resting state is an active one from the neuronal point of view. But does this have the significance that is claimed for it? The possibility has been raised that the activity associated with resting state metabolism has some non-cognitive or other special functional status, and; “...that the very high baseline or ongoing metabolic activity of the brain not only supports processes necessary for the maintenance of the proper responsiveness of neurons for the transient and ever changing functions of the brain but also instantiates a sustained functionality” (Raichle et al., 2001). We will return to this ‘sustained functionality’ in the next section, but first consider the notion of ‘responsiveness’. This refers to the possibility that a certain ‘baseline’ activity in neural networks may enable them to respond appropriately to changes in input and demand—specifically, to respond rapidly and with a linear relationship to the input. Models of network dynamics suggest that this may depend on there being a relatively high level of ongoing excitatory balanced with inhibitory activity (Salinas and Sejnowski, 2001; van Vreeswijk and Sompolinsky, 1996). Raichle and Gusnard therefore posit that: “...in the brain, a large majority of its metabolic activity is devoted to ongoing synaptic processes associated with maintaining a proper balance between excitatory and inhibitory activity. Maintenance of this balance allows neurons to respond appropriately to correlational changes in their input and establish the functional connectivity as required for a particular task” (Raichle et al., 2001).

These ideas are very interesting, but the relationship between the resting state and the baseline firing of a network in this sense is not clear. Is the suggestion that only the regions most active in the resting state have these properties? This seems unlikely, and we know of no evidence to support this possibility. One would expect that the minimum level of activity at which a response to an unexpected stimulus is adequate would be similar for all regions. As noted earlier, although OEF is constant across the brain at rest, the level of neural signaling varies widely across the cortex, being greatest in certain ‘default mode’ regions that have therefore been described as “active but not activated” at rest (Raichle and Gusnard, 2002). A region may indeed need to maintain a minimum

level of neural activity in order to function properly, a level that is therefore irreducible under normal physiological conditions. It is quite possible that when activity during an experiment is close to this minimum, the linear assumptions underlying additivity become compromised. If such a minimum were the same for all regions, it could hardly define the neuronal activity in all regions at rest—at most it could account for a certain level of firing in those regions *least* active. It could not explain why other regions have a particularly *high* level of resting activity. Even if one argued that these active ‘default mode’ regions require a higher minimum activity level than other regions because they play a special role in the control of functional networks, it would be odd if this minimum level of activity could then easily be reduced below such an essential baseline, as appears to be commonplace during the performance of various tasks (see next section). In fact, the very frequency with which activity decreases versus rest are observed in various regions suggests strongly that their high level of activity during the resting task is not necessary in any basic physiological sense, but rather something that varies with task demands; that is, it suggests that an increase in activity in these regions is provoked when a subject is required to perform the resting task. This may, of course, turn out not to be the case, but for now logic dictates that there is no necessary correspondence between these postulated network properties and ‘default mode’ regions, i.e., those most active in the resting state. Furthermore, the possibility that some of the neural activity seen at rest does not support cognitive processing is in fact another argument against scanning at rest, and in favor of using specific experimental tasks and design, to avoiding confounding qualitatively different kinds of neural activity. Indeed, taking such steps, critical when the aims of the research are cognitive in nature, may also be advantageous in physiological studies.

Another suggestion for possible ‘intrinsic’ functionality of the brain was made recently by Raichle and Gusnard, in a reference to the literature on predictive coding and ‘top-down’ computational mechanisms in the brain (see e.g. [Kording and Wolpert, 2004](#)). It is suggested that the brain maintains “an intrinsic probabilistic model of anticipated events and that the majority of this ongoing neural activity is devoted to maintaining an internal representation of that model with which naturally impoverished sensory information (input) is compared and integrated” ([Raichle and Gusnard, 2005](#)). Although such internal models are in an important sense ‘intrinsic’, it is not clear to us that there is any direct correspondence between such processing and the sense in which brain activity is ‘intrinsic’ in the resting state. Are the ‘default mode’ regions particularly important in the generation and maintenance of such representations and their comparison with the outside world? This seems unlikely as these mechanisms have been proposed as general principles on which much of cortical function, and perception and learning in the most general sense, is based (see [Kording and Wolpert, 2004](#); [Friston, 2005](#)). But even if the ‘default’ network does play such a role, we propose that the way to establish this is by employing specific experimental manipulations, and we make a case for this in the next section.

In summary, while the substantial energy consumption of the brain is clearly an interesting area of research in its own right, it has limited implications for the cognitive neuroscientist. It is furthermore not necessarily peculiar to the resting task, despite the other special metabolic properties of ‘rest’. We therefore conclude that the ‘tip of the iceberg’ argument does not, in fact, support any notion of a default mode of brain function that is associated with rest or any other particular task or cognitive state. This leaves perhaps the most

important element in the case for a default mode, the observation that the pattern of brain activity at rest is consistent and therefore constitutes a functionally meaningful network. This raises the critical questions of what this activity might mean in processing terms, and how best to investigate it.

Task-induced deactivations and the cognitive nature of ‘rest’

Before considering the cognitive nature of rest, we would first emphasize again our agreement with the notion that it is likely to be an active state, both physiologically and psychologically. However, knowing this does not in itself tell us anything about the functions of the regions engaged during rest, or how these functions are carried out. Furthermore, there is a danger that describing resting brain functionality as ‘intrinsic’ could imply that it has somewhat mysterious functions not amenable to study using ‘tasks’. The ‘default mode network’ has been characterized as subserving ‘intrinsic’, ‘ongoing’ functions that are qualitatively distinct from those engaged during tasks other than rest. Raichle and Gusnard (2002) mention “...the intriguing possibility that the spontaneous, ongoing activity of the brain may actually generate globally coherent processes by itself”. [Fox et al. \(2005\)](#) recommend “...shifting one's perspective of brain function from the view of a system simply responding to changing contingencies to one operating on its own, intrinsically, with sensory information modulating rather than determining the operation of the system.” This notion of ‘intrinsic’ activity is appealing but is surely only surprising when posed in opposition to a straw man, the view that the brain does nothing unless it is instructed to. We thus turn to the question of what the cognitive nature of ‘rest’, and the putative ‘default mode’ of the brain, may be, and to the related issue of the consistency, or otherwise, of the network it engages.

There is little doubt that certain regions do tend to show activity decreases during a range of tasks compared to a resting task, and it was such observations that helped spark interest in a ‘default mode’ in the first place ([Shulman et al., 1997](#); [Binder et al., 1999](#); [Mazoyer et al., 2001](#)). According to Raichle et al., “whereas cortical increases in activity have been shown to be task specific and, therefore, vary in location depending on task demands, many decreases appear to be largely task independent, varying little in their location across a wide range of tasks. This consistency with which certain areas of the brain participate in these decreases made us wonder whether there might be an organized mode of brain function that is present as a baseline or default state and is suspended during specific goal-directed behaviors” ([Raichle et al., 2001](#)). Four principal regions are reported to show these ‘task-independent decreases’ (TIDs) in Gusnard and Raichle's influential Nature Neuroscience review (2001). These are medial parietal cortex/precuneus, superior and inferior medial frontal regions, and posterior lateral parieto-occipital cortices. A number of studies have also demonstrated correlated activity between these areas, and others, in the resting state (e.g., [Biswal et al., 1995](#); [Greicius et al., 2003](#); [Fox et al., 2005](#)). So can we determine what this network of regions is doing? If so, what is its relevance?

Discovering the functions of a resting state network

[Gusnard and Raichle \(2001\)](#) emphasize the importance of studying the ‘default mode’. It is therefore particularly notable that in the last section of this article, they consider its possible functions by citing studies in which relative activity *increases* have been

demonstrated in the ‘TID’ regions they highlight, in response to cognitive task manipulations. In the case of the precuneus and posterior cingulate, “associated with the highest resting metabolic rates in the human cerebral cortex”, it is pointed out that these regions show specific increases in activity during visuospatial and emotional processing tasks (Vogt et al., 1992; Maddock, 1999) and thus may play a role in ‘monitoring’ of the environment and in assessing the emotional significance of events (see also Raichle et al., 2001). We believe this to be a telling inference; they are suggesting that although the precuneus/posterior cingulate may indeed frequently be active at ‘rest’, an understanding of the processing such activity subserves depends on the employment of the right tasks and the delineation of the circumstances of activity changes. Comparable observations about posterior lateral cortices, and dorsal and ventral medial PFC are also made (for a similar line of reasoning see Beckmann et al., 2005). It is clear from these observations that the cognitive nature of rest is at present almost entirely a matter of speculation. More importantly, once again, the message must surely be that the resting task seems cognitively interesting, so we should unpack it by devising appropriate tasks. Indeed, various investigators have begun to do just this (e.g., Foster and Wilson, 2006; Gilbert et al., 2006).

Let us suppose for a moment that there is indeed a network of regions whose activity is coordinated in the service of some set of processes maximally engaged when volunteers are instructed to ‘just rest’. Given this, how would we discover the function or functions subserved by this network? It is our belief that, given the unconstrained nature of ‘resting’ states, and just as Gusnard and Raichle’s examples indicate, 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. This is because there is an inherent circularity to inferences made from neuroimaging studies in which the cognitive processes are undefined. If we know a/ that regions A, B and C are active at ‘rest’, and b/ that task manipulations thought to reflect processes X and Y alter the level of activity in these regions, we can (with certain assumptions about the consistency of structure–function mappings in the brain) infer c/, that during ‘rest’, processes X and Y are engaged. If on the other hand we know c/, that ‘rest’ is associated with processes X and Y (for example from behavioral studies) and observe a/, that regions A, B and C are active at ‘rest’, we can infer that these regions may play a role in these processes. We cannot, however, do both at once, and ‘rest’ is by definition a difficult state to study behaviorally. Furthermore, it is likely that any experimental manipulations that can help to elucidate the processing that takes place at ‘rest’ are going to be more productive in an imaging study than the resting task, because they constrain processing to a greater extent. In practice, therefore, the study of ‘rest’ is only informative if one already knows the functions of the regions engaged, which we do not, or if one already knows and can control the processing that takes place in the resting task, which we do not. Thus again, observations of brain responses during the resting task in fact demand the use of specific experimental manipulations.

Although we have taken a simple subtraction design as an example, we would emphasize that analogous arguments apply to other designs. For example, correlated activity between regions X and Y may be observed during a resting task, but a meaningful interpretation of this correlation must ultimately refer to some model of how it instantiates or enables information processing, and thus depends in part on knowledge about the processing demands

of the task. A correlation observed in a context that is relatively well defined in processing terms will therefore be more informative than a correlation observed during a resting task. There is ample empirical support for the notion that the coupling of activity within networks is modulated in specific ways according to task demands (e.g., Friston et al., 1997). However, if a claim is to be made that the connectivity between X and Y is consistent across different task contexts, this is an empirical question again best addressed by cognitively well-defined studies. We consider the question of the consistency of such connectivity further in the next section.

Generality of task-independent decreases

We have argued that the study of rest is not the best way of understanding the function of regions and networks apparently engaged at rest. A second, perhaps more fundamental concern, is whether the regions that show activity decreases during experimental tasks compared to the resting task are consistent across studies. As well as the four principal regions reviewed by Gusnard and Raichle (2001), such TIDs have been reported in other studies in various other regions including lateral prefrontal cortex, medial temporal cortex, and orbitofrontal cortex, among others (e.g. see Mazoyer et al., 2001).

To some extent this variation may of course be due to differences in statistical power, analysis methods and thresholding, and the magnitude of TIDs in different regions may vary. However, ‘real’ factors to do with the cognitive processes involved are likely also to play a part. In a meta-analysis of 5 studies comparing high-level tasks to resting baselines, Wicker et al. demonstrated common decreases for rest versus tasks only in medial and anterior frontal regions (Wicker et al., 2003). More critically, however, in other studies, specific tasks have elicited activity *increases* in the ‘default mode regions’ compared to rest or passive fixation conditions. To cite just a few examples, Zysset et al. demonstrated activity increases in medial PFC and in precuneus for two tasks, episodic retrieval and evaluative judgements, compared to a passive fixation baseline (Zysset et al., 2002). Knauff et al. showed increases in the precuneus in several different reasoning tasks versus rest, as did Ghaem et al. during mental navigation (Knauff et al., 2003; Ghaem et al., 1997). Given that ‘default mode’ regions can show high levels of activity during experimental tasks as well as the resting task, task differences across studies probably explain many discrepancies in regions showing ‘task-independent’ decreases, supporting Wicker et al.’s (2003) contention. Critically, however, these findings illustrate that not only is ‘rest’ difficult to define cognitively, it is also not unique as a state in which high levels of activity are found in those regions referred to as the ‘default mode network’.

Attempts have also been made to define resting state networks using connectivity analyses, and there is no doubt that inter-regional connectivity can be demonstrated reliably across subjects during resting tasks (e.g., Beckmann et al., 2005; Biswal et al., 1995; Fox et al., 2005; Fransson, *in press*; Greicius et al., 2003). Such analyses clearly go beyond regional analyses insofar as they show that regional effects within an individual are correlated, but this does not preclude the possibility of functional dissociations within the networks any more than do the regional analyses we have already considered. Between-study comparisons to address this issue are difficult at present because of the range of different methods employed, but some individual findings are worthy of consideration. Greicius et al. (2003) assessed the connectivity of the

‘default mode network’ by analyzing resting data to determine the regions whose activity was correlated with that in the two most active regions, in posterior and anterior cingulate cortices. Although activity was correlated between these two regions, their respective functionally connected networks appeared to be as different as they were similar. The methods used do not allow such differences, or similarities, to be confirmed statistically, but the findings are consistent with the possibility that, even at rest, functional connectivity patterns – just like subtractive analyses – may dissociate different elements within the set of active regions. The existence of multiple elements within resting networks is also suggested by observations that networks engaged during, for example, motor tasks can also show correlated activity during rest (Biswal et al., 1995; see Fransson, *in press* for analogous findings using a working memory task). More recent observations by Beckmann et al. (2005) are particularly striking, and like those of Greicius et al. (2003), imply that activity in the resting task does not represent some unitary ‘default mode’, but rather is likely to fractionate. An independent components analysis of resting data from 10 subjects yielded 23 independent spatiotemporal components, several of which were interpreted – on the basis, as we have already noted, of data from studies employing well-defined cognitive tasks – as representing distinct kinds of processing.

There is no doubt that the observation of ‘TIDs’ and high regional activity at ‘rest’, as well as correlated activity between regions, has served to stimulate interest in just what it is this network is engaged in. But the likelihood of functional dissociations between the behavior of different regions engaged during the resting task is another reason to conclude that the study of rest is not the most productive way to understand their functions. Rather, it is better to employ specific experimental manipulations in order to tease apart contextually dependent functional relationships between different regions and sets of regions, and to understand the factors responsible for both the variability and the consistency within these data.

The default mode as a theoretical synthesis

In considering the empirical foundations of the idea of resting state as default mode, we have argued that the three principal claims are each fundamentally flawed. The case we have presented also has implications for the theoretical synthesis of these claims, which we now summarize. Firstly, the absence of evidence that a high energy consumption is peculiar to rest means that there is no specific link between this second claim and either of the others. Secondly, to the extent that an interest in task-induced deactivations with respect to rest follows from the belief that the latter is a baseline state, we note that its choice appears entirely arbitrary with respect to neural activity and cognitive processing. The balance at rest between oxygen supply and demand has no direct relevance to the study of other tasks and processes. Thirdly, although an interest in rest as a baseline may follow from observations of consistent TIDs, this is again an arbitrary choice. Comparing, within or across studies, a task *Z* – such as rest – with alternative tasks A, B, C and D, and finding that A to D have some regional activity changes in common relative to rest, does not compel us to infer that *Z* has any special status as a baseline for tasks E, F and G. Finally, even were such analyses to demonstrate that rest differs from all alternative tasks in a consistent set of regions, studying well-defined tasks is in most circumstances the best way to pursue this finding. Before concluding, we consider the possible exceptions to these circumstances.

Possible utility of resting scans

We have argued that the resting task should not be used when there is any intention to interpret data with respect to cognitive processing. We do recognize, however, that there are circumstances under which processing considerations may be secondary and that, under these circumstances, one might be willing to accept the vagaries of the resting state in order to benefit from its ease of acquisition and from the fact that it can be sustained during the collection of long time-series. We envisage a number of situations in which this could be so: for example, methodological development work may require no inferences about the meaning of measured activity with respect to processing. Furthermore, a clinician would be very interested in an observation that has nosological, diagnostic or prognostic value even if it could not be used to provide a mechanistic understanding of the disease process. If the resting task provided a setting in which such observations could be made, it might prove very useful indeed, as we have already noted in our discussion of resting state metabolism (and see e.g., Li et al., 2002). However, in many such situations a task better constrained in cognitive terms would be preferable; it would perhaps be a rare clinician who resisted the temptation to go beyond the data and to speculate upon the cognitive meaning of group-wise regional differences at rest. Furthermore, a non-neural basis for any differences based on resting scans (or scans in any single state) cannot be ruled out, for example, age-related or drug effects on neurovascular coupling. Hence unless clinical requirements mean that such a distinction is unimportant, it is advisable in such studies to look at interactions of group (or drug) with an experimental manipulation (see Buckner et al., 2000; Honey and Bullmore, 2004).

Summary and conclusions

In summary, we do not dispute the active nature of the ‘resting’ state, nor dismiss all its potential applications, but we do challenge its claim to a special status, and also the utility of the concept of a default mode for understanding brain function. We allow that the state adopted by the human brain in the absence of any explicit goal other than to ‘rest’ may be regarded as a baseline in some habitual or evolutionary sense. We also accept that the apparent equilibrium between vascular supply and demand in the resting task justifies its status as a metabolic baseline in certain physiological contexts. However, we see no sense in which these qualities of the resting task are relevant to cognitive neuroimaging experiments. They do not impact upon subtractions or other measurements, nor do they imply that rest has any special qualities in terms of processing. There is therefore no reason to believe that the use of rest as a reference condition has any specific bearing on the interpretation of the patterns of activity associated with comparisons between other task conditions. We also find no specific link between the brain’s energy consumption and the notion of rest as a default mode. The substantial energy use of the brain at rest does not appear to us to distinguish this state from other task states whose overall energy expenditure might be measured.

In fact, we can find nothing wrong with the simple hypothesis that the high level of neural activity at rest and in other ‘low-level’ tasks in some brain regions represents a greater level of processing than that engaged in the same regions during what experimenters might suppose to be more ‘demanding’ tasks. To the extent that

this is something that cognitive neuroscience has not appreciated sufficiently so far, and to the extent that it indicates the limits of our current approach to task design and concepts of processing ‘demand’, we are in complete agreement with the proponents of the ‘default mode’ that this activity should not be ignored. However, we do doubt that this ‘intrinsic’ activity, although interesting, has any special significance. There may be some consistency in the network of regions active in the resting task, but without a theoretical synthesis that also identifies this as a qualitatively and quantitatively important baseline state, the idea of a default mode has little utility. Instead, we have argued that the physiological functions and processing the resting task subserves will be better studied by employing specific experimental manipulations. A modern systems neuroscience needs to be sophisticated in cognitive terms as well as in physiological and network terms. This requires the use of well-designed cognitive tasks if one is to understand how the brain supports cognition.

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