the brain; there are others, and how they can all be weaved into a single principle that governs how the cortex functions remains as elusive as it has always been.

[1]University College London, London, UK

*Correspondence: s.zeki@ucl.ac.uk (S. Zeki).

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Science & Society

Understanding the Brain, By Default

James M. Shine[1] and Michael Breakspear[2,3,*]

In 2001 Raichle and colleagues showed that, at rest, brain activity fluctuates near a metabolically active equilibrium: a 'default mode' of brain function. This finding broke ranks with the prevailing 'task–rest' dichotomy to position the brain as continuously active, balancing the deployment of resources according to current and anticipated needs.

The advent of noninvasive neuroimaging in the early 1980s spawned a new field of human brain mapping. The initial focus of the field sought to catalog patterns of neuronal activity uniquely associated with distinct psychological functions. However, early work also established that a set of distributed frontoparietal cortical regions was consistently engaged across a diversity of attentionally demanding tasks. These regions were hypothesized to support our proclivity to orient toward salient features of the world. Intriguingly, meta-analytic studies also revealed a distinct set of distributed regions that were 'deactivated' during these tasks [1]. A key question became whether these regions 'activate' during states that do not require attentional focus or, rather, represent an active baseline architecture of the resting brain. In 2001 a research group from Washington University in St. Louis addressed this question [2], and in doing so established the notion of a 'default mode' of brain function.

The prevailing strategy in this fledgling field was to isolate a particular cognitive function (e.g., the ability to distinguish between faces and houses) and to acquire positron emission tomography (PET) or blood oxygen level-dependent (BOLD) MRI data during numerous repetitions of pertinent trials. Statistical contrasts between trials that differed only in this condition then yielded the corresponding functionally localized regions. Philosophical issues aside [3], this approach yielded a corpus of knowledge linking particular cognitive functions to specific brain locations (e.g., face perception and the 'fusiform face area').

But therein lies the rub: the brain does not function as a singular entity, selectively engaging isolated regions, but rather as a complex system [4] that continuously integrates representations of the body and of the environment across tasks. Whereas identifying particular brain regions associated with unique functions was certainly informative, the field was left without a deeper understanding of the 'glue' that holds all of these distinct functions together across states and tasks. Raichle and colleagues had the insight to estimate energy utilization in the brain during the 'resting state' to establish what occurs in 'task-negative' regions of the brain in the absence of an explicit, exogenous task. Hence, rather than applying the traditional logic of the field (i.e., task-based contrasts), Raichle and colleagues measured metabolic activity in regions of the brain during the (eyes closed) 'resting' state [2]. Would task-negative regions be activated when not under active task constraints, (i.e., have higher than baseline metabolic load) or would they simply return to a baseline (or equilibrium) state, similar to task-positive regions?

To examine these questions, the authors used a quantitative measure of neural activity calculated from O^{15}-labeled PET data: the oxygen extraction fraction (OEF). The OEF for each region can be calculated from O^{15}-labeled PET data by comparing the amount of oxygen delivered with the amount of oxygen utilized [5]. Similar to the BOLD signal, the OEF is sensitive to one of the unique characteristics of cerebral autoregulation, in which there is typically higher perfusion in a region than is required. In other words, the brain 'waters the garden to appease a thirsty flower'. This effect

causes an increase in the proportion of oxygenated hemoglobin in the blood (hence, an increase in the BOLD signal) and a decrease in the proportion of oxygen utilized by the neural tissue (hence, a decrease in the OEF). OEF is hence sensitive to transient changes in local perfusion. A companion measure also derived from O^{15}-labeled PET data, cerebral blood flow (CBF), reflects local gross metabolic load.

Strikingly, Raichle and colleagues [2] showed that regional OEF during the resting state was homogeneous across the brain (Figure 1, top row). That is, most regions were at their intrinsic equilibrium. Specific interrogation of the cortical regions that exhibited reductions in activity during the performance of cognitive tasks (midline areas in the posterior cingulate and precuneus and in the medial prefrontal cortex) again showed no evidence of an OEF that was distinct from the rest of the brain. That is, these regions (along with the rest of the gray matter) were not activated by resting state but were effectively at their metabolic equilibrium.

In contrast to regional OEF, there was substantial regional variability in patterns of CBF across the brain (Figure 1, bottom row). Crucially, resting-state PET acquisition revealed a particular signature of regional blood flow, with relatively high perfusion in the midline frontal and parietal cortex along with the insula and lateral cerebellum (Figure 1). So, although these regions were at their equilibrium, they were nonetheless drawing a larger amount of baseline blood flow. Importantly, these patterns included the set of regions that had been shown to consistently deactivate during the suite of goal-directed cognitive tasks [1]. The combined results of the study (OEF + CBF) thus showed that, while all regions in the brain were essentially at their intrinsic equilibrium, that set point was spatially inhomogeneous, with a set of regions furnished with sufficiently rich blood supply to facilitate higher metabolic turnover even when at equilibrium. Although the activity of these regions was transiently lower during attentionally demanding cognitive tasks, they were nonetheless metabolically active during rest: not activated, but rather at equilibrium: 'We posit that areas decreasing their activity in this manner may be tonically active in the baseline state, as distinguished from areas that are transiently activated in support of varying goal-directed activities'.

The authors had thus found evidence for what they coined as a default mode of brain function: an energetic 'baseline level of local neuronal activity' to which all brain regions return when not engaged in an attentionally demanding external task. This pattern established an 'equilibrium . . . between the local metabolic requirements necessary to sustain a long-term modal level of neural activity and the level of blood flow in a particular region' that presumably affords equal attention to interoceptive and broader exteroceptive context, thus simultaneously refining models and priming to new stimuli. Importantly, this concept aligned elegantly with concepts espoused by William James, suggesting an intriguingly link between brain imaging and psychological theory.

Here was evidence of a system of regions that is metabolically active while we are at rest, with eyes closed, and alone with our thoughts. Somewhat more speculatively: could this pattern somehow reflect the neural correlates of the perception of 'self'? Or was it simply a physiological signature of the brain processes characterizing the 'untethered mind'? The possibilities seemed almost endless and in many ways have been the driving force behind the explosion of resting-state fMRI studies, which now occupy a substantial portion of current functional neuroimaging activity.

The authors of the 2001 paper favored a somewhat differed picture. In their interpretation the authors drew on the function of these regions inferred from

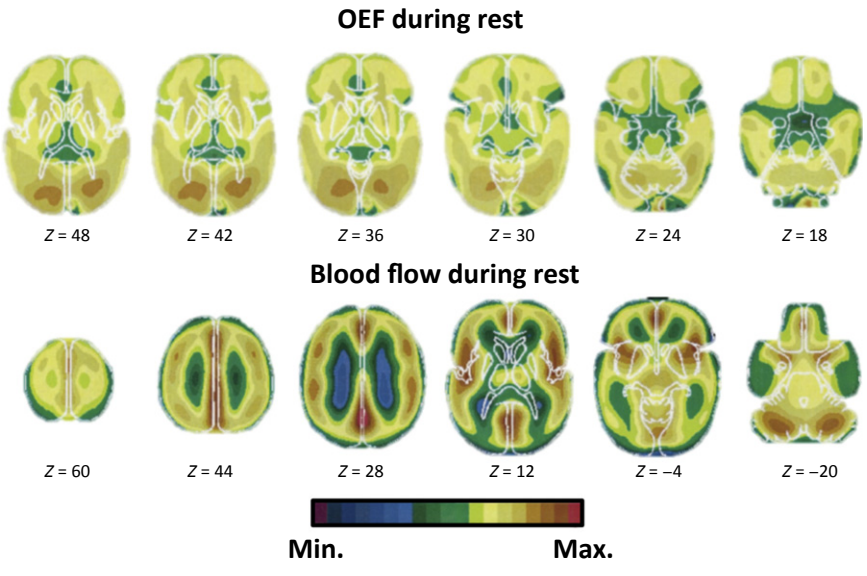

Figure 1. The Default Mode of the Resting Brain. Top: Oxygen extraction fraction (OEF) during rest. Note the relatively homogeneous pattern across the brain (with an increase in the bilateral occipital cortex, consistent with less visual cortex activity in the 'eyes-closed' acquisition). Bottom: Blood flow during rest. Note the higher signal intensity in the midline frontal and parietal regions, along with the insula and cerebellum. Adapted, with permission, from [2].

electrophysiological recordings as well as their involvement in stroke, psychosis, and dementia. Raichle and colleagues suggested that these regions act in a role more consistent with a 'sentinel' function, where information 'broadly arising in the external and internal milieu is gathered and evaluated'. Thereby, the signals for items of interest and/or danger are assessed [2]. Thus, the posterior cingulate cortex and adjacent precuneus can be posited as a 'tonically active region of the brain that may continuously gather information about the world around, and within, us', pausing when attention is drawn to a particularly salient stimulus.

With the notion of a default mode now established, the constellation of areas deactivated across tasks but at equilibrium at rest became known as the 'default-mode network'. A few years later, members from the same team showed that the resting fMRI time series from the same regions were anticorrelated with respect to regions typically associated with externally focused attention (i.e., the dorsal attention network) [6], providing tentative evidence for a functional dissociation similar to the one described in their original manuscript. However, a more nuanced view of the 'default' regions has subsequently emerged: many of the default-mode regions are in fact recruited during task execution, providing the tasks mandate specific processes, including future prospection, autobiographical reasoning, or episodic recall [7]. Notably, these observations remain consistent with the original default-mode proposal, given the salience of these processes to sentinel functioning.

The identification of the default mode overlapped historically with broader developments that repositioned the brain as a complex, dynamical system. Placing the default-mode network within this context has been the subject of intense research. For instance, graph-theoretical analyses of resting-state functional connectivity reveal that the default-mode network is enriched with high-degree structural and functional hub regions [8], suggesting that default-mode regions may act as information-processing way stations for a distributed network of cortical regions. Other studies have shown that, in contrast to primary processing regions that 'refresh' on the order of milliseconds, the regions of the default network exhibit a relatively long information-processing timescale, tracking information on the order of seconds [9]. Computational modeling research aligns well with these results and has led to the suggestion that default regions may provide a stabilizing effect over information processing at relatively fast timescales [10], forming the basis of a hierarchical temporal system that can coordinate activity over multiple timescales. How these fluctuations coincide with fast cortical activity – including 'up' and 'down' states that occur on the order of milliseconds – is a fascinating question for future research.

All major scientific paradigms that are initially heralded with glory invariably attract caveats and controversies. Critics of the default mode argue that its core simplicity is also its Achilles' heel; namely, that the unconstrained nature of resting-state acquisitions limits firm cognitive interpretation and that inferences drawn from functional studies of the default-mode regions in task-related fMRI are vulnerable to reverse inference when applied to resting-state acquisitions (e.g., [11]). In (partial) response to this critique, considerable research has documented the importance of spontaneous (pre-task) brain states on task performance [12]. The field of resting-state fMRI is also beset with technical challenges and controversies [13], including around issues such as the impact of global signal regression, head motion, and physiological confounds. Interestingly, the original paper – by deriving its outcomes of interest from quantitative O^{15}-labeled PET – was able to eschew many of these problems (although comparable controversies did arise regarding the initial use of O^{15}-labeled PET as a measure of neuronal activity [5]). Finally, the notion of resting-state cortical activity as being in equilibrium has been challenged by recent work on the non-stationary nature of resting-state cortical activity [14], with empirical and computational analyses highlighting instead a dynamic landscape that includes metastability, multistability, and criticality in its portfolio [15]. However, the slow timescale of PET would effectively average out such dynamics: this slow metabolic equilibrium is consistent with the time invariant 'ergodic' measures of such fast dynamics.

By any metric, the 2001 manuscript by Raichle and colleagues [2] has been overwhelmingly influential and important. Seventeen years later, the paper still harnesses an impressive volume of citations, directing clinical applications and computational assays. The ideas in the paper reinvigorated discussions on a 'Jamesian' view of the brain, defined new fields, and formed the basis of important questions that still resonate with scientists almost two decades after its publication. As a new generation of researchers grapples with and dissects the default mode of the brain, a close look suggests that it is well worth revisiting the quantification, nuances, and speculations of the original paper.

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[1]The University of Sydney, Sydney, NSW, Australia
[2]QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia
[3]Metro North Mental Health Service, Brisbane, QLD, Australia

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*Correspondence:
michael.breakspear@qimrberghofer.edu.au
(M. Breakspear).

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Science & Society

All in the Family: Repeats and ALS/FTD

Amrutha Pattamatta,[1,2] John D. Cleary,[1,2] and Laura P.W. Ranum[1,2,3,4,*]

In 2011, an intronic (G_4C_2)•(G_2C_4) expansion was shown to cause the most common forms of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). This discovery linked ALS with a clinically distinct form of dementia and a larger group of microsatellite repeat diseases, and catalyzed basic and translational research.

Discoveries of novel human disease genes generate scientific interest because they open doors into understanding the causes and mechanisms of disease. It is rare, however, for a gene discovery to captivate scientists the way that the 2011 discovery of the *C9orf72* expansion mutation did. In back-to-back papers published in *Neuron*, two independent groups led by Rademakers and Traynor reported the discovery of an intronic GGGGCC (or G_4C_2) expansion mutation as the most common genetic cause of both ALS and FTD. This discovery captured the attention of scientists all over the world because it identified a common molecular cause for two clinically distinct diseases – ALS and FTD – and because it connected ALS and dementia to a large group of previously described microsatellite repeat expansion disorders.

Historically, ALS and FTD were thought to be distinct disorders. ALS is a fatal neuromuscular disorder that leads to the degeneration of upper and lower motor neurons, resulting in paralysis and eventually death. In contrast, FTD is a neurodegenerative disease affecting primarily the frontal and anterior temporal lobes, which is characterized by behavioral changes, apathy, and dementia during the later stages of diseases. A series of separate gene mutations identified in the 1990s and 2000s as causing ALS (e.g., superoxide dismutase, *SOD1*) or FTD (e.g., progranulin, *GRN*) were consistent with the distinct clinical features of these disorders [1,2]. Although ALS and FTD are clinically distinct, the high frequency of their comorbidity in some families suggested a common underlying genetic mutation(s), at least in some cases. The search for the underlying gene mutation was narrowed in 2006 with the discovery of a genetic locus for familial ALS/FTD on chromosome 9p21 [3]. Eventually, in 2011, two groups independently used deep sequencing of large numbers of independent families to discover a hexanucleotide expansion in the first intron of *C9orf72* gene as the leading cause of familial ALS and FTD [4,5]. This surprising discovery created a rich scientific delta by bringing together scientists from the three separate fields of dementia, ALS, and microsatellite expansion disorders.

Two decades before the discovery of the *C9orf72* expansion mutation, the microsatellite expansion field was born with the demonstration that CGG and CAG expansion mutations cause fragile X syndrome and spinal bulbar muscular atrophy (SBMA), respectively [6]. These discoveries, and the demonstration that expansion mutations can change in length when transmitted from one generation to the next, provided a molecular explanation for 'anticipation', namely the earlier onset and more severe disease in consecutive generations that are observed in many of these disorders. These discoveries also led to an intense hunt for expansion mutations in other neurologic diseases such as Huntington's disease, myotonic dystrophy, and multiple spinocerebellar ataxias. There are now more than 40 known diseases caused by the expansion of repeats present in the 5′ untranslated regions (5′-UTRs), exons, introns or 3′-UTRs of their respective genes. Typically, the molecular mechanisms of these diseases have been classified as protein loss of function, RNA gain of function, or protein gain of function.

Early in 2006, linkage analysis in a large Dutch family with autosomal dominant inheritance of both ALS and FTD