Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging

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Abstract | The majority of functional neuroscience studies have focused on the brain's response to a task or stimulus. However, the brain is very active even in the absence of explicit input or output. In this Article we review recent studies examining spontaneous fluctuations in the blood oxygen level dependent (BOLD) signal of functional magnetic resonance imaging as a potentially important and revealing manifestation of spontaneous neuronal activity. Although several challenges remain, these studies have provided insight into the intrinsic functional architecture of the brain, variability in behaviour and potential physiological correlates of neurological and psychiatric disease.

Blood oxygen level dependent signal
(BOLD). Signal used by fMRI as a non-invasive but indirect measure of changes in neuronal activity.

Noise
Modulation in a measured signal that is unrelated to the effect of interest. Noise is usually minimized through averaging, allowing the effect of interest to be emphasized.

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Much of what is currently known about brain function comes from studies in which a task or stimulus is administered and the resulting changes in neuronal activity and behaviour are measured. From the electrophysiology work of Hubel and Wiesel[1] to cognitive activation paradigms in human neuroimaging[2], this approach to study brain function has been very successful. A simple example of this approach is a paradigm that requires subjects to open and close their eyes at fixed intervals (FIG. 1). Modulation of the functional magnetic resonance imaging (fMRI) blood oxygen level dependent (BOLD) signal attributable to the experimental paradigm can be observed in distinct brain regions, such as the visual cortex, allowing one to relate brain topography to function. However, spontaneous modulation of the BOLD signal which cannot be attributed to the experimental paradigm or any other explicit input or output is also present. Because it has been viewed as 'noise' in task-response studies, this spontaneous component of the BOLD signal is usually minimized through averaging. This Review takes spontaneous brain activity as its focus. Although spontaneous activity has been studied both in animals and humans across many spatial and temporal scales[3,4], this Review focuses specifically on slow (<0.1 Hz) fluctuations in the BOLD signal.

Why should one be interested in the noise in the BOLD signal? There is both a theoretical and an empirical motivation. The theoretical motivation for studying spontaneous activity stems from an understanding of brain energy metabolism. The resting human brain represents only 2% of total body mass but consumes 20% of the body's energy, most of which is used to support ongoing neuronal signalling[5–9]. Task-related increases in neuronal metabolism are usually small (<5%) when compared with this large resting energy consumption[9]. Therefore, most of our knowledge about brain function comes from studying a minor component of total brain activity. If we hope to understand how the brain operates, we must take into account the component that consumes most of the brain's energy: spontaneous neuronal activity. The empirical motivation for studying spontaneous BOLD activity arose from the observation that spontaneous BOLD fluctuations measured in the left somatomotor cortex are specifically correlated with spontaneous fluctuations in the right somatomotor cortex and with medial motor areas in the absence of overt motor behaviour[21]. This finding has since been replicated by several groups[10–15] (FIG. 2).The observation that spontaneous BOLD activity is not random noise, but is specifically organized in the resting human brain has generated a new avenue of neuroimaging research. These studies have provided insight into the functional topography of the brain, aided the evaluation of neuroanatomical models, accounted for variability in evoked responses and human behaviour, and raised many interesting questions and challenges for future work.

We begin this Review with a description of the current methods used to study spontaneous BOLD activity and the spatial and temporal properties of spontaneous BOLD fluctuations. We then examine the interaction of

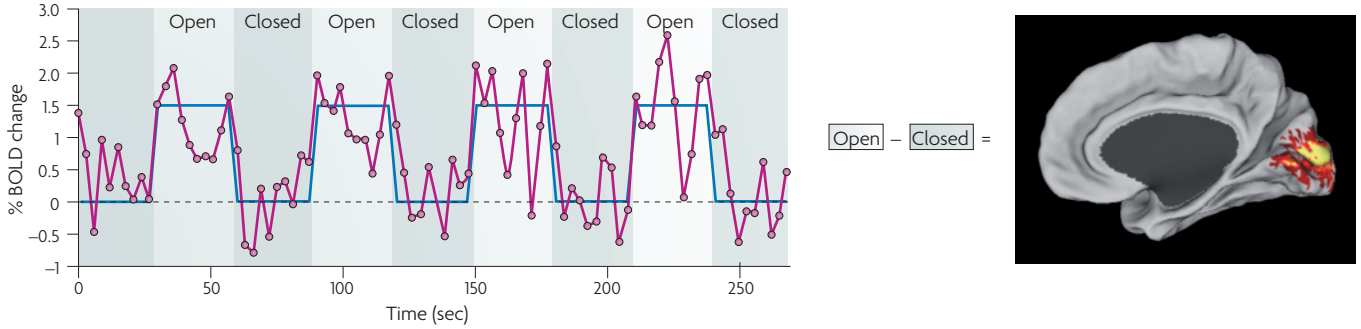

Figure 1 | **Traditional fMRI analysis and BOLD noise.** Unaveraged blood oxygen level dependent (BOLD) time course (magenta) from a region in the primary visual cortex during a simple task paradigm that requires subjects to open and close their eyes. The paradigm is shown in blue (delayed to account for the haemodynamic response). Traditional functional magnetic resonance imaging (fMRI) analysis involves correlating BOLD data with a stimulation time-course across multiple blocks. This in effect averages across each condition and performs a subtraction, minimizing 'noise' in the BOLD signal and highlighting regions that are modulated by the task paradigm. In this case, subtraction of the eyes-closed condition from the eyes-open condition identifies a BOLD signal intensity difference in the primary visual cortex (shown on the right).

spontaneous activity with task conditions and address several important questions regarding how spontaneous BOLD activity should be interpreted. We briefly discuss what is known about the physiology of spontaneous BOLD activity and conclude with a discussion of areas for future advancement in the field.

Methods for analysing spontaneous BOLD data

Spontaneous neuronal activity refers to activity that is not attributable to specific inputs or outputs; it represents neuronal activity that is intrinsically generated by the brain. As such, fMRI studies of spontaneous activity attempt to minimize changes in sensory input and refrain from requiring subjects to make responses or perform specific cognitive tasks. Most studies are conducted during continuous resting-state conditions such as fixation on a cross-hair or eyes-closed rest. Subjects are usually instructed simply to lie still in the scanner and refrain from falling asleep. After data acquisition, two important data analysis issues must be considered: how to account for non-neuronal noise and how to identify spatial patterns of spontaneous activity.

Accounting for non-neuronal noise. An important difference between studies of spontaneous activity and more traditional studies of task-evoked responses is that the latter usually involve averaging across many trials. This averaging eliminates noise and increases confidence that the effect being studied is not an artefact. In studies of spontaneous activity, the signal being analysed and interpreted is the noise that task-evoked studies seek to remove by averaging. A natural concern, therefore, is that spontaneous activity results are contaminated by or even due to an artefact, such as scanner instability or non-neuronal physiological fluctuations. Consistent with this concern, spontaneous BOLD fluctuations have been observed in a water phantom[16] and physiological fluctuations, such as cardiac or respiratory activity, account for a significant fraction of spontaneous BOLD variance in human data[17–20]. Fortunately, a large amount of work has gone into addressing this concern.

One strategy to account for non-neuronal noise is to use a high sampling rate, which prevents aliasing of higher frequency cardiac or respiratory activity[11,12,21,22]; however, this comes with the limitation of reduced spatial coverage. Alternatively, physiological parameters can be measured during BOLD acquisition and removed from the data through linear regression[18–20,23,24]. Finally, noise sources can be isolated from the BOLD data itself through techniques such as independent components analysis (ICA, see below)[25–27], regressing out signals that are common to all voxels (the global signal)[16,28,29] or signals from regions that are likely to have a relatively high degree of physiological artefact relative to the amount of neuronal activity, such as the ventricles or white matter[24,29].

In a sense, these strategies take the place of the averaging in task-evoked studies and attempt to ensure that spontaneous BOLD analyses are not simply interpretations of non-neuronal noise. Thoughtful implementation allows the neurobiologically meaningful information in spontaneous BOLD data to be emphasized.

Identifying spatial patterns. Techniques for identifying spatial patterns of coherent BOLD activity, an analysis often referred to as functional connectivity (BOX 1), are also required. The simplest technique is to extract the BOLD time course from a region of interest (called a seed region) and determine the temporal correlation between this extracted signal and the time course from all other brain voxels (FIG. 2). This approach is widely used owing to its inherent simplicity, sensitivity and ease of interpretation[10–14,24,29–36]. However, it has some disadvantages. The results are dependent on the *a priori* definition of a seed region, multiple systems cannot be studied simultaneously and the extracted waveform may not be a true independent variable when assessing statistical significance. In response to these limitations other more sophisticated techniques for analysing spontaneous BOLD data have been proposed.

Hierarchical clustering still requires *a priori* definition of seed regions[37–40]. However, instead of extracting the time course from just one seed region, the time

Water phantom
Glass sphere containing water that is used to study fMRI signal properties in a non-biological system.

Linear regression
Computation of a scaling factor such that multiplication of a regressor time course by this scaling factor will remove the greatest amount of variance when subtracted from a signal of interest.

Voxel
A volume element that is the smallest distinguishable, box-shaped part of a three-dimensional space.

courses from many seed regions are obtained and a correlation matrix is constructed. A clustering algorithm is then used to determine which regions are most closely related and which regions are more distantly related. This information enables the creation of a hierarchical tree or topological map, which is useful for visualizing the relationships between large numbers of regions.

ICA is perhaps the second most popular technique for analysing spontaneous BOLD data[22,26,27,41–43]. This approach does not require *a priori* definition of seed regions. Instead, sophisticated algorithms analyse the entire BOLD data set and decompose it into components that are maximally independent in a statistical sense. Each component is associated with a spatial map. Some maps reflect noise components whereas others reflect neuro-anatomical systems. Because this technique is data driven and automatically isolates sources of noise, it holds tremendous promise and its use is increasing. However, there are still several challenges. First, results are highly dependent on the number of components one asks the algorithm to produce. Second, the user must determine which components reflect noise and which components look like neuro-anatomical systems, introducing *a priori* criteria for system selection. Finally, the sophistication of the algorithm introduces interpretive complexities; for example, if the magnitude of a spatial component is reduced in Alzheimer's disease[44] does this relate to a reduction in temporal coherence, a reduction in fluctuation magnitude or a change in the relationship between components?

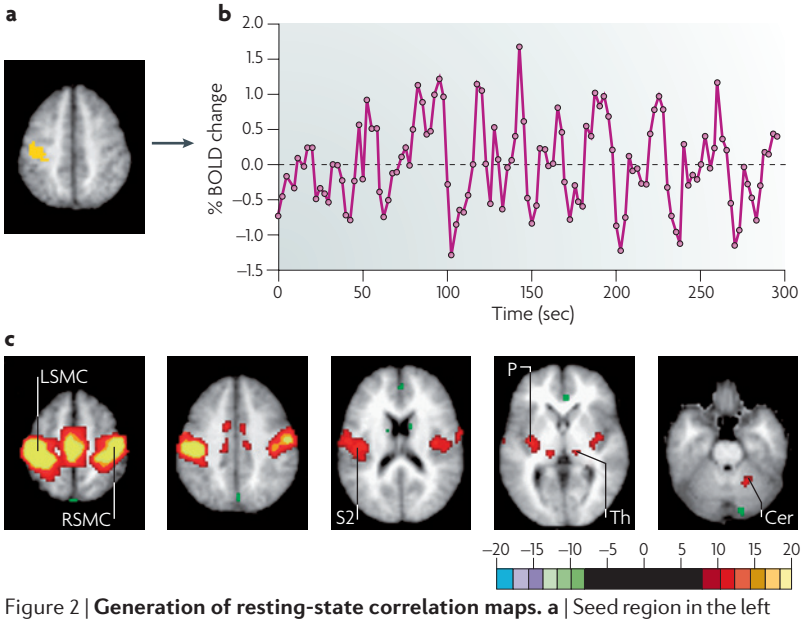

Figure 2 | **Generation of resting-state correlation maps. a** | Seed region in the left somatomotor cortex (LSMC) is shown in yellow. **b** | Time course of spontaneous blood oxygen level dependent (BOLD) activity recorded during resting fixation and extracted from the seed region. **c** | Statistical z-score map showing voxels that are significantly correlated with the extracted time course. Their significance was assessed using a random effects analysis across a population of ten subjects. In addition to correlations with the right somatomotor cortex (RSMC) and medial motor areas, correlations are observed with the secondary somatosensory association cortex (S2), the posterior nuclei of the thalamus (Th), putamen (P) and cerebellum (Cer).

In summary, there are several approaches for dealing with non-neuronal noise in spontaneous BOLD data and several techniques for identifying patterns of coherent activity[41,44–46]. We have restricted our Review to the three most common techniques for identifying spatial patterns, although many others have been proposed[47–49]. Future advances will undoubtedly come from further technique development and combining multiple techniques within the same study[50]. Although different techniques each have strengths and weaknesses, they converge on a similar finding: neuro-anatomical systems in the human brain can be identified on the basis of correlation patterns in spontaneous BOLD activity.

Properties of spontaneous BOLD activity

Spatial topography and coherence. The observation that the somatomotor system is coherent in its spontaneous activity has been replicated many times[10–15,21] (FIG. 2). By placing seed regions in additional brain areas, many other neuro-anatomical systems have been shown to be coherent in their spontaneous activity, including visual[10,11], auditory[10], task-negative/default mode[29–32], hippocampus or episodic memory[24,33], language[10,34], dorsal attention[32,35] and ventral attention systems[35]. Many of these systems have also been identified using hierarchical clustering[37,38] and ICA[22,26,27,41–43]. A consistent finding is that regions with similar functionality — that is, regions that are similarly modulated by various task paradigms — tend to be correlated in their spontaneous BOLD activity.

Interestingly, regions with apparently opposing functionality have been found to be negatively correlated or anticorrelated in their spontaneous activity[29–31] (FIG. 3). Specifically, regions routinely exhibiting activity increases in response to attention demanding cognitive tasks[51] are anticorrelated with a set of regions routinely exhibiting activity decreases[52]. Although further work is needed to understand the role of global normalization in these anticorrelations, this finding suggests that complex inter-system relationships revealed by task paradigms are reflected in patterns of ongoing spontaneous activity.

Given that correlation patterns of spontaneous activity reflect functional topography, these patterns could be used to predict the task-response properties of brain regions. For example, the degree to which a subject's left somatomotor cortex resting-state correlation map is lateralized to the left hemisphere predicts how lateralized that subject's activation map will be in response to right-hand finger tapping[15]. The finding that a region is correlated with the hippocampus during the resting state is predictive of that region's response to episodic memory tasks[33]. Interestingly, most memory tasks implicate only a subset of regions[53,54], whereas the hippocampal formation resting-state correlation map reveals the full distribution of memory-related regions assessed across multiple experiments[33]. Patterns of spontaneous activity could thus serve as a functional localizer, providing *a priori* hypotheses about the way in which the brain will respond across a wide variety of task conditions.

In addition to predicting how brain regions will respond to a task, spatial patterns of spontaneous activity may also predict an individual's task performance or

Power spectral density function
The distribution of power at each frequency in a time-varying signal, generally displayed with power on the y-axis and frequency along the x-axis.

Electroencephalography
(EEG). A technique used to measure neural activity by monitoring electrical signals from the brain that reach the scalp. EEG has good temporal resolution but relatively poor spatial resolution.

Magnetoencephalography
(MEG). A non-invasive technique that allows the detection of the changing magnetic fields that are associated with brain activity on a timescale of milliseconds.

Local field potential
Electrical fields recorded from microelectrodes in the brain that are thought to reflect the weighted average of input signals on the dendrites and cell bodies of neurons in the vicinity of the electrode.

Hypercapnia
Situation occurring when the amount of dissolved carbon dioxide in blood rises above its physiological mean of about 40 Torr.

behaviour. Specifically, individual differences in the spatial topography of spontaneous activity have been shown to correspond to individual differences in pre-scan anxiety[50] and performance on working memory tasks[50,55]. The idea that an individual's spontaneous brain activity may predict that person's aptitude for different tasks, intelligence or personality promises to be a major focus for future research.

Finally, correlation patterns of spontaneous activity can be used to further our understanding of neuro-anatomical models developed on the basis of task-activation studies[35,40]. For example, a model of attention consisting of two interacting neuro-anatomical systems, a dorsal and ventral attention system, has been proposed[51]. Although this model was consistent with a number of task-related imaging results, it was unclear if task-related manipulations of attention were necessary to distinguish the two systems or which regions might mediate the interaction between them. Recent work has distinguished these two attention systems on the basis of resting-state correlation patterns and identified potential regions of interaction in the frontal lobe[35]. Furthermore, disruption of this intrinsic organization corresponds to attentional deficits following stroke and normalizes with functional recovery[56]. Given the large number of neuro-anatomical models that have been developed or studied using task-activation paradigms, it is likely that many models could benefit from the examination of correlation patterns in spontaneous activity.

In summary, much is now known about the topography and coherence of spontaneous BOLD fluctuations. The correlation structure of spontaneous activity can provide insight into the fundamental functional architecture of the human brain.

Box 1 | **Functional connectivity**

A term that appears frequently in the literature when discussing correlations in spontaneous blood oxygen level dependent (BOLD) fluctuations is 'functional connectivity' which may refer to any study examining inter-regional correlations in neuronal variability[146,147]. This applies to both resting-state and task-state studies, and can refer to correlations across subjects, runs, blocks, trials or individual BOLD time points, an ambiguity that can become confusing[48,147]. This Review is focused specifically on functional connectivity assessed across individual BOLD time points during resting conditions, however there is an extensive body of work involving other types of functional connectivity, which has produced many interesting results. For example, studies have related inter-regional correlations during task performance to behaviour[148,149], genetics[150] and even personality[150].

An important question is whether the various types of task-state functional connectivity and resting-state functional connectivity measure the same or different phenomena. As spontaneous activity continues during task conditions, a correlation during task performance probably represents some combination of underlying spontaneous activity and traditional task-related responses related to stimulus input, behavioural output or attention. One way to address this question is to determine if the effects observed in studies of task-state functional connectivity are also present in patterns of spontaneous activity. For example, it has been shown that the correlation between language areas in the brain during a language task relates to reading ability[149]. The correlation between these same areas during rest showed some relation to reading ability, but it was not significant. Further studies of this sort are needed to better understand the relationship between the extensive literature on functional connectivity and correlations in spontaneous BOLD activity during the resting state.

Temporal properties. It is clear that the spatial properties of spontaneous BOLD activity distinguish it from random noise but, interestingly, so do the temporal properties. Specifically, random noise (also called white noise) can be characterized by a flat power spectral density function, meaning that all frequencies are present to an equal degree. By contrast, spontaneous BOLD follows a 1/f distribution, meaning that there is increasing power at lower frequencies[16,57]. These lower frequencies are represented in a specific fashion such that the slope of the power spectral density function will be close to –1 when plotted on a log-log plot. This 1/f distribution has also been observed in studies of spontaneous electroencephalography (EEG)[58,59], magnetoencephalography (MEG)[58], local field potential recordings[60] and human behavioural variability[61–63].

An important question is which frequencies in this 1/f distribution are responsible for the spatially specific correlation patterns seen in spontaneous BOLD. A study focused on this question showed that only frequencies below 0.1 Hz contribute to regionally specific BOLD correlations, with faster frequencies relating to cardiac or respiratory factors[12]. Based on this finding, the majority of spontaneous BOLD studies low-pass filter data at a cut-off of 0.08 or 0.1 Hz. An interesting question that has not been systematically investigated is whether there is a lower limit to the frequencies contributing to spatially specific correlations. It is also not known if BOLD continues to exhibit a 1/f frequency distribution in the lower frequency range. Paradigms with longer acquisitions are needed to answer these questions.

Beyond the frequency distribution, other types of temporal information may prove interesting. For example, temporal lags between spontaneous BOLD fluctuations in different regions forming a coherent spatial pattern may inform us about causality or the direction of influence[64]. Similarly, it would be interesting to know if and how spontaneous BOLD correlations change over time. Do spontaneous BOLD fluctuations synchronize and desynchronize throughout the resting state similar to the transient synchrony often observed in animal work[4] or are they temporally consistent?

Magnitude of spontaneous BOLD fluctuations. Spontaneous fluctuations in the BOLD signal can be of equal magnitude to brain responses observed in response to tasks or stimuli[14,65]. Currently, it is unclear how the magnitude of spontaneous BOLD fluctuations should be interpreted, however, this question is beginning to be addressed. The magnitude and coherence of spontaneous BOLD fluctuations are globally decreased with hypercapnia[66] and in subjects under the influence of cocaine[67], isoflurane[36] or sevoflurane anaesthesia[68], but globally increased with midazolam-induced sedation[69]. The magnitude of spontaneous BOLD fluctuations increases in the visual cortex when resting with eyes open compared with resting with eyes closed[70] and decreases in the default system during performance of a working memory task compared with rest[73]. The relationship between the magnitude of spontaneous BOLD fluctuations and regional metabolic parameters, such as glucose or oxygen consumption, is a promising avenue for future work.

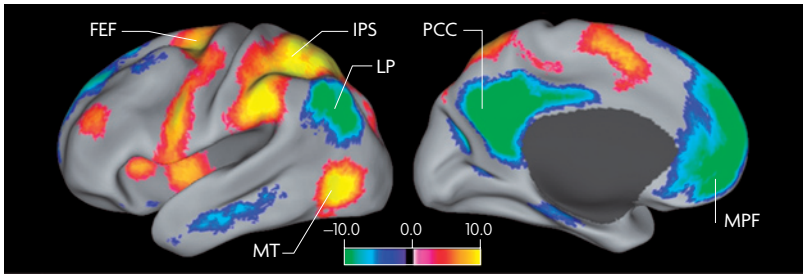

Figure 3 | **Intrinsically defined anticorrelated networks in the human brain.** Positive nodes, shown in warm colours, are significantly correlated with seed regions involved in focused attention and working memory (task-positive seeds) and significantly anticorrelated with seed regions that are routinely de-activated during attention-demanding cognitive tasks (task-negative seeds). Negative nodes, shown in cool colours, are significantly correlated with task-negative seeds and significantly anticorrelated with task-positive seeds. The task-positive seeds are the intra-parietal sulcus (IPS), frontal eye field (FEF) and middle temporal (MT) area . The task-negative seeds are the posterior cingulate/precuneus (PCC), lateral parietal cortex (LP) and medial prefrontal cortex (MPF). Modified, with permission, from REF. 29 © (2005) National Academy of Sciences.

Spontaneous activity during task conditions

The influence of spontaneous activity on task-related responses and behaviour. Up to this point, we have discussed spontaneous BOLD activity primarily during resting-state conditions. However, spontaneous activity continues during task performance, showing a similar neuro-anatomical distribution to that observed at rest[14,71-73]. What is the effect of this continuing spontaneous activity on task-related neuronal responses and behaviour? Using voltage-sensitive dye imaging in anaesthetized cats, it was shown that the spontaneous state of the system at the time of stimulus presentation determines the neuronal response to the stimulus[74,75]. Recently, a similar finding has been reported in awake behaving humans, showing that coherent spontaneous activity accounts for variability in event-related BOLD responses[14] (FIG. 4). Specifically, it was shown that ongoing spontaneous activity, as measured in the right somatomotor cortex, can account for variability in left somatomotor cortex BOLD responses following right-handed button presses. These studies suggest that measured neuronal responses represent an approximately linear superposition of task-evoked neuronal activity and ongoing spontaneous activity. Furthermore, it may be possible to dramatically improve the signal-to-noise ratio in event-related BOLD studies by correcting for underlying spontaneous activity[14].

These results are of particular interest when one considers the large number of studies showing that variability in measured BOLD responses correlates with variability in human behaviour[76-82]. If spontaneous activity accounts for much of the variability in BOLD responses and variability in BOLD responses is correlated with behaviour, then we are left with the possibility that the coherent spontaneous activity observed during the resting state contributes to inter-trial variability in human behaviour. This hypothesis is made more salient by the observation that many types of behavioural variability follow a 1/f frequency distribution similar to that of spontaneous BOLD[61–63].

We recently tested this hypothesis and found that spontaneous fluctuations within the human somatomotor system are correlated with trial-to-trial variability in the force of a button press[57]. When the spontaneous activity in the somatomotor system is low, subjects press the button a bit harder than when the spontaneous activity is high. The finding that spontaneous BOLD fluctuations account for inter-trial variability in behaviour within subjects complements the previously cited studies of inter-subject variability[50,55,56]. Together, these results highlight the functional importance of spontaneous BOLD activity by showing a direct correspondence with variability in human behaviour.

The influence of task conditions on spontaneous activity. Although it appears that the basic correlation structure of spontaneous activity continues during task performance some changes may occur. The idea that neuronal networks re-organize in the context of different task conditions has a strong precedent[83] and animal studies have shown changes in neuronal synchrony depending on the context of the task[4,84]. Many groups have compared patterns of correlated BOLD activity during rest with those obtained during task performance or stimulus presentation[34,65,72,73,85-90]. The general consensus of these studies is that the correlation between two regions that are similarly activated by the task or stimulus increases during task conditions, whereas the correlation between other regions is decreased.

There are two potential explanations for the changes in regional correlations observed during task performance. First, there may be a true re-organization involving facilitation and depression of synapses[83], leading to changes in the correlation structure of spontaneous activity. A second possibility is that the correlation structure of spontaneous activity remains constant between task and rest, and that the observed changes in correlations are due to a simple superposition of spontaneous and task-evoked activity[14]. A study in the somatomotor system supports this second possibility, showing that, after correction for evoked activity, the correlation in the underlying spontaneous activity remains the same[72]. The degree to which the correlation structure of spontaneous activity changes under task conditions remains an important but unanswered question and may require improved techniques for distinguishing concurrent spontaneous and task-related activity.

The studies discussed above have focused on changes in the correlation structure of spontaneous activity during task performance, but other studies have compared correlations before and after task performance[91,92]. One study found reduced cross-hemisphere motor correlations after muscle fatigue[92], whereas another study found no consistent group differences after performance of a cognitive task[91]. Similarly, the correlation structure of brief resting periods interspersed with task performance has also been studied and found to be similar to results obtained with continuous resting data[93]. These experimental approaches are important as observed changes in correlations are not complicated by concurrent task-evoked activity. Additional studies in this area

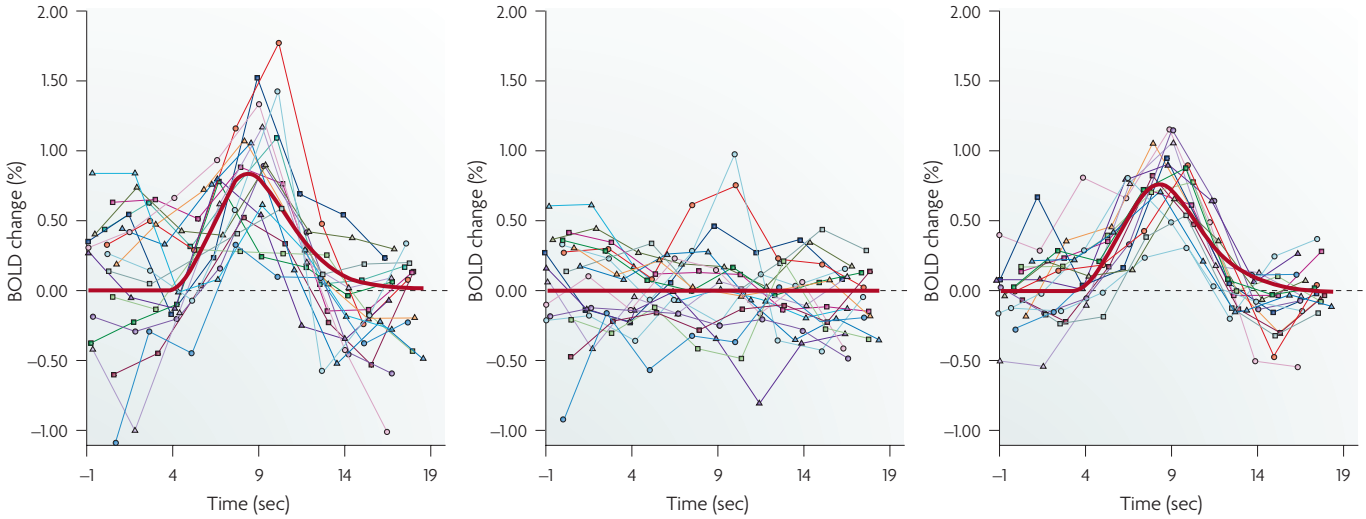

Figure 4 | **Coherent spontaneous fluctuations account for variability in event-related BOLD responses. a** | Raw left somatomotor cortex event-related blood oxygen level dependent (BOLD) responses for 18 right-handed button presses from a single subject. **b** | The corresponding activity in the right somatomotor cortex during each button press can be used as an approximation of the ongoing spontaneous activity in the left somatomotor cortex. **c** | Left somatomotor cortex responses after subtraction of spontaneous fluctuations measured in the right somatomotor cortex show a decrease in variance and an increase in signal-to-noise ratio. The thick orange line in each graph represents the best fit gamma function to all data points. Modified, with permission, from *Nature Neurosci.* REF. 14 © (2006) Macmillan Publishers Ltd.

may provide insight into the origin of the spontaneous fluctuations and the neuronal correlates of experience-based learning[94].

Interpreting spontaneous BOLD activity

Do spontaneous BOLD correlations reflect anatomical connections? Given the specific neuro-anatomical organization of spontaneous BOLD activity, this is a natural question. Only a few studies have directly addressed this issue, probably due in large part to the difficulty of directly assessing anatomical connectivity in humans. A study of patients with callosal agenesis found reduced cross-hemisphere correlations suggesting that reduced anatomical connectivity is related to a reduction in spontaneous BOLD correlations[95]. Additional studies on patients with more specific abnormalities in brain connectivity, such as callosotomy, are warranted. Other studies have examined the relationship between spontaneous BOLD correlations and anatomical connectivity using diffusion tensor imaging (DTI)[22,96]. These studies suggest some relationship between the two factors, but were limited either by not having spontaneous BOLD and DTI data from the same subjects[22] or by restricting the analysis to adjacent gyri[96]. Further studies combining DTI and spontaneous BOLD are needed.

Further insight into the relationship between spontaneous BOLD correlations and anatomy may come from an experimental system in which anatomical connectivity can be more easily assessed and manipulated — that is, in an animal model. Recently, spontaneous BOLD correlation patterns have been studied in anaesthetized macaque monkeys and the results were compared with established anatomical connections seen by tract tracing[36] (FIG. 5). Although there is a correspondence, there are also BOLD correlations between regions in the monkey visual system that have no direct anatomical connections, suggesting that polysynaptic pathways must also have a role[36]. Future studies in monkeys that examine BOLD correlations and tract tracing within the same animal or in which specific fibre tracts have been lesioned could be informative.

Is spontaneous BOLD activity due to unconstrained tasks? A critical question regarding the interpretation of spontaneous BOLD activity is the extent to which it is due to unconstrained behaviour or conscious mentation. Undoubtedly, when subjects are asked to rest quietly in the scanner they perform mental 'tasks' that result in changes in neuronal activity[97]. If these uncontrolled tasks are responsible for the coherence patterns observed in spontaneous BOLD activity, then resting-state BOLD studies may be no more interesting than poorly controlled task-activation studies.

Although spontaneous behaviour is likely to contribute to resting-state BOLD fluctuations, it is unlikely to be the predominant source for several reasons. First, similar topography of BOLD correlations can be observed across different behavioural states, including different resting conditions[29,35], task performance[71-73], sleep[98,99] and even anaesthesia[27,36,68] (FIG. 5). Second, coherent spontaneous fluctuations have been observed within systems associated with specific behaviour even in the absence of that behaviour[14,21,72] (FIG. 2). Third, task-evoked activity due to a specific behaviour seems to be distinct from and superimposed on underlying spontaneous activity[14,72] (FIG. 4). Fourth, spontaneous cognition, such as mental imagery, results in patterns of neuronal activity in visual regions that are distinct from patterns observed in spontaneous activity[65]. Finally, coherent spontaneous fluctuations are present continuously within a large number of

Callosal agenesis
A rare birth defect in which the corpus callosum fails to develop.

Diffusion tensor imaging
(DTI). An MRI imaging technique that takes advantage of the restricted diffusion of water through myelinated nerve fibres in the brain to map the anatomical connectivity between brain areas.

Mentation
Mental activities of which a subject is consciously aware.

Mental imagery
The conscious recollection of an object or a scene in its absence.

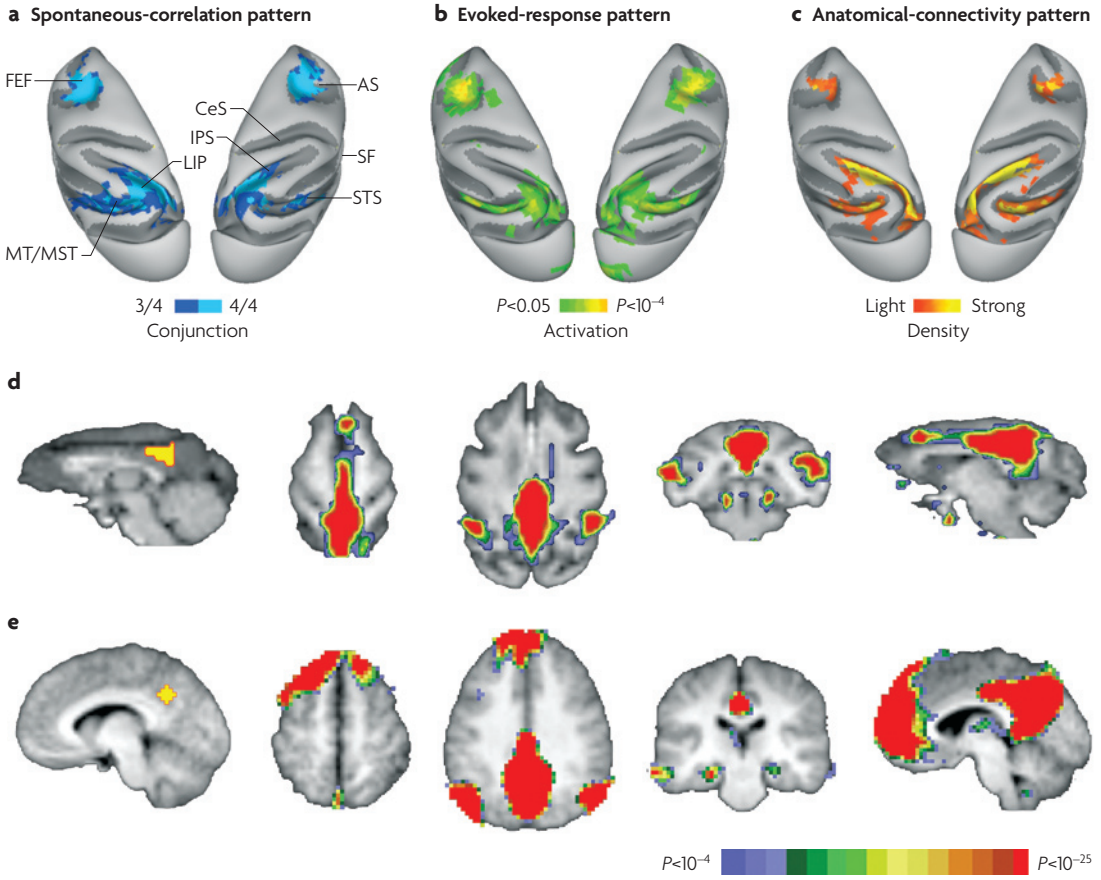

Figure 5 | **Spontaneous BOLD activity in the anaesthetized macaque monkey.** Cortical patterns of spontaneous activity in the anaesthetized macaque monkey correspond to anatomical connections and are similar to patterns observed in resting humans. **a** | Dorsal view of a conjunction map of blood oxygen level dependent (BOLD) correlations within the monkey oculomotor system. Voxels that significantly correlated with three (dark blue) or four (light blue) oculomotor seed regions are shown. **b** | Activation pattern evoked by performance of a saccadic eye movement task (average of two monkeys). **c** | Density of cells labelled by retrograde tracer injections into the right lateral intraparietal area (LIP). The left hemisphere injection data are duplicated by reflection of the right hemisphere to facilitate visual comparison. **d** | Significant BOLD correlations in eight anaesthetized macaque monkeys with a seed region in the posterior cingulate/precuneus (left). **e** | Significant BOLD correlations in 10 awake humans during resting fixation with a similar seed region. AS, arcuate sulcus; CeS, central sulcus; FEF, frontal eye field; IPS, intraparietal sulcus; MT/MST, middle temporal area/medial superior temporal area; SF, sylvian fissure; STS, superior temporal sulcus. Modified, with permission, from *Nature* REF. 36 © (2007) Macmillan Publishers Ltd.

neuro-anatomical systems (FIGS 2,3). It is difficult to imagine a behaviour that would simultaneously modulate every known brain system, each in its own coherent fashion. These factors all suggest that unconstrained behaviour in the scanner would result in BOLD modulations that are in addition to, not the source of, spontaneous coherent BOLD fluctuations.

Based on this evidence, spontaneous BOLD fluctuations observed during the resting state may be partitioned into two conceptual layers[73]. The first layer relates to the unconstrained behaviour or conscious mentation that subjects perform during resting conditions. This layer is conceptually similar to BOLD modulations induced by external-task paradigms and is likely to vary depending on the activity of a given subject. The second layer, which we will refer to as intrinsic activity, underlies the first layer and persists across different states or conditions. Owing to its consistency across different resting conditions[29,35] — task performance[71-93], sleep[98,99] and anaesthesia[27,36,68] — this intrinsic activity is more similar to anatomy than to transient task-evoked activity patterns. This layer of intrinsic activity is probably responsible for most of the spontaneous BOLD fluctuations observed during awake resting conditions, although future experiments may help to clarify this issue.

Resting-state activity and the default mode. An interesting observation that came from traditional imaging studies that compared average brain activity at rest with average activity during a task was that there were a set of regions that routinely decreased their activity during task performance[52]. The fact that some brain regions were more active at rest than during task performance led to the hypothesis that the brain remained active in an organized fashion during the resting state: this was called the 'default mode' of brain function[100]. The regions that routinely

Box 2 | **The fMRI BOLD signal**

The blood oxygen level dependent (BOLD) signal of functional magnetic resonance imaging (fMRI) arises from the magnetic properties of haemoglobin and the manner in which brain metabolism and blood flow are related to changes in neuronal activity[9,110]. Fully oxygenated haemoglobin in arteries has little effect on the magnetic field of an MRI scanner. However, when haemoglobin loses oxygen to the tissue as it passes through the capillaries of the brain the resulting de-oxygenated haemoglobin disrupts the MRI magnetic field in proportion to the amount of oxygen lost. When brain activity increases, blood flow and glucose consumption increase much more than oxygen consumption. As a result the amount of de-oxygenated haemoglobin decreases in the area of increased activity and the BOLD signal is enhanced. When activity decreases, the reverse happens. Current evidence on the cell biology of these events links the changes in blood flow and metabolism to the synaptic activity of glutamate and its recycling through astrocytes[9]. Therefore, although the fMRI BOLD signal arises from changes in blood flow and metabolism, it is intimately related to ongoing neuronal events in the excitatory synapses of the brain.

exhibit a decrease in activity during task performance became known as the 'default-mode network' and were thought to mediate processes that are important for the resting state[100]. How do we relate these concepts derived from traditional task-based imaging with coherent spontaneous BOLD fluctuations observed during the resting state? The finding of organized spontaneous activity during rest supports the notion that there is a default mode of brain function. However, the default-mode concept may need to be expanded beyond the resting state to include states such as sleep and anaesthesia. Furthermore, it must be noted that the default network is by no means the only brain system exhibiting coherent fluctuations in spontaneous activity during rest. Instead, all brain systems are active and are likely to contribute to whatever functionality is ongoing during resting conditions. The default network is therefore not unique in showing resting-state activity, but is unique in its response to cognitive tasks. Exactly what functionality is mediated by this network and why it is suppressed by cognitive tasks is a topic outside the scope of this Review, but studies of intrinsic brain activity, specifically of negative correlations, may shed some light on these issues[29–31].

The physiology of spontaneous BOLD

Electrophysiological correlates. The BOLD signal is not a direct measure of neuronal activity, but reflects local variations in de-oxyhaemoglobin concentration that are determined by a combination of blood flow, blood volume and oxygen metabolism[9] (BOX 2). So, how do spontaneous BOLD fluctuations relate to electrical measures of neuronal activity? A prime candidate for the electrophysiological correlate of spontaneous BOLD fluctuations is the fluctuation in the power of higher frequency electrical activity[60]. For example, brain electrical activity in the gamma frequency band fluctuates at 60–100 Hz but the power, or amplitude, of gamma at a particular moment fluctuates at a much slower rate[60], These fluctuations in power exhibit 1/f behaviour[58–60] and are correlated across large regions of cortex[60]. The strongest support for this hypothesis comes from simultaneous recordings of spontaneous fMRI fluctuations with electrical measures of brain activity such as EEG in humans[32,101–104] and local field potential recordings in monkeys[105]. Fluctuations in the power of high-frequency electrical activity are correlated with spontaneous BOLD fluctuations both locally[105] and across widely distributed neuro-anatomical systems[32].

Another promising, and potentially related, candidate is the slow (<0.1 Hz) electrical fluctuation that has been observed with DC-coupled EEG[106]. These slow electrical fluctuations are themselves correlated with changes in the power of higher frequency bands[106]. The idea that slow fluctuations may modulate the power of higher frequency activity has been referred to as 'nested' frequencies and may be an important principle in brain organization[3,106,107]. Rapid fluctuations such as alpha or gamma activity might coordinate neuronal activity across small spatial scales, whereas slower fluctuations in the power of these frequency bands may be required for long-range coordination. There is evidence for such a frequency–space trade-off in the brain[3]. Whether spontaneous BOLD activity is directly related to slow electrical fluctuations previously seen with DC-coupled EEG or to changes in the power of higher frequency electrical activity remains to be determined.

Finally, much animal work has focused on slow (~1 Hz) fluctuations in electrical membrane potential, referred to as up and down states[108,109]. Whether this phenomenon is related to the slow fluctuations in the BOLD signal remains a topic for future work.

Beyond the electrophysiological correlates of spontaneous BOLD activity, further insight into BOLD physiology may be gained by relating spontaneous BOLD fluctuations to a rich literature on spontaneous fluctuations observed in various haemodynamic and metabolic parameters, as well as spontaneous fluctuations in neurotransmitter release (BOX 3).

Spontaneous versus task-evoked physiology. Although much is known about the physiology underlying task- or stimulus-evoked BOLD responses[9,110], we must remember that the physiology underlying spontaneous fluctuations in the BOLD signal might not be the same. In many cases, spontaneous fluctuations seem to be regulated differently than task or stimulus-evoked brain responses. For example, nitric oxide synthase inhibition blocks stimulus-related increases in blood flow, but spontaneous fluctuations in blood flow can remain unchanged[111]. Similarly, the molecular mechanism of synaptic vesicle release in response to an action potential appears to be distinct from the mechanism involved in spontaneous neurotransmitter release[112,113]. Both spontaneous and task-evoked BOLD responses depend on T2* BOLD contrast[114] and future investigation of the similarities and differences in the underlying physiology will be important for interpreting spontaneous BOLD activity.

Box 3 | **Spontaneous haemodynamic, metabolic and neurotransmitter fluctuations**

Spontaneous low-frequency fluctuations have been observed in numerous haemodynamic and metabolic parameters including oxygen availability[151–153], nicotinamide adenine dinucleotide (NADH) levels[154], cytochrome oxidase activity[155–157], blood volume[155,156] and blood flow[22,111,158,159]. Some of these fluctuations bear similarity to particular aspects of spontaneous blood oxygen level dependent (BOLD) activity. For example, 1/f frequency distributions have been observed in blood flow[159]. Bilateral synchrony has been observed in metabolic fluctuations[155,156], blood volume[155,156] and blood flow[111]. Finally, flow-sensitive imaging in human subjects reveals fluctuations in cerebral blood flow with similar spatial patterns to those seen with BOLD[22,158].

Interestingly, these spontaneous haemodynamic and metabolic fluctuations may or may not be related to underlying changes in electrical activity. For example, a tight coupling was found between spontaneous haemodynamic fluctuations and bursts of electrical activity[111]. However, spontaneous fluctuations in blood volume and cytochrome oxidase activity have been measured under conditions of electrocortical silence[155,156]. Further work is needed to link spontaneous BOLD fluctuations to the primarily invasive recordings of haemodynamic and metabolic fluctuations, although non-invasive techniques, such as near-infrared spectroscopy, are making important advances in this regard[157].

An interesting and potentially related area of research is the examination of spontaneous neurotransmitter release at neuronal synapses[112,113,160]. In this field, the term 'spontaneous' refers not only to activity present in the absence of an explicit task or stimuli, but also to neurotransmitter release present in the absence of neuronal spikes or action potentials. As BOLD is thought to reflect primarily dendritic potentials related to synaptic input[110], this spontaneous neurotransmitter release could be an important component of spontaneous BOLD fluctuations. Support for this comes from the observation that fluctuations in spontaneous neurotransmitter release show a 1/f frequency distribution, similar to that of BOLD[161]. It will be interesting to know if this spontaneous neurotransmitter release is itself related to fluctuations in the power of higher frequency electrical activity recorded with local field potentials.

Conclusions and future directions

We now know much about spontaneous BOLD fluctuations. They are not random noise, but are specifically correlated between functionally related brain regions and relate to known anatomical systems. They cannot be attributed to cardiac or respiratory factors, and they correlate well with fluctuations in the power of high-frequency neuronal activity. Spontaneous BOLD correlation patterns persist across different resting states, including sleep and anaesthesia, suggesting that they are an intrinsic property of the brain as opposed to being the result of unconstrained mental activity. Inter-subject variability in these correlation patterns relates to the inter-subject variability in activation patterns and task performance. Finally, spontaneous BOLD fluctuations do not disappear during task conditions, but continue, contributing to inter-trial variability in measured BOLD responses and behaviour. Although much is known, more has yet to be discovered, and there are several research directions that promise interesting results in the near future.

Spontaneous BOLD activity and neurophysiology. The study of spontaneous activity is by no means unique to fMRI and has been investigated both in animals and humans across many spatial and temporal scales[3,4] using various techniques[3,108,109,115–120]. Similarly, the notion that neuronal synchrony (both spontaneous and task-related) may be important for brain function has a strong electrophysiological precedent[4,84]. Investigations into spontaneous fluctuations in the BOLD signal will benefit greatly from a synthesis of the concepts and conclusions derived from this large body of electrophysiological work.

Future experiments focused on such a synthesis could benefit from applying the spatial topography of BOLD correlations to guide recordings using other techniques. For example, BOLD correlation patterns in the monkey could guide the placement of electrodes at multiple sites for invasive electrophysiological recordings. Human patient populations with implanted subdural electrode grids could be used to look for spatial patterns similar to those seen with BOLD. Finally, BOLD correlation patterns in normal human subjects could be used to identify recording sites for non-invasive techniques like optical imaging or to generate *a priori* hypotheses about coherence patterns in MEG.

Comparison of BOLD correlation patterns between groups. One of the most promising applications of spontaneous BOLD activity is the comparison of correlation patterns between groups. As there is no task, studies can be conducted in subjects unwilling or unable to adhere to task paradigms and may circumvent concerns about differences in task performance or task strategy. Most work in this area has focused on comparing normal subjects to patients with neurological or psychiatric disease. Disturbances in the correlation structure of spontaneous activity have been reported for a number of pathological states including Alzheimer's disease[44,121–123], multiple sclerosis[15,124], depression[125–127], schizophrenia[49,128–131], attention deficit hyperactivity disorder[132,133], autism[134], epilepsy[135], blindness[136] and spatial neglect following stroke[56]. These pathological disturbances in intrinsic activity have been related to the severity of disease[56,127,131] and recovery from functional deficits[56], and have shown good segregation between healthy and patient populations[44,122], suggesting that intrinsic activity may hold valuable diagnostic and prognostic information. Relating these disturbances in spontaneous BOLD activity to underlying differences in anatomy[137] and physiology, determining the sensitivity and specificity of the observed effects, and assessing the impact of treatment, are likely to become major topics of future work.

In addition to neurological or psychiatric disease, spontaneous fluctuations in BOLD activity can be used in other instances where performance differences make group comparisons difficult or impossible. For example,

Near-infrared spectroscopy
A form of optical imaging in which arrays of lasers and detectors are used to measure changes in the absorption of near-infrared light caused by neural activation.

changes in the correlation structure of spontaneous activity can be assessed across development[138], pharmacological manipulation[67,126,139], sleep[98,99], anaesthesia[27,68] and even species[36] (FIG. 5). The insights that this approach could provide into brain maturation, altered states of consciousness and evolution may be profound.

Result comparison, re-analysis and data sharing. Owing to the nature of spontaneous BOLD data, a single dataset can be used for multiple analyses and can address a variety of questions. Furthermore, the paradigms used to study spontaneous BOLD activity are relatively simple compared with task-based imaging studies. These factors make spontaneous BOLD data ideally suited for re-analysis and inclusion in a database. Recently a free online analysis package and database focused on the study of spontaneous BOLD activity termed BrainSCAPE (Spontaneous Correlation Analysis Processing Engine) was launched[140]. This tool allows users to upload, analyse and share their spontaneous BOLD data as well as analyse shared data from other laboratories. By providing access to multiple datasets, processed in a similar fashion, across health, disease and even species, the effects in one study can easily be confirmed and compared with results from other datasets. We anticipate that this collaboration will accelerate advances in the field and prove valuable in assessing the sensitivity and specificity of intrinsic abnormalities underlying human disease.

Potential functional role of spontaneous BOLD. What is the purpose of spontaneous BOLD activity? The enormous cost of spontaneous activity in terms of energy consumption and its specific organization in the brain seems to suggest that it serves an important role in brain function. The specifics of this role are unknown but several suggestions have been made. One possibility is that spontaneous activity serves as a record or memory of previous use, showing correlations between regions that have been modulated together in a task-dependent manner[94,120]. Another possibility is that spontaneous activity serves to organize and coordinate neuronal activity[3,141,142] and that this coordination is more prominent between regions that commonly work in concert. This is similar to the temporal binding hypothesis[4,84], although spontaneous BOLD occurs at a much slower, broader and more permanent scale. Finally, spontaneous activity may represent a dynamic prediction about expected use[143,144], with correlations occurring between regions that are likely to be used together in the future. Such a Bayesian perspective on brain function has a strong theoretical background and is gaining experimental support[145].

These possibilities are not mutually exclusive and all of them may be important in helping us understand the role of spontaneous activity in brain function. In conclusion, spontaneous activity, as observed through fluctuations in the fMRI BOLD signal, is opening new doors and providing new insights that may one day surpass the knowledge gained from task-response studies that have dominated neuroscience for the past 50 years.

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