Disease and the brain's dark energy

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Abstract | Brain function has traditionally been studied in terms of physiological responses to environmental demands. This approach, however, ignores the fact that much of the brain's energy is devoted to intrinsic neuronal signaling. Recent studies indicate that intrinsic neuronal activity manifests as spontaneous fluctuations in the blood oxygen level-dependent (BOLD) functional MRI (fMRI) signal. The study of such fluctuations could potentially provide insight into the brain's functional organization. In this article, we begin by presenting an overview of the strategies used to explore intrinsic neuronal activity. Considering the possibility that intrinsic signaling accounts for a large proportion of brain activity, we then examine whether the functional architecture of intrinsic activity is altered in neurological and psychiatric diseases. We also review a clinical application of brain mapping, in which intrinsic activity is employed for the preoperative localization of functional brain networks in patients undergoing neurosurgery. To end the article, we explore some of the basic science pursuits that have been undertaken to further understand the physiology behind intrinsic activity as imaged with BOLD fMRI.

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Introduction

The driving force behind the apparent acceleration of the expansion of our universe is believed by many to be a previously unaccounted-for 'dark energy', which constitutes approximately 75% of the total mass–energy in the cosmos.[1] Like our cosmos, the brain also has its own 'dark energy'. Indeed, 'visible' elements of brain activity—neuronal responses to environmentally driven demands—account for less than 5% of the brain's energy budget, leaving the majority devoted to intrinsic neuronal signaling.[2] This disproportionate allocation of energy resources has reawakened a longstanding interest in intrinsic brain activity and the possibility that such signaling might also be important for interpreting, responding to and even predicting environmental needs.[3] As with the cosmos, the challenge for neuroscience is to understand the functions associated with the brain's dark energy. Remarkably, spontaneous fluctuations ('noise') in the blood oxygen level-dependent (BOLD) functional MRI (fMRI) signal are providing a unique insight into the organization of intrinsic activity in the human brain. The implications of such insight for our understanding of brain diseases, as explored in this Review, loom large.

In the absence of overt perceptual input and behavioral output, spontaneous fluctuations in neuronal activity—as reflected in the spontaneous activity of the BOLD fMRI signal—can be observed throughout the gray matter, and the magnitudes of these fluctuations can be equal to task-evoked activity.[4] Strikingly, these spontaneous fluctuations demonstrate temporal coherence between brain regions that are anatomically connected and are functionally related through co-activity in response to task performance (Figure 1).[5–7] By calculating the coherence of spontaneous fluctuations across various brain regions, multiple functional networks have been identified, including the following:[8] primary input–output regions such as sensorimotor, visual, and auditory areas; higher integrative networks such as the language, attention, default mode (Box 1) and control networks (Figure 1a); and cortico-subcortical networks involving the thalamus, basal ganglia, limbic system, and cerebellum (Figure 1b).[9] Coherence in spontaneous activity persists across various states of consciousness and behavior in humans, such as during task performance, wakeful rest, sleep, and loss of consciousness induced by anesthetics or sedatives, and has also been demonstrated in other species under anesthesia.[9] Thus, spontaneous fluctuations in the BOLD signal represent a widespread, robust phenomenon that clearly fits the criteria for intrinsic neuronal activity in the brain—a hypothesis confirmed by comparison of the signal with ongoing electrical activity.[10,11] Most studies of spontaneous fluctuations have been performed during wakeful rest. Functional networks generated under such conditions are, therefore, commonly referred to as 'resting-state' networks, even though these networks transcend purely resting states (see Supplementary References online for an extensive list of additional references).

This Review examines intrinsic neuronal activity as imaged with BOLD fMRI, placing a particular emphasis on how functional mapping using this activity has been applied in the context of neurological and psychiatric disease. We begin, however, by introducing the multitude of analytical techniques employed to evaluate intrinsic brain activity data from fMRI.

Competing interests
The authors declare no competing interests.

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Key points

- The majority of the brain's energy is devoted to intrinsic neuronal signaling
- Intrinsic neuronal activity manifests as spontaneous fluctuations in the blood oxygen level-dependent functional MRI (fMRI) signal and exhibits synchrony within neuroanatomically and functionally related brain regions
- Many established methods, each with its own advantages and disadvantages, are available for characterizing synchrony in intrinsic neuronal activity (functional connectivity)
- Changes in functional connectivity have been reported in various neurological and psychiatric diseases, and such alterations might have potential as clinical biomarkers in the long term
- Functional connectivity has potential as a preoperative functional brain mapping tool to indicate the regions that should be avoided during surgery
- Much of the progress that has been made in our basic science understanding of intrinsic neuronal activity, as detected by fMRI, will aid the interpretation of clinical changes during disease

Methodology

Functional connectivity mapping

Seed-based correlation mapping is one of the most widely adopted techniques for studying co-fluctuations in intrinsic neuronal activity, or functional connectivity (here referring to intrinsic as opposed to task-evoked co-fluctuations).[12] The high adoption rate of the seed-based approach is partly attributable to simplicity of implementation, and to the ease with which the results can be interpreted. In this approach, the BOLD signal time course is first extracted from a 'seed' region of interest (ROI). Time courses are subsequently extracted from every voxel in the brain. Finally, correlations are computed between the seed's time course and each voxel's time course, generating a correlation map (Figures 1 and 2a). The Pearson product-moment correlation method is the most widely used measure of functional connectivity,[13–18] but various alternative parametric and non-parametric techniques have also been used in the literature.[19–23]

As the BOLD signal contains both neuronal and non-neuronal elements, several non-neuronal contributions are typically removed from the correlation maps via linear regression. These nuisance signals include BOLD activity from ventricles and white matter, as well as time courses representing head position and movement. Low-frequency power variations in cardiac and respiratory function have been shown to contribute to correlated activity,[24] and are similarly removed whenever possible. These non-neuronal physiological contributions are minor,[25] and their removal does not dramatically alter the spatial distribution of functional networks.[24] The average signal from the entire brain (the global signal) seems to correlate with some of these physiological signals,[24] as well as with vascular signals, especially near the cavernous sinus and the circle of Willis. Some groups, therefore, employ further linear regression to remove the contribution of the global signal (Box 2).[14,26] Correlated activity of neuronal origin is mostly confined to frequencies <0.1 Hz, so spectral filtering is typically performed to retain only low frequencies.[25]

Independent component analysis (ICA) is a more mathematically sophisticated approach to mapping functional connectivity than seed-based correlation mapping.[8,27] In ICA, the data are decomposed into multiple components by maximizing statistical independence (usually of spatial patterns). The result of such analysis is a set of spatially unique maps that group correlated regions together, with one group for each independent component. Multiple functional networks can, therefore, be generated simultaneously, with each one segregated into a unique independent component (Figure 2b).

Seed-based correlation and ICA represent the two most commonly used methods in functional connectivity MRI (fcMRI) studies. Each method offers a set of technical advantages and disadvantages. A seed-based approach provides a targeted analysis for hypothesis-driven experiments with a priori ROIs, and generates results with a straightforward interpretation—the computed map represents correlations with the focal ROI. Multiple regions must, however, be manually defined before analysis in order to generate multiple network maps. Linear regression must also be performed before correlation analysis to remove confounding sources of non-neuronal variance. By contrast, ICA requires no a priori regional definition and can simultaneously extract multiple networks and often separate many sources of non-neuronal variance related to movement, ventricles, white matter and respiration.[8] The number of components to be used (the number of 'bins' for grouping the data), however, must be defined before ICA is performed. A low number of components can result in multiple networks grouped together into one map, and a high number can fragment a single network into multiple maps. Empirical observations suggest that a range of values can usually be found that largely satisfy the experimental question being asked. Furthermore, various algorithms have been developed to automatically estimate data dimensionality and, hence, aid selection of the independent component number. A standard algorithm has yet to be established for finding an 'optimal' number of independent components,[8] which often depends on the individual experiment.[8] During the post-processing stage, independent components need to be assigned to known networks, either by manual identification or with semi-automated techniques that compare ICA results against known network templates.[8,28–31]

Even though seed-based correlation and ICA are quite distinct in terms of methodology, the functional networks that these techniques generate are quite comparable.[8,28,32] Interestingly, both methods have largely been used in a complementary way to characterize changes with disease. Most ICA studies are performed at the network level, where each network is defined as a separate component, and the objective is to look for connectivity changes with respect to the entire network. By contrast, most seed-based studies are performed at the inter-regional level, where the seed is defined as a small, spatially localized region, and the objective is to look for connectivity changes between the seed and other voxels in the brain. Seed-based correlation and ICA are by no means restricted to these particular levels of spatial specificity; however, as most studies are performed in the ways described above, the results of these two techniques

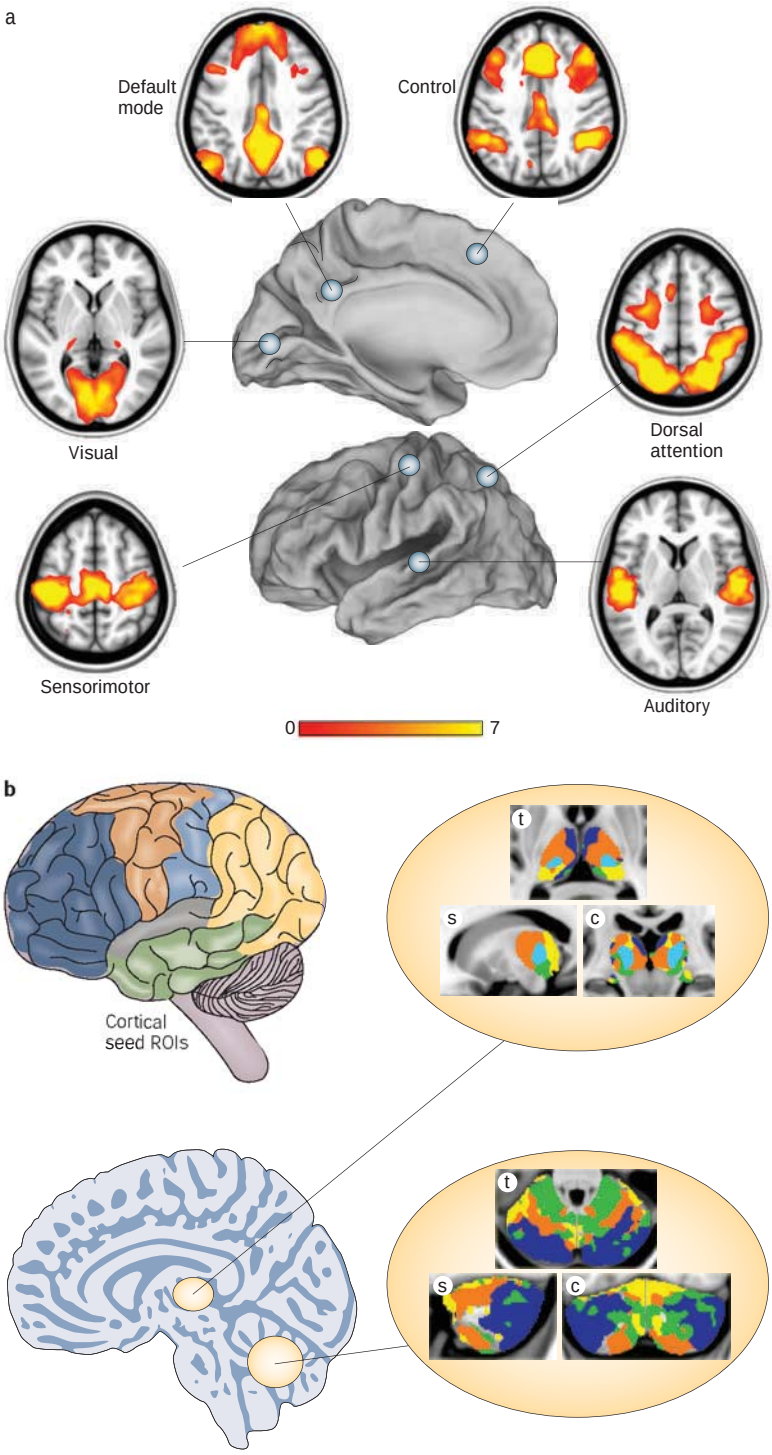

Figure 1 | Intrinsic neuronal activity is synchronous within neuroanatomically and functionally related regions of the brain. a | By comparing the neuronal activity between a seed region (each blue circle) and the rest of the brain, one can generate a correlation map of brain regions that share similar neuronal activity to that of the seed. Here, we show six of the major networks: visual, sensorimotor, auditory, default mode, dorsal attention, and executive control. The scale numbered 0–7 indicates relative correlation strength. b | Correlations in intrinsic neuronal activity are not confined to the cortex but extend to subcortical regions such as the thalamus and the cerebellum. The top left panel shows the cortex partitioned into multiple regions: prefrontal (dark blue), motor and premotor (orange), somatosensory (light blue), parietal and occipital (yellow), and temporal cortex (green). In the right-hand panels, the thalamus and the cerebellum are colored according to the cortical partition that is most correlated with each subcortical region. Correlations in intrinsic activity closely match connectional anatomy derived from nonhuman primates. For an expanded discussion, see Supplementary Figure Legend 1 online. Abbreviations: c, coronal; s, sagittal; t, transverse. Permission obtained from Oxford University Press © Zhang, D. et al. Cereb. Cortex doi:10.1093/cercor/bhp182.

can provide non-overlapping information reflecting various spatial levels of neuronal synchrony.

Spatial levels of neuronal synchrony

Synchrony in intrinsic activity is typically characterized to be network specific, but a closer inspection reveals synchrony at multiple spatial levels. At the whole-brain level, the global signal (averaged across all brain regions) is positively correlated with much of the gray matter. Moreover, the global signal has been shown to represent more than just the average of network-specific signals,[33] and might be influenced by global changes, such as the level of arousal (Figure 2a, left-hand panel). Moving towards the direction of greater spatial specificity, synchrony in intrinsic activity also exists between networks such as the default mode network (DMN) and the dorsal attention network (DAN; Figure 2a, middle panel).[7,14,26,34] Even within a network, heterogeneity of neuronal synchrony exists,[7,35,36] although this heterogeneity is often poorly characterized. By use of seed-based mapping, many networks can be reproducibly generated using a variety of canonical seed locations, although detectable differences in the correlation maps can exist depending on the exact seed used. One way to study these differences is to use partial correlation mapping (Figure 2a, right-hand panel),[35] which can be conceptualized as simulating a functional lesion by mathematically removing the neuronal activity contribution from a specific ROI (see Zhang et al.[37] for an exact mathematical definition of partial correlation). In the context of using intrinsic activity as a biomarker for disease, one must keep in mind that functional connectivity occurs at multiple spatial levels, and that various diseases might be sensitive to connectivity changes on different spatial scales.

Various specialized methods exist to distinguish and visualize the multiple levels of spatial integration. Frequently, a special type of seed-based correlation is used. Multiple ROIs, often termed nodes, are defined in representative regions of multiple functional networks, and the neuronal activity time course from each ROI is extracted. By calculating the correlation in neuronal activity among these nodes, one can construct a tree that represents the relatedness of the nodes, using algorithms such as hierarchical clustering (Figure 2b).[38] A conceptually similar tree can be derived through ICA by systematically varying the number of a priori-defined components. In effect, this approach varies the threshold of statistical independence for the separate components

Box 1 | The default mode network and its role in disease

The default mode network (DMN) is a collection of brain regions characterized by a canonical pattern of coactivity both in relation to task performance and independent of task performance. The DMN typically exhibits more activity during rest than during task engagement,[152] and also demonstrates persistent intranetwork synchrony across a variety of states of consciousness and behavior.[14,18,26,122,123] Compared with other networks, the DMN is unique in the direction of its response to task performance, which probably relates to its baseline level of neuronal and metabolic activity[56,153] and its role in brain function.[154] The DMN is not unique, however, in demonstrating correlated intrinsic activity; multiple networks exhibit coherent resting state activity that persists across different states.[4,27,119,122,123]

DMN alterations have been reported in numerous neuropsychiatric diseases. This focus on the DMN is especially appropriate for diseases such as Alzheimer disease, in which parts of this network have been clearly implicated. However, a disproportionate and unhelpful focus on the DMN also exists in non-hypothesis-driven exploratory studies. Many of the early pioneering functional connectivity MRI experiments were necessarily limited in the scope of their focus, but comprehensive exploratory analyses can now be easily conducted to study multiple resting state networks at multiple levels of spatial integration with a variety of freely available analysis tools (Supplementary References online). There are two advantages to this approach. First, classifying connectivity changes across multiple brain networks can provide drastically improved sensitivity and specificity in distinguishing among pathological conditions and comorbidities. Second, a demonstration of no altered connectivity in other networks provides an easy experimental control for a variety of potential confounds.

and, thus, is analogous to generating the tree at different hierarchy levels (Figure 2b).[5,39] Given that the vertical nature of hierarchical clustering inherently limits node categorization to a single branch of the tree, however, more-appropriate ways might be found to topologically represent the brain, such as visualization schemes from graph theory.

Graph theory

Analogous to hierarchical clustering, graph theory uses multiple nodes—typically termed a graph network—to represent the entire brain. The relationship among these nodes is not, however, represented by a tree. Instead, the connections between the nodes are defined directly by their functional connectivity strength (or a binarized version of connectivity strength).[7,40,41] For visualization, such nodes are often topologically mapped by their anatomical Cartesian coordinates (Figure 2c) or by their functional similarity, which is estimated by means of algorithms such as multidimensional scaling[38,42] or spring embedding.[43] In addition to visualization tools, graph theory offers quantitative ways to describe various properties of graph-network architecture, including a special case termed 'small-world' properties.

The brain's functional architecture exhibits a set of features, known as small-world properties,[44] that are common to many naturally occurring and man-made networks. The information contained in these networks introduces connectional complexity that can be architecturally distinguished from many types of simple networks (those networks that can be constructed from a basic set of instructions). A small-world network can be differentiated from a network of random connections, as the former possesses a higher level of region-specific connectivity (high local clustering and modular organization). In addition, small-world networks are characterized by short connectivity pathways that globally join all nodes. These 'short path lengths' distinguish small-world networks from simple networks of lattice-like connections or serial connections that have long path lengths. An economical small-world network achieves these small-world characteristics with a low total number of connections; thus, such networks have high efficiency. By contrast, a fully connected network has high wiring costs.[45]

The quantitative measurements offered by graph theory allow characterization of the traditionally abstract concepts of integration (for example, high clustering and short path length) and segregation (for example, modularity), thereby providing a statistical means to distinguish between two populations on the basis of these concepts (Box 3). A multitude of partially overlapping network measures can be used in graph theory (see Bullmore and Sporns[45] for a review of graph theoretical analysis). The measures that are most useful for describing the brain's neuronal activity and distinguishing a state of health from a state of disease have yet to be determined. For example, segregation of functional regions by use of modularity measures shows high similarity to networks generated with ICA and seed-based correlation,[46] although differences in connectivity maps exist between graph theory measures and other methods, and these require further investigation. In the context of disease, differences in small-world properties can be detected between patients with certain diseases and controls,[47–49] signifying that global functional connectivity changes might be associated with certain neuropathologies.

Regional synchrony

Functional connectivity maps demonstrate the property of 'local bloom', whereby neighboring voxels are highly correlated, and the level of correlation decreases as a function of distance. In gray matter, the slope of this decrease is not uniform and can exhibit marked transitions between distinct functional networks. These changes in correlation can be used to generate borders that define separate functional areas.[50] This parcellation scheme defines functional networks that are similar to those generated with traditional seed-based mapping and ICA. Within the boundaries of a localized functional area, heterogeneity in the neuronal activity waveforms can often be detected in adjacent voxels, presumably reflecting variation in local information processing. One method that has been proposed to investigate this variation is regional homogeneity.[51] In this method, a local cluster of voxels is defined around a given center and the variation in neuronal activity within this cluster is measured.[52] Regional homogeneity is a relatively new method; however, this technique has already been applied to several neuropsychiatric diseases (Supplementary References online).

Intrinsic brain activity and disease

Practical considerations

ICA and seed-based approaches differ dramatically in implementation; however, the techniques are unified

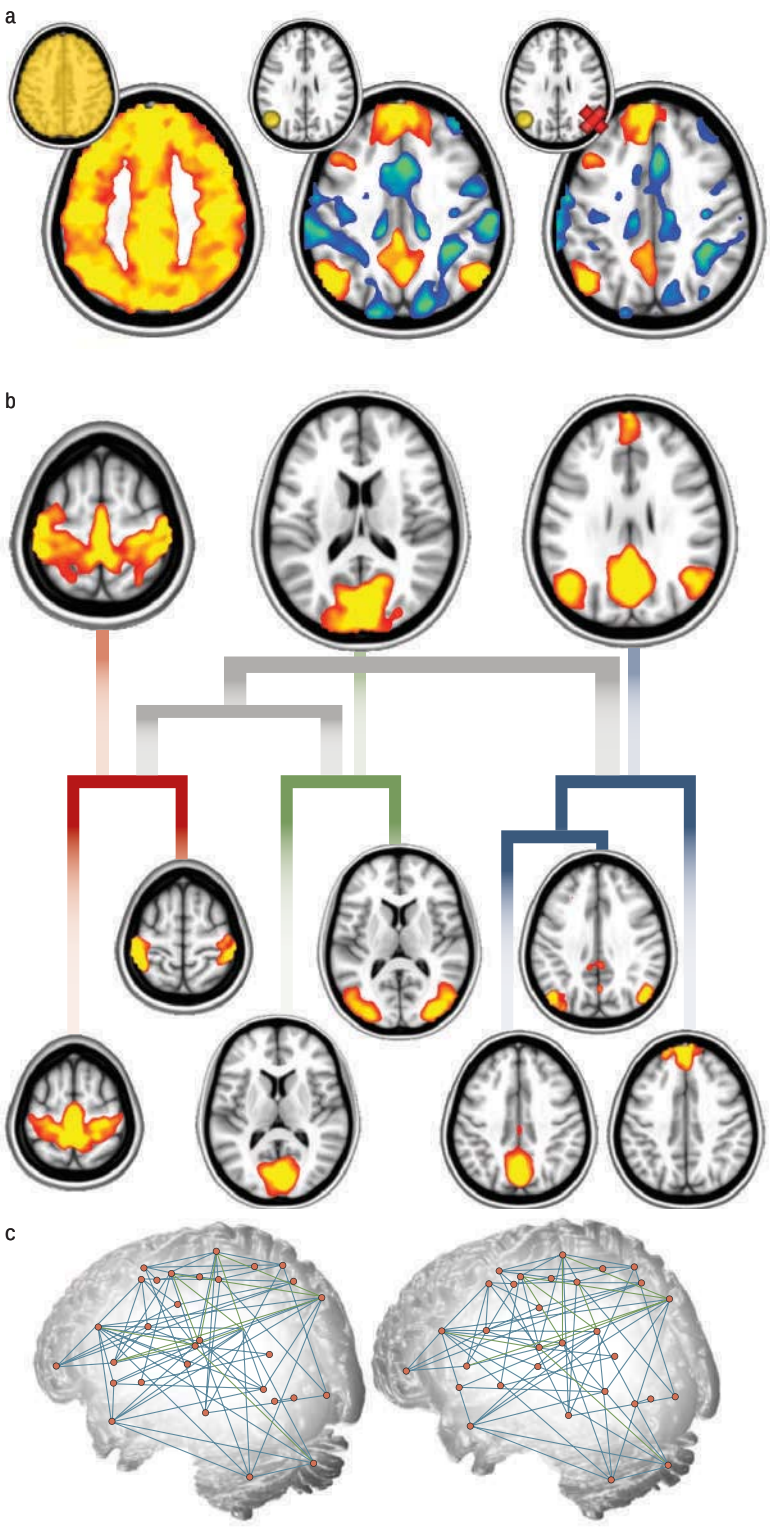

Figure 2 | Functional connectivity on different spatial scales visualized using various complementary techniques. a | Seed-based correlation mapping. The global signal (seed, left inset) demonstrates widespread—albeit nonuniform—correlations throughout the gray matter (left-hand image). At the network level, a map of the default mode network (middle image, yellow; note cross-network anticorrelations in blue; global signal regressed) can be generated with a seed in the left lateral parietal cortex (yellow circle, middle inset). For a finer dissociation of subnetwork structure (right-hand image), partial correlation is performed. The seed is again in the left lateral parietal cortex, but now the shared signal contributed by the right lateral parietal cortex (red cross, right inset) is eliminated (compare with corpus callosotomy in Figure 3b). b | Independent component analysis decomposition and hierarchical clustering in three of the most robustly observed networks (sensorimotor, visual and default mode). By using 30 and 130 independent component decompositions, networks and subnetworks can be hierarchically clustered. c | Graph network stereogram (animated online[155]). Canonical nodes of major functional networks (orange circles) are used to construct this topological graph. The blue and green lines represent positive and negative correlations, respectively. Correlations are strongest within a functional network but nevertheless span across networks. For an expanded discussion, see Supplementary Figure Legend 2 online.

in their goal of characterizing synchrony in intrinsic neuronal activity and often generate similar results.[8,28,32] To be considered clinically useful, functional connectivity results must be spatially consistent and statistically robust across individuals and scanning sessions. Several studies that used either seed-based or ICA approaches have demonstrated these desired properties.[20,47,53,54] The duration of fMRI data acquisition varies widely among studies, ranging from <1 min to >30 min. As a general rule, studies that employ scan times of 15 min and examine 15 or more individuals produce reliable maps of major functional networks. During image acquisition, individuals usually rest quietly in the scanner, and often visually fixate on a crosshair to minimize major state transitions between wakefulness and sleep during the scan. After the functional connectivity results are generated, many statistical methods are available to quantify any population differences observed and to test the diagnostic power of these differences (Box 3).

Alzheimer disease

One of the first studies to use fcMRI to examine disease pathophysiology was performed by Li et al.[55] in patients with either Alzheimer disease (AD) or mild cognitive impairment (MCI). As the hippocampus is prone to structural atrophy and neuropathological lesions in AD, this hypothesis-driven study examined left–right hippocampal functional connectivity in the two patient populations. Compared with an appropriate age-matched control group, patients with AD showed decreased bilateral hippocampal connectivity, as measured using a seed-based ROI approach. This fcMRI study was also one of the first to test the diagnostic value of using intrinsic brain activity as a biomarker that distinguishes patients from healthy controls by calculating sensitivity and specificity using a receiver operating characteristic curve (ROC). Subsequently, by means of ICA, Greicius et al.[28] related hippocampal connectivity to a larger collection of brain regions within the DMN,[56] and showed that DMN connectivity was reduced in the AD group compared with healthy individuals. Although the study

Box 2 | Negative correlations and the global signal

In the existing literature, examples abound of changes in the strength of negative correlations (anticorrelations) in various disease states.[57,64,66,72,88] In interpreting these changes, one first needs to be aware of the mathematical bias[33,156,157] towards negative correlations induced by regression of the global signal and by frame-to-frame-intensity stabilization,[33,57] which are routinely performed by many groups. Despite ongoing controversy, considerable evidence suggests that anticorrelations have a biological basis[33,34,143] with respect to the default mode network and the task-positive network, which roughly comprises the dorsal attention network plus the control and salience networks.[32,73,74] Less clear is how global signal regression contributes to anticorrelations in other networks and to changes in anticorrelation strength with disease. However, having an awareness of the findings and issues associated with global signal regression provides a starting point for a balanced interpretation of negative correlations (an extended discussion of functional connectivity MRI anticorrelations is provided elsewhere[33]).

by Greicius et al.[28] was not performed strictly during rest, but rather during a low-cognitive-demand task, this work marked the first of an extended series of fcMRI investigations by numerous groups into the role of the DMN in neuropsychiatric diseases.

A follow-up study by Sorg et al.[57] confirmed that patients with MCI had decreased network-level connectivity in the DMN and DAN compared with healthy individuals.[58] By contrast, this group demonstrated no changes in other networks extracted with ICA. The network-level abnormalities observed in the patients with MCI suggested that additional spatially specific interregional abnormalities might also be present, especially in the DMN.

Further investigations that built on Li et al.'s[55] original seed-based study demonstrated decreased connectivity in AD between the hippocampus and other regions within the DMN, such as the medial prefrontal cortex (PFC)[59,60] and the posterior cingulate cortex (PCC),[57,61] consistent with the emerging storyline of changes within the DMN. Interestingly, asymptomatic carriers of the apolipoprotein E 4 allele, a genetic risk factor for AD, also exhibited modulation in the DMN, although these individuals showed an increase rather than a decrease in connectivity.[29] Notably, these carriers were selected from a much younger age group than the patients with AD or MCI studied previously, and were examined at a stage before before cognitive and structural degeneration are thought to occur.

The relatively consistent involvement of the DMN in AD across these fcMRI studies is in agreement with converging evidence from various modalities showing that this network is preferentially affected by processes that characterize the disease, namely amyloid deposition, structural atrophy, and metabolic disruption.[62] Furthermore, different neurodegenerative diseases preferentially target different functional systems,[63] so the localization of fcMRI disruptions is likely to depend heavily on the type of neurodegeneration.

Beyond the network level, AD-related connectivity changes have also been reported globally within the brain. Of note, two studies[47,64] used an anatomical parcellation of the brain into approximately 100 extended regions[65] to generate all possible pairwise functional connectivity values. Numerous increases and decreases in connectivity were detected in patients with AD versus controls in both studies.[47,64] Graph theoretical analysis revealed a loss of small-world properties in AD, with a notable reduction in the clustering coefficient—a sign of reduced local connectivity.[47] An ROC curve that was based solely on the clustering coefficient had high sensitivity and specificity for detecting the disease,[47] suggesting that global as well as local connectivity[55] might be altered in AD. Since the results of this ROC analysis[47] are reminiscent of the sensitivity and specificity values from Li et al.'s ROC analysis of inter-regional connectivity within the hippocampus,[55] testing whether the combination of global and local connectivity features adds discriminative power to group differentiation might be of great interest. Multivariate studies of this nature are beginning to be performed with fcMRI and hold promise in reliably distinguishing people with AD from healthy individuals (Box 3).[66]

Depression

Studies of depression based on fcMRI have reported several notable findings, including connectivity changes in patients with the disorder, correlation of connectivity strength with disease symptoms, and recovery of connectivity in affected individuals following pharmacological treatment.[31,67–69] Anand et al.[67] pursued a hypothesis-driven approach that focused on specific regions in the subcortex, dorsal anterior cingulate cortex (ACC) and amygdala to investigate the effect of depression on intrinsic signaling. Unmedicated patients with depression demonstrated a decrease in connectivity between the dorsal ACC and several other structures, namely the amygdala, pallidostriatum and medial thalamus (in particular, the lateral mediodorsal and ventral lateral nuclei).[67] Following 6 weeks of sertraline treatment, connectivity was partially restored in the disrupted pathways, particularly between the dorsal ACC and the medial thalamus.[68] The same research group reported similar decreases in corticolimbic connectivity in bipolar disorder.[69]

Greicius and colleagues[31] used ICA to focus specifically on changes in the DMN associated with depression. The researchers examined the prefrontal and cingulate regions (areas not investigated by Anand and colleagues in their study),[67] as alterations in these parts of the DMN had been previously linked with depression. Compared with individuals with no psychiatric disorder, patients with depression exhibited increased connectivity in the subgenual ACC, precuneus and medial thalamus in the independent component representing the DMN (with the medial thalamus including mainly the medial mediodorsal, medial pulvinar, ventral anterior and anterior nuclei).[31] Of note, the medial thalamus regions that were defined by Anand et al.[67] and Greicius et al.[31] exhibited some degree of overlap but were not identical. The nonoverlapping areas differed in their principal cortical targets[70] and, thus, differed in their functional connectivity.[37] Greicius et al. found that connectivity strength in the subgenual ACC was also of clinical relevance, as the degree of connectivity correlated with the duration of the depressive episode.[31]

As fcMRI analysis becomes increasingly comprehensive and sophisticated, advanced classification algorithms, such as linear support vector machines, have great promise as diagnostic tools in depression (Supplementary References online) and, indeed, other diseases.

Schizophrenia

The existing literature on fcMRI in schizophrenia provides a good example of the varied and creative endeavors that have been presented as initial forays into the clinical arena. Unfortunately, this process can sometimes generate results that are discordant and do not lend themselves to any general formulations of clinically diagnostic patterns.

At the functional network and subnetwork levels, several studies have reported increased connectivity in people with schizophrenia compared with healthy individuals. Using medial PFC and PCC seeds, Whitfield-Gabrieli et al.[71] reported that both patients with schizophrenia and nonpsychotic first-degree relatives demonstrated increases in connectivity in the DMN, and that the extent of connectivity between these seeds was correlated with the degree of psychopathological symptoms. Zhou et al.[72] examined the DMN and the DAN, as well as the control and salience networks,[32,73,74] in a multi-ROI inter-regional comparison to look for changes in connectivity that were associated with schizophrenia. Patients with schizophrenia frequently exhibited increased connectivity compared with controls. Follow-up studies by the same laboratory reported that patients with schizophrenia had decreases in connectivity in the dorsolateral PFC,[75] hippocampus and other structures.[76]

Salvador et al.[77] investigated connectivity by decomposing neuronal activity into three temporal frequency bands. In all three frequency bands, consistent and significant increases in connectivity were found between the dorsolateral PFC and the basal ganglia in patients with schizophrenia. Other groups found that the disease was mainly associated with decreases in connectivity, notably between the PCC and the cerebellum,[78] the mediodorsal thalamus and the ACC,[79] and the ventral PFC and the amygdala.[80] Lui et al.[81] performed seed-based correlation in regions of the brain that had a decrease in gray matter volume—specifically, the superior temporal gyrus, the middle temporal gyrus and the ACC. The researchers could not find group-level differences in connectivity, although altered functional connectivity with the right superior temporal gyrus and the middle temporal gyrus correlated with the severity of a patient's clinical symptoms.

Jafri et al.[30] used ICA to generate several components, including the DMN, parietal, visual, frontal and temporal independent components. Patients with schizophrenia exhibited increased connectivity between many of these components compared with controls. By using the 100-ROI approach to parcellate the brain,[65] however, Liang et al.[82] showed that patients with schizophrenia had widespread decreases in connectivity. This latter study largely used the same set of patients who had previously exhibited increases in connectivity within functional networks.[72] Conceivably, separate and opposing physiological processes could exist at different spatial scales, and such an assertion warrants further attention. Liu et al.[48] extended Liang and colleagues' 100-ROI approach[82] by measuring graph theoretical variables in a large group of individuals that overlapped substantially with the group in the Liang et al. study. The researchers found decreases in connectivity strength and disruptions in small-world properties in patients with schizophrenia, which were characterized by reductions in the clustering coefficients and long connectivity path lengths. Measurements that characterize small-world properties also correlated with duration of illness. One major difference between the Liu et al. study and most other connectivity investigations was that the former used partial correlation analysis to eliminate the influence of around 98 regions for every pairwise partial correlation performed. This method was previously shown to generate vastly different brain topology maps from typical functional networks, with the former resembling local connectivity networks rather than spatially distributed networks.[38] Of note, different ROI parcellation schemes generate diverse graph network results.[83]

As the above discussions illustrate, vastly differing methods have often been employed in the schizophrenia fcMRI literature; therefore, cross-study comparisons are difficult or impossible to make. Other contributing factors that prevent generalizations from being made with respect to this disorder include the potential complication of disparate disease subtypes and the multitude of prescribed medications that have varying mechanisms of action. As a starting point, the schizophrenia fcMRI field would benefit from formulating more-homogeneous experimental

Box 3 | Distinguishing between two groups of individuals

Most published studies compare patient populations with healthy controls by means of a two-sample, two-tailed t-test to demonstrate statistically significant differences with disease (after correction for multiple comparisons). Comparisons between different patient populations can be made on the basis of consideration of a single difference in functional connectivity (univariate analysis)[28,55] or across a combination of regions to potentially achieve much higher discriminative power (multivariate analysis).

Multiregion pattern analysis of task-evoked fMRI images has been used with considerable success to predict certain mental states (Supplementary References online). These classification algorithms are general statistical frameworks that can also be applied to functional connectivity measurements. The first step is to select characteristics (features) to be used as discriminators in classification, such as the choice of functional connectivity pairs in the present context. Often, regions that individually show a statistical difference between groups are selected as features in multivariate classification. A more principled approach to feature selection would require a more complex understanding of the underlying disease mechanism (or a basis function[158,159]). For example, autism is hypothesized to involve a relative decrease in global connectivity.[114] In this case, increased sensitivity might be accomplished by detecting global changes such as those constructed with graph theory, rather than by detecting localized connectivity deficits. In other diseases, the deficit might be highly localized,[63] allowing feature selection to be confined to the relevant locations. Many classification algorithms are available, such as those based on linear or nonlinear discriminants, non-parametric density estimation, and support vector machines (Supplementary References online). Success of classification relies on accurate clinical diagnosis to train the classifier. In situations where clinical diagnostic accuracy is low or where unknown subgroups of disease states could exist, more-exploratory analyses, such as cluster analysis, might be useful in detecting group heterogeneity. Excellent reviews of pattern recognition and classification are available.[160,161]

designs than currently exist. For seed-based analysis, initiating a move away from spatially extended ROI definitions that average over functionally heterogeneous brain regions and adopting more spatially restricted brain parcellation strategies would be prudent.[41] For ICA analysis, defined independent components should be comparable across studies. Indeed, these components should be ideally compared against standardized spatial templates of known functional networks or subnetworks. Following the standardization of techniques, reproducible results need to be established across studies and across data sets in order for the schizophrenia fcMRI field to develop. Depository databases, such as BrainSCAPE,[9] represent essential data-sharing entities for contributing and gaining access to multiple data sets to perform reproducibility studies. From facilities that contain a sufficiently large collection of data, researchers might be able to establish population subtypes, according to the nature and severity of disease symptoms, extent of recovery, the types of comorbidities present, or the medications used by patients. Reproducible results that are established by use of standardized techniques can also serve as experimental controls for validating new data sets before more methodologically creative endeavors are undertaken.

Autism

Only a few published articles exist in the autism fcMRI literature. A strength of these publications, however, is the relative agreement exhibited by the cross-study results, which mostly relate to the DMN. In patients with autism, Cherkassky et al.[84] and Monk et al.[85] both reported reductions in inter-regional connectivity in the anterior–posterior axis of the DMN, specifically between the ventral ACC or medial PFC and the PCC[84], and between the dorsomedial PFC and the PCC.[85] Kennedy and Courchesne[86] examined the DMN and DAN using a seed-based approach that defined each network as a single ROI—an approach that was conceptually similar to network-level ICA studies.[29] Compared with controls, patients with autism exhibited decreased connectivity in the medial PFC and the lateral parietal and angular gyrus regions of the DMN. However, no changes between the two groups were detected in the DAN. Cherkassky et al.[84] reported decreases in connectivity between the parahippocampal gyrus and other DMN structures in the group with autism, whereas Monk and colleagues[85] reported increases in connectivity between these regions in these individuals. The reason for these discrepant connectivity results is unclear, although fMRI acquisition length might be a contributing factor (24 s rest periods spliced together[84] versus 10 min of continuous acquisition[85]). In addition to group connectivity differences, Monk et al.[85] also found a correlation between the severity of restricted and repetitive behaviors and the strength of parahippocampal gyrus–PCC connectivity.

Attention-deficit hyperactivity disorder

Using a seed-based approach, Tian et al.[87] demonstrated that individuals with attention-deficit hyperactivity disorder (ADHD) had increases in connectivity between the dorsal ACC and the frontoinsular cortex, the thalamus and the cerebellum. A subsequent study[49] used a 100-ROI brain parcellation and graph theoretical analysis to reveal altered small-world properties, suggestive of increased short-range connectivity and decreased long-range connectivity in the ADHD group. Another study reported a decrease in the correlation between the PCC and medial PFC, as well as a reduction in the negative correlation between the PCC and ACC.[88] Together, the findings from this study further support the idea that long-range disconnection might be a feature of ADHD.

Other diseases

A number of original fcMRI studies have been performed with respect to various other neuropsychiatric diseases; however, the results of these studies are awaiting independent follow-up investigations.

Church et al.[89] investigated the effect of Tourette syndrome on two specific functional networks, the task control network and the cingulo-opercular network.[40,90] These researchers had previously characterized the developmental profile of functional connectivity changes in healthy children and adults, and found that alterations—both increases and decreases—in connectivity were common with increasing age.[90] In the newer study,[89] Church and colleagues used functionally derived focal ROIs to construct a connectivity matrix. The researchers then compared this matrix in 33 patients aged 10–15 years with Tourette syndrome and a similar number of age-matched controls. Patients with Tourette syndrome were less well developed in terms of their connectivity network than were controls. Indeed, individuals with the disorder exhibited both increases and decreases in connectivity strengths with age. Interestingly, individual pairwise correlation values were not markedly different between patients with Tourette syndrome and the control group. However, when multiple functional connectivity values were collectively assessed, the group difference reached statistical significance and, hence, indicated a pattern of developmental delay in people with the disorder. The results of this study suggest that connectivity at the network level might be preferentially disrupted over specific inter-regional disturbances, and could help provide mechanistic insights into the disease process.[89]

He et al.[91] used a seed-based approach focused on the dorsal and ventral attention networks to study functional connectivity changes in patients with stroke who exhibited focal right-hemisphere lesions that caused spatial neglect. This study was not performed strictly in the resting-state; however, deterministic task-evoked responses were regressed out of the time course before functional connectivity analysis was performed.[27,92] Directly lesioned areas, such as the ventral attention network, showed an expected pattern of disruption in connectivity. The structurally normal DAN also exhibited disrupted connectivity, however, suggesting that a functional interaction existed between the two systems before stroke,[93] and that one network was functionally altered after another was physically lesioned. Furthermore, the degree of attention network connectivity correlated with severity of spatial neglect and recovery.

To date, only three studies have investigated fcMRI changes in patients with temporal lobe epilepsy. As each investigation has examined a different network, the results of these studies have not yet been reproduced. Waites et al.[94] demonstrated decreased connectivity in the language network in patients with temporal lobe epilepsy compared with controls, although task-evoked fMRI responses were similar between the two groups. Patients with this form of epilepsy also exhibited disrupted connectivity within the temporal lobe, including the hippocampus,[95] and within a frontoparietal network[96] that most closely resembled the control and salience networks. In another study, patients with generalized seizures showed altered connectivity between the PCC and other parts of the DMN.[97]

Various other neurological conditions have been studied by the fcMRI approach. Lowe et al.[98] performed one of the first fcMRI pathophysiology studies, demonstrating decreases in inter-regional somatomotor connectivity in patients with multiple sclerosis. Evidence from De Luca et al.,[99] while not directly validating the work of Lowe and colleagues, did provide support for the latter's findings. In a single case report, a patient with traumatic brain injury who presented with memory loss exhibited disrupted connectivity between the left hippocampus and other structures, as well as a reduction in the volume of the left hippocampus.[100] By use of ICA, individuals with amyotrophic lateral sclerosis were shown to have reduced connectivity in major canonical regions of the DMN and the premotor cortex compared with controls.[101] Blind patients demonstrated decreases in connectivity between visual and other regions of the brain, notably between the homotopic visual cortex and the somatomotor, somatosensory and parietal cortices.[102,103] In an ICA analysis of the DMN, patients with diabetic peripheral neuropathic pain displayed increases in connectivity in lateral parietal and frontal pole areas of the network, but decreases in connectivity in the subgenual medial PFC.[104] A population study of females with post-traumatic stress disorder revealed that individuals with the condition had decreased connectivity between the PCC and other areas of the DMN compared with healthy women.[105] Patients in a persistent vegetative state demonstrated existent[106] but decreased[107] DMN connectivity in comparison with controls, although one should be aware that similar decreases in DMN connectivity are associated with deep sleep.[108] Further studies are needed to dissociate disruptions as a result of a loss of consciousness from those specific to the persistent vegetative state.

Normal development and aging

Functional networks exist at a very young age, and are even seen in premature infants scanned at term-equivalent age.[109] The unique aspect of the functional connectivity profile in young individuals is the absence of long-range connections. Spatially localized networks, such as the sensorimotor and visual system networks, exist as functionally coherent units very early in life,[109,110] but other networks that span multiple cortical lobes do not develop their characteristic topography until much later.[111] Indeed, some networks do not fully mature until young adulthood is reached.[43,90,112]

Many neuropsychiatric diseases that manifest at an early age have been linked to developmental abnormalities, such as delayed maturation of cortical thickness in ADHD,[113] and possible increases in local to global connectivity in autism.[114] The fcMRI literature on these diseases, as well as Tourette syndrome (a possible co-morbidity of ADHD), suggests that a similar developmental theme might extend to observations relating to intrinsic activity, although many more studies are needed to substantiate this assertion. Other diseases such as AD typically manifest during adulthood, and our understanding of these disorders stands to benefit from investigating variation between healthy individuals[115] and people with disease as both groups age.

Use of regionally confined measures

Regional homogeneity has been shown to be modulated in a variety of diseases, and multivariate classification schemes have been used to determine the diagnostic value of this measure in disease (Supplementary References online). Like functional connectivity measurements, this technique shows promise as a clinically diagnostic tool; however, the functional interpretation of changes in regional homogeneity is less straightforward than for distinct inter-regional connectivity alterations. One interesting issue to address will be how changes in regional homogeneity correlate with changes in functional connectivity within the same regions of the brain.

Other regionally confined measures, such as the amplitude of intrinsic activity, have been reported and compared between disease and control groups.[116] The spatial distribution of the amplitude of spontaneous fluctuations, which is highest in the PCC and the medial PFC and lowest in the cerebellum and subcortical structures, might be related to metabolic correlates of neuronal activity.[56]

Neurosurgical application

Arguably, one of the most widely used clinical applications for traditional task-evoked fMRI is preoperative functional mapping in the planning of brain tumor and epilepsy resections.[117] In this application, the task-evoked imaging technique is primarily used to localize areas associated with motor and language function, so that these regions can be avoided during surgery, thereby reducing the risk of damage. Similarly, fcMRI can be used for presurgical identification and localization of functional networks. Moreover, the analysis of intrinsic signaling potentially offers several advantages over task-evoked fMRI mapping. Resting-state scans completely avoid performance-related confounds, which are commonly present in patients with motor or cognitive deficits. Furthermore, patients exhibit increased tolerance and compliance during scans in the absence of task demands. Excessive head motion and incorrect task performance are common problems in children, although major resting state networks have been successfully imaged with the use of standard anesthetics and sedatives in this age group.[109,110,118–120] One should be aware, however, that functional connectivity changes occur under deep anesthesia and in deep sleep.[6,108] Indeed, the detection of subtle fcMRI changes during various cognitive or resting states remains an active area of investigation.[121–123]

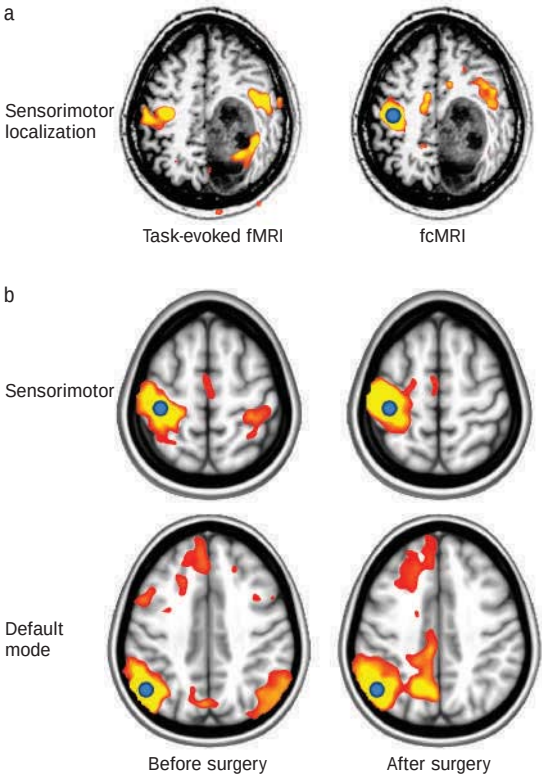

Figure 3 | Functional connectivity and brain lesions. a | A large brain tumor (glioblastoma multiforme) can be seen in the right hemisphere, causing localized necrosis and compression effects. Task-evoked functional MRI (fMRI) was performed during bilateral finger tapping. Functional connectivity MRI (fcMRI) was performed using a seed in the left sensorimotor cortex (blue circle). Both techniques could map sensorimotor cortex near the tumor even though compression effects had shifted this cortical tissue anteriorly. Intraoperative cortical stimulation mapping confirmed MRI localization. Artifactual activation is visible inside the tumor on task-evoked fMRI but not fcMRI. In other patients with brain tumors, task-evoked fMRI failed to generate sensorimotor localization, probably because neurological deficits prevented proper task performance.[54] Permission obtained from Lippincott Williams & Wilkins © Zhang, D. et al. Neurosurgery (in press). b | Neurosurgical resection of the corpus callosum. In this case study,[118] a 6 year-old child was scanned at rest before and after complete sectioning of the corpus callosum to treat intractable epilepsy. Many functional networks, including the sensorimotor and default mode network (seed, blue circle), reproducibly demonstrate interhemispheric functional connectivity. After corpus callosotomy, however, these networks lose the ability to synchronize their intrinsic activity across hemispheres. For an expanded discussion, see Supplementary Figure Legend 3 online.

Another advantage of fcMRI over task-evoked imaging is that the former enables multiple functional networks to be imaged simultaneously, thereby dramatically reducing the acquisition time needed for a comprehensive assessment of functional network status.

Several studies performed in the sensorimotor cortex have examined the potential use of fcMRI in neurosurgery.[124,125] Not only did fcMRI compare favorably with task-evoked fMRI for accurately identifying this cortical region (Figure 3a),[54,124,125] but fcMRI also fared well in this endeavor against the 'gold standard' technique used in neurosurgery, namely intraoperative cortical stimulation mapping.[54,125] Like cortical stimulation mapping, fcMRI could distinguish a hand representation from a tongue representation, a result that is consistent with the motor homunculus.[125] As a result of their dense anatomical interconnectivity, somatomotor and somatosensory functional activities are usually highly correlated during both task-evoked fMRI and fcMRI, although both types of activity can be clearly dissociated with partial correlation.[54] This dissociation provides a detailed delineation of the two systems and, more importantly, demarcates the central sulcus, which provides supporting mapping information to intraoperative somatosensory evoked potential mapping.

Both seed-based analysis[54,125] and ICA[54,124] have the capacity to be used in presurgical functional mapping, although whether a difference in detection sensitivity exists for simple versus sophisticated analysis methods remains to be determined, especially as scan length is a critical parameter in the clinical setting. The vast majority of patients with brain tumors (or epilepsy) have morphologically undistorted anatomy in the hemisphere contralateral to the insult. In these cases, a seed-based approach involving the use of standardized seeds in the healthy hemisphere would provide fast and reliable results with minimal manual intervention. In other cases with extensive distortion of anatomy or with functional reorganization, ICA would be the preferred method.[54] Future studies might wish to extend the current findings and examine other functional networks, notably the language network.[126] The feasibility of mapping the language network has previously been demonstrated,[127] although the high variability in localizing areas critical for language production[128] suggests that ICA might be preferred over a seed-based approach as the analysis method.

Correlates of intrinsic activity

If the measurement of intrinsic activity is to move beyond simply serving as a biomarker of disease in the clinical arena, the physiological mechanisms responsible for intrinsic signaling need to be understood. This understanding will probably require an integrative approach involving knowledge of various relationships, such as functional activity with underlying anatomical structure, and hemodynamics with electrical activity.

Structural correlates

The spatial structures of coherent spontaneous BOLD fluctuations provided the most convincing preliminary evidence that the BOLD signal was predominantly of neuronal origin rather than non-neuronal, artifactual noise. By comparison with gross dissections and invasive tracers in nonhuman primates, these spontaneous fluctuations were observed to be synchronous within brain regions that were anatomically connected by large white matter tracts.[6] For example, many functional networks exhibit synchronous activity in homotopic areas of the left and right hemispheres, and this functional connectivity is probably achieved via an anatomical connection in the

corpus callosum. More-definitive proof of a structural basis for left–right hemisphere functional connectivity came from studies of structural deficits stemming from abnormal development, brain lesions or neurosurgical intervention (Figure 3b).[118,129,130] More generally, an underlying theme that emerges between functional and structural connectivity comparisons is that coherent BOLD fluctuations are present in glutamatergically connected regions of the brain. The degree to which other neurotransmitters contribute to BOLD fluctuations remains to be determined.[131]

Connectivity comparisons have also been performed in a noninvasive manner by examining fcMRI alongside diffusion-weighted imaging (DWI). This latter imaging technique reconstructs anatomical pathways on the basis of the restricted Brownian motion of water molecules, which preferentially move parallel to the fiber tracts.[132] Functionally correlated networks demonstrate a high degree of correspondence with DWI-reconstructed anatomy in a variety of networks.[7,133] Indeed, in the thalamocortical network, the results of fcMRI and DWI have been shown to correspond well with each other, thereby providing cross-validation of the two techniques. In addition, both techniques correspond well to histological delineation and invasive tract tracing, thereby providing a 'gold standard' validation of the two techniques.[134] The advantage of combining fcMRI with DWI is that together these techniques can provide a comprehensive characterization of connectivity in all areas of the brain. The data from such analyses are invaluable for creating structural and functional 'connectomes' of brain architecture.[135] The need for both types of connectomes stems from the observation that these two measures of brain architecture do not always agree. This is often because functional connectivity reflects activity generated across multiple synaptic connections, whereas polysynaptic structural connectivity, determined on a large scale throughout the brain, cannot be imaged with high fidelity with currently available tools (see Figure 1b, lower panel for an example of polysynaptic connections between the cortex and cerebellum).[6,136,137] In agreement with this observation, a multi-ROI analysis of functional and structural connectivity showed that many functional pathways did not have corresponding direct structural pathways.[7] A proportion of these discrepant results can be explained by indirect structural pathways linking functional units. However, one should be aware that DWI is prone to missing connections and also establishing false connections where fibers cross and where fibers diverge from 'bottleneck' regions of the brain. The search for solutions to these problems is an active area of investigation.[138,139]

The degree of structural connectivity has been shown to correlate with the strength of functional connectivity,[140] thereby providing a potentially straightforward structural explanation for many of the changes in functional connectivity in disease states. Indeed, in patients with multiple sclerosis, DWI measures of connectivity in the corpus callosum correlated with fcMRI strength in the sensorimotor cortex[141] and in individuals with autism, morphometric measures of the corpus callosum size correlated with fcMRI strength between the PCC and the medial PFC.[84] Furthermore, combining fcMRI with DWI should benefit preoperative neurosurgical planning. This combined imaging approach should allow avoidance of resection of white matter tracts linking functional networks near tumor sites and epileptic foci.

Electrophysiological correlates

Observations of intrinsic neuronal activity are not confined to fMRI, and have been reported by use of a variety of measurement modalities (Supplementary References online). Relating the findings from fMRI to the results from other approaches is important to achieve a better integrated understanding of the physiology of intrinsic activity.[142] Several dual-modality studies have demonstrated high correlations between spontaneous BOLD fluctuations, slow cortical potentials, and the band-limited power of fast electrical activity (Supplementary References online). Interestingly, electrophysiological evidence indicates that infraslow (<0.1 Hz) spontaneous fluctuations can display marked changes in synchrony over time.[143] Future studies could investigate whether similar dynamics in neuronal synchrony are observed in spontaneous fluctuations of the fMRI BOLD signal. In the same way that intrinsic activity was masked through trial-averaging in traditional fMRI experiments,[144] temporal dynamics in functional connectivity might be masked through time-averaging.

Conclusions

Intrinsic neuronal activity is present in all gray matter regions tested to date and exhibits coherent signaling that is both specific in spatial distribution and consistent across a spectrum of behaviors and states of consciousness. Several well-established techniques are available for analyzing intrinsic neuronal signaling imaged by BOLD fMRI and for performing group classification. Results from studies in patient populations show that BOLD fMRI can detect altered functional connectivity in individuals with certain diseases, thereby distinguishing patients from healthy controls with high sensitivity and high specificity, and demonstrating a correlation between connectivity strength and disease severity. Many challenges must be overcome before clinical adoption is feasible, notably the ability to discriminate among various diseases on the basis of functional connectivity changes and the applicability of using fcMRI in single patients.

The functional importance of intrinsic neuronal activity remains to be determined. The ongoing nature of intrinsic neuronal activity has led some to suggest a role for intrinsic signaling in synaptic homeostasis, as well as in predicting and responding to future environmental events.[145] Early empirical evidence suggests that intrinsic activity is not independent of other brain processes, and seems to be modulated with task performance.[146] Thus, intrinsic activity might be coupled with task-evoked signals through consistent phase relationships in neuronal activity occurring at various frequencies ('nested' frequencies) or through power relationships at various frequencies.[147,148] Importantly, intrinsic activity alone can account for a percentage of the bias and variability observed in simple

perceptual[149,150] and behavioral[151] parameters. It is not entirely inconceivable that interaction between intrinsic and evoked neuronal activity can be extrapolated to more-complex systems involving higher cognitive functions that affect complex perceptions and behaviors such, as those that may underlie neuropsychiatric diseases. Ultimately, measurement of intrinsic activity might provide a clinical diagnostic tool, as well as helping us to understand the physiology behind some of the most complex diseases that affect the human brain.

Review criteria

PubMed was searched for published literature on intrinsic brain activity and functional MRI (fMRI) using the terms "resting state fMRI", "functional connectivity fMRI", "intrinsic activity fMRI" and "spontaneous activity fMRI". Articles deemed relevant to the basic science of intrinsic activity and to clinical pathophysiology relating to such signaling were selected for review. The literature search was extended to the reference lists of these articles and papers identified through Scopus and Google Scholar.

1. Bahcall, N. A., Ostriker, J. P., Perlmutter, S. & Steinhardt, P. J. The cosmic triangle: revealing the state of the universe. Science 284, 1481–1488 (1999).
2. Raichle, M. E. & Mintun, M. A. Brain work and brain imaging. Annu. Rev. Neurosci. 29, 449–476 (2006).
3. Llinas, R. R. I of the Vortex: From Neurons to Self (The MIT Press, Cambridge, 2001).
4. Fox, M. D., Snyder, A. Z., Zacks, J. M. & Raichle, M. E. Coherent spontaneous activity accounts for trial-to-trial variability in human evoked brain responses. Nat. Neurosci. 9, 23–25 (2006).
5. Smith, S. M. et al. Correspondence of the brain's functional architecture during activation and rest. Proc. Natl Acad. Sci. USA 106, 13040–13045 (2009).
6. Vincent, J. L. et al. Intrinsic functional architecture in the anesthetized monkey brain. Nature 447, 83–86 (2007).
7. Honey, C. J. et al. Predicting human resting-state functional connectivity from structural connectivity. Proc. Natl Acad. Sci. USA 106, 2035–2040 (2009).
8. Beckmann, C. F., DeLuca, M., Devlin, J. T. & Smith, S. M. Investigations into resting-state connectivity using independent component analysis. Philos. Trans. R. Soc. Lond. B Biol. Sci. 360, 1001–1013 (2005).
9. Fox, M. D. & Raichle, M. E. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat. Rev. Neurosci. 8, 700–711 (2007).
10. He, B. J., Snyder, A. Z., Zempel, J. M., Smyth, M. D. & Raichle, M. E. Electrophysiological correlates of the brain's intrinsic large-scale functional architecture. Proc. Natl Acad. Sci. USA 105, 16039–16044 (2008).
11. Lu, H. et al. Synchronized delta oscillations correlate with the resting-state functional MRI signal. Proc. Natl Acad. Sci. USA 104, 18265–18269 (2007).
12. Friston, K. J., Frith, C. D., Liddle, P. F. & Frackowiak, R. S. Functional connectivity: the principal-component analysis of large (PET) data sets. J. Cereb. Blood Flow Metab. 13, 5–14 (1993).
13. Biswal, B., Yetkin, F. Z., Haughton, V. M. & Hyde, J. S. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn. Reson. Med. 34, 537–541 (1995).
14. Fox, M. D. et al. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc. Natl Acad. Sci. USA 102, 9673–9678 (2005).
15. Lowe, M. J., Mock, B. J. & Sorenson, J. A. Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations. Neuroimage 7, 119–132 (1998).
16. Xiong, J., Parsons, L. M., Gao, J. H. & Fox, P. T. Interregional connectivity to primary motor cortex revealed using MRI resting state images. Hum. Brain Mapp. 8, 151–156 (1999).
17. Cordes, D. et al. Mapping functionally related regions of brain with functional connectivity MR imaging. AJNR Am. J. Neuroradiol. 21, 1636–1644 (2000).
18. Greicius, M. D., Krasnow, B., Reiss, A. L. & Menon, V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc. Natl Acad. Sci. USA 100, 253–258 (2003).
19. Salvador, R., Suckling, J., Schwarzbauer, C. & Bullmore, E. Undirected graphs of frequency-dependent functional connectivity in whole brain networks. Philos. Trans. R. Soc. Lond. B Biol. Sci. 360, 937–946 (2005).
20. Damoiseaux, J. S. et al. Consistent resting-state networks across healthy subjects. Proc. Natl Acad. Sci. USA 103, 13848–13853 (2006).
21. Roebroeck, A., Formisano, E. & Goebel, R. Mapping directed influence over the brain using Granger causality and fMRI. Neuroimage 25, 230–242 (2005).
22. Friston, K. J., Harrison, L. & Penny, W. Dynamic causal modelling. Neuroimage 19, 1273–1302 (2003).
23. Honey, C. J., Kotter, R., Breakspear, M. & Sporns, O. Network structure of cerebral cortex shapes functional connectivity on multiple time scales. Proc. Natl Acad. Sci. USA 104, 10240–10245 (2007).
24. Birn, R. M., Diamond, J. B., Smith, M. A. & Bandettini, P. A. Separating respiratory-variation-related fluctuations from neuronal-activity-related fluctuations in fMRI. Neuroimage 31, 1536–1548 (2006).
25. Cordes, D. et al. Frequencies contributing to functional connectivity in the cerebral cortex in "resting-state" data. AJNR Am. J. Neuroradiol. 22, 1326–1333 (2001).
26. Fransson, P. Spontaneous low-frequency BOLD signal fluctuations: an fMRI investigation of the resting-state default mode of brain function hypothesis. Hum. Brain Mapp. 26, 15–29 (2005).
27. Arfanakis, K. et al. Combining independent component analysis and correlation analysis to probe interregional connectivity in fMRI task activation datasets. Magn. Reson. Imaging 18, 921–930 (2000).
28. Greicius, M. D., Srivastava, G., Reiss, A. L. & Menon, V. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. Proc. Natl Acad. Sci. USA 101, 4637–4642 (2004).
29. Filippini, N. et al. Distinct patterns of brain activity in young carriers of the APOE- 4 allele. Proc. Natl Acad. Sci. USA 106, 7209–7214 (2009).
30. Jafri, M. J., Pearlson, G. D., Stevens, M. & Calhoun, V. D. A method for functional network connectivity among spatially independent resting-state components in schizophrenia. Neuroimage 39, 1666–1681 (2008).
31. Greicius, M. D. et al. Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. Biol. Psychiatry 62, 429–437 (2007).
32. Seeley, W. W. et al. Dissociable intrinsic connectivity networks for salience processing and executive control. J. Neurosci. 27, 2349–2356 (2007).
33. Fox, M. D., Zhang, D., Snyder, A. Z. & Raichle, M. E. The global signal and observed anticorrelated resting state brain networks. J. Neurophysiol. 101, 3270–3283 (2009).
34. Chang, C. & Glover, G. H. Effects of model-based physiological noise correction on default mode network anti-correlations and correlations. Neuroimage 47, 1448–1459 (2009).
35. Fransson, P. & Marrelec, G. The precuneus/posterior cingulate cortex plays a pivotal role in the default mode network: evidence from a partial correlation network analysis. Neuroimage 42, 1178–1184 (2008).
36. Vincent, J. L. et al. Coherent spontaneous activity identifies a hippocampal–parietal memory network. J. Neurophysiol. 96, 3517–3531 (2006).
37. Zhang, D. et al. Intrinsic functional relations between human cerebral cortex and thalamus. J. Neurophysiol. 100, 1740–1748 (2008).
38. Salvador, R. et al. Neurophysiological architecture of functional magnetic resonance images of human brain. Cereb. Cortex 15, 1332–1342 (2005).
39. Smith, S. M., Miller, K. L., Mackay, C. E., Filippini, N. & Beckmann, C. F. Towards a functional hierarchy of resting-state networks [abstract 402 SU-PM]. Presented at the 15th Annual Meeting, Organization for Human Brain Mapping.
40. Dosenbach, N. U. et al. Distinct brain networks for adaptive and stable task control in humans. Proc. Natl Acad. Sci. USA 104, 11073–11078 (2007).
41. Hagmann, P. et al. Mapping the structural core of human cerebral cortex. PLoS Biol. 6, e159 (2008).
42. Achard, S., Salvador, R., Whitcher, B., Suckling, J. & Bullmore, E. A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs. J. Neurosci. 26, 63–72 (2006).
43. Fair, D. A. et al. Functional brain networks develop from a "local to distributed" organization. PLoS Comput. Biol. 5, e1000381 (2009).
44. Watts, D. J. & Strogatz, S. H. Collective dynamics of 'small-world' networks. Nature 393, 440–442 (1998).
45. Bullmore, E. & Sporns, O. Complex brain networks: graph theoretical analysis of structural and functional systems. Nat. Rev. Neurosci. 10, 186–198 (2009).
46. He, Y. et al. Uncovering intrinsic modular organization of spontaneous brain activity in humans. PLoS One 4, e5226 (2009).

47. Supekar, K., Menon, V., Rubin, D., Musen, M. & Greicius, M. D. Network analysis of intrinsic functional brain connectivity in Alzheimer's disease. PLoS Comput. Biol. 4, e1000100 (2008).
48. Liu, Y. et al. Disrupted small-world networks in schizophrenia. Brain 131, 945–961 (2008).
49. Wang, L. et al. Altered small-world brain functional networks in children with attention-deficit/hyperactivity disorder. Hum. Brain Mapp. 30, 638–649 (2009).
50. Cohen, A. L. et al. Defining functional areas in individual human brains using resting functional connectivity MRI. Neuroimage 41, 45–57 (2008).
51. Zang, Y., Jiang, T., Lu, Y., He, Y. & Tian, L. Regional homogeneity approach to fMRI data analysis. Neuroimage 22, 394–400 (2004).
52. Baumgartner, R., Somorjai, R., Summers, R. & Richter, W. Assessment of cluster homogeneity in fMRI data using Kendall's coefficient of concordance. Magn. Reson. Imaging 17, 1525–1532 (1999).
53. Shehzad, Z. et al. The resting brain: unconstrained yet reliable. Cereb. Cortex 19, 2209–2229 (2009).
54. Zhang, D. et al. Preoperative sensorimotor mapping in brain tumor patients using spontaneous fluctuations in neuronal activity imaged with fMRI: initial experience. Neurosurgery (in press).
55. Li, S. J. et al. Alzheimer disease: evaluation of a functional MR imaging index as a marker. Radiology 225, 253–259 (2002).
56. Raichle, M. E. et al. A default mode of brain function. Proc. Natl Acad. Sci. USA 98, 676–682 (2001).
57. Sorg, C. et al. Selective changes of resting-state networks in individuals at risk for Alzheimer's disease. Proc. Natl Acad. Sci. USA 104, 18760–18765 (2007).
58. Corbetta, M. & Shulman, G. L. Control of goal-directed and stimulus-driven attention in the brain. Nat. Rev. Neurosci. 3, 201–215 (2002).
59. Wang, L. et al. Changes in hippocampal connectivity in the early stages of Alzheimer's disease: evidence from resting state fMRI. Neuroimage 31, 496–504 (2006).
60. Allen, G. et al. Reduced hippocampal functional connectivity in Alzheimer disease. Arch. Neurol. 64, 1482–1487 (2007).
61. Zhang, H. Y. et al. Detection of PCC functional connectivity characteristics in resting-state fMRI in mild Alzheimer's disease. Behav. Brain Res. 197, 103–108 (2009).
62. Buckner, R. L. et al. Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. J. Neurosci. 25, 7709–7717 (2005).
63. Seeley, W. W., Crawford, R. K., Zhou, J., Miller, B. L. & Greicius, M. D. Neurodegenerative diseases target large-scale human brain networks. Neuron 62, 42–52 (2009).
64. Wang, K. et al. Altered functional connectivity in early Alzheimer's disease: a resting-state fMRI study. Hum. Brain Mapp. 28, 967–978 (2007).
65. Tzourio-Mazoyer, N. et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15, 273–289 (2002).
66. Wang, K. et al. Discriminative analysis of early Alzheimer's disease based on two intrinsically anti-correlated networks with resting-state fMRI. Med. Image Comput. Comput. Assist. Interv. Int. Conf. Med. Image Comput. Comput. Assist. Interv. 9, 340–347 (2006).
67. Anand, A. et al. Activity and connectivity of brain mood regulating circuit in depression: a functional magnetic resonance study. Biol. Psychiatry 57, 1079–1088 (2005).
68. Anand, A. et al. Antidepressant effect on connectivity of the mood-regulating circuit: an FMRI study. Neuropsychopharmacology 30, 1334–1344 (2005).
69. Anand, A., Li, Y., Wang, Y., Lowe, M. J. & Dzemidzic, M. Resting state corticolimbic connectivity abnormalities in unmedicated bipolar disorder and unipolar depression. Psychiatry Res. 171, 189–198 (2009).
70. Jones, E. G. The Thalamus (Cambridge University Press, Cambridge, 2007).
71. Whitfield-Gabrieli, S. et al. Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. Proc. Natl Acad. Sci. USA 106, 1279–1284 (2009).
72. Zhou, Y. et al. Functional disintegration in paranoid schizophrenia using resting-state fMRI. Schizophr. Res. 97, 194–205 (2007).
73. Dosenbach, N. U. et al. A core system for the implementation of task sets. Neuron 50, 799–812 (2006).
74. Vincent, J. L., Kahn, I., Snyder, A. Z., Raichle, M. E. & Buckner, R. L. Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. J. Neurophysiol. 100, 3328–3342 (2008).
75. Zhou, Y. et al. Functional dysconnectivity of the dorsolateral prefrontal cortex in first-episode schizophrenia using resting-state fMRI. Neurosci. Lett. 417, 297–302 (2007).
76. Zhou, Y. et al. Altered resting-state functional connectivity and anatomical connectivity of hippocampus in schizophrenia. Schizophr. Res. 100, 120–132 (2008).
77. Salvador, R. et al. Frequency based mutual information measures between clusters of brain regions in functional magnetic resonance imaging. Neuroimage 35, 83–88 (2007).
78. Bluhm, R. L. et al. Spontaneous low-frequency fluctuations in the BOLD signal in schizophrenic patients: anomalies in the default network. Schizophr. Bull. 33, 1004–1012 (2007).
79. Welsh, R. C., Chen, A. C. & Taylor, S. F. Low-frequency BOLD fluctuations demonstrate altered thalamocortical connectivity in schizophrenia. Schizophr. Bull. doi:10.1093/schbul/sbn145.
80. Hoptman, M. J. et al. Amygdalofrontal functional disconnectivity and aggression in schizophrenia. Schizophr. Bull. doi:10.1093/schbul/sbp012.
81. Lui, S. et al. Association of cerebral deficits with clinical symptoms in antipsychotic-naive first-episode schizophrenia: an optimized voxel-based morphometry and resting state functional connectivity study. Am. J. Psychiatry 166, 196–205 (2009).
82. Liang, M. et al. Widespread functional disconnectivity in schizophrenia with resting-state functional magnetic resonance imaging. Neuroreport 17, 209–213 (2006).
83. Wang, J. et al. Parcellation-dependent small-world brain functional networks: a resting-state fMRI study. Hum. Brain Mapp. 30, 1511–1523 (2009).
84. Cherkassky, V. L., Kana, R. K., Keller, T. A. & Just, M. A. Functional connectivity in a baseline resting-state network in autism. Neuroreport 17, 1687–1690 (2006).
85. Monk, C. S. et al. Abnormalities of intrinsic functional connectivity in autism spectrum disorders. Neuroimage 47, 764–772 (2009).
86. Kennedy, D. P. & Courchesne, E. The intrinsic functional organization of the brain is altered in autism. Neuroimage 39, 1877–1885 (2008).
87. Tian, L. et al. Altered resting-state functional connectivity patterns of anterior cingulate cortex in adolescents with attention deficit hyperactivity disorder. Neurosci. Lett. 400, 39–43 (2006).
88. Castellanos, F. X. et al. Cingulate-precuneus interactions: a new locus of dysfunction in adult attention-deficit/hyperactivity disorder. Biol. Psychiatry 63, 332–337 (2008).
89. Church, J. A. et al. Control networks in paediatric Tourette syndrome show immature and anomalous patterns of functional connectivity. Brain 132, 225–238 (2009).
90. Fair, D. A. et al. Development of distinct control networks through segregation and integration. Proc. Natl Acad. Sci. USA 104, 13507–13512 (2007).
91. He, B. J. et al. Breakdown of functional connectivity in frontoparietal networks underlies behavioral deficits in spatial neglect. Neuron 53, 905–918 (2007).
92. Fair, D. A. et al. A method for using blocked and event-related fMRI data to study "resting state" functional connectivity. Neuroimage 35, 396–405 (2007).
93. Fox, M. D., Corbetta, M., Snyder, A. Z., Vincent, J. L. & Raichle, M. E. Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. Proc. Natl Acad. Sci. USA 103, 10046–10051 (2006).
94. Waites, A. B., Briellmann, R. S., Saling, M. M., Abbott, D. F. & Jackson, G. D. Functional connectivity networks are disrupted in left temporal lobe epilepsy. Ann. Neurol. 59, 335–343 (2006).
95. Bettus, G. et al. Decreased basal fMRI functional connectivity in epileptogenic networks and contralateral compensatory mechanisms. Hum. Brain Mapp. 30, 1580–1591 (2009).
96. Zhang, Z. et al. Impaired attention network in temporal lobe epilepsy: a resting FMRI study. Neurosci. Lett. 458, 97–101 (2009).
97. Lui, S. et al. Differential interictal activity of the precuneus/posterior cingulate cortex revealed by resting state functional MRI at 3T in generalized vs. partial seizure. J. Magn. Reson. Imaging 27, 1214–1220 (2008).
98. Lowe, M. J. et al. Multiple sclerosis: low-frequency temporal blood oxygen level-dependent fluctuations indicate reduced functional connectivity initial results. Radiology 224, 184–192 (2002).
99. De Luca, M., Smith, S., De Stefano, N., Federico, A. & Matthews, P. M. Blood oxygenation level dependent contrast resting state networks are relevant to functional activity in the neocortical sensorimotor system. Exp. Brain Res. 167, 587–594 (2005).
100. MacDonald, C. L. et al. Verbal memory deficit following traumatic brain injury: assessment using advanced MRI methods. Neurology 71, 1199–1201 (2008).
101. Mohammadi, B. et al. Changes of resting state brain networks in amyotrophic lateral sclerosis. Exp. Neurol. 217, 147–153 (2009).
102. Liu, Y. et al. Whole brain functional connectivity in the early blind. Brain 130, 2085–2096 (2007).
103. Yu, C. et al. Altered functional connectivity of primary visual cortex in early blindness. Hum. Brain Mapp. 29, 533–543 (2008).
104. Cauda, F. et al. Altered resting state in diabetic neuropathic pain. PLoS One 4, e4542 (2009).
105. Bluhm, R. L. et al. Alterations in default network connectivity in posttraumatic stress disorder related to early-life trauma. J. Psychiatry Neurosci. 34, 187–194 (2009).
106. Boly, M. et al. Functional connectivity in the default network during resting state is preserved in a vegetative but not in a brain dead patient. Hum. Brain Mapp. 30, 2393–2400 (2009).
107. Cauda, F. et al. Disrupted intrinsic functional connectivity in the vegetative state. J. Neurol. Neurosurg. Psychiatry 80, 429–431 (2009).

108. Horovitz, S. G. et al. Decoupling of the brain's default mode network during deep sleep. Proc. Natl Acad. Sci. USA 106, 11376–11381 (2009).
109. Fransson, P. et al. Resting-state networks in the infant brain. Proc. Natl Acad. Sci. USA 104, 15531–15536 (2007).
110. Kiviniemi, V. et al. Slow vasomotor fluctuation in fMRI of anesthetized child brain. Magn. Reson. Med. 44, 373–378 (2000).
111. Gao, W. et al. Evidence on the emergence of the brain's default network from 2-week-old to 2-year-old healthy pediatric subjects. Proc. Natl Acad. Sci. USA 106, 6790–6795 (2009).
112. Fair, D. A. et al. The maturing architecture of the brain's default network. Proc. Natl Acad. Sci. USA 105, 4028–4032 (2008).
113. Shaw, P. et al. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proc. Natl Acad. Sci. USA 104, 19649–19654 (2007).
114. Courchesne, E. & Pierce, K. Why the frontal cortex in autism might be talking only to itself: local over-connectivity but long-distance disconnection. Curr. Opin. Neurobiol. 15, 225–230 (2005).
115. Andrews-Hanna, J. R. et al. Disruption of large-scale brain systems in advanced aging. Neuron 56, 924–935 (2007).
116. Zang, Y. F. et al. Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. Brain Dev. 29, 83–91 (2007).
117. Matthews, P. M., Honey, G. D. & Bullmore, E. T. Applications of fMRI in translational medicine and clinical practice. Nat. Rev. Neurosci. 7, 732–744 (2006).
118. Johnston, J. M. et al. Loss of resting interhemispheric functional connectivity after complete section of the corpus callosum. J. Neurosci. 28, 6453–6458 (2008).
119. Greicius, M. D. et al. Persistent default-mode network connectivity during light sedation. Hum. Brain Mapp. 29, 839–847 (2008).
120. Kiviniemi, V. Endogenous brain fluctuations and diagnostic imaging. Hum. Brain Mapp. 29, 810–817 (2008).
121. McAvoy, M. et al. Resting states affect spontaneous BOLD oscillations in sensory and paralimbic cortex. J. Neurophysiol. 100, 922–931 (2008).
122. Fransson, P. How default is the default mode of brain function? Further evidence from intrinsic BOLD signal fluctuations. Neuropsychologia 44, 2836–2845 (2006).
123. Greicius, M. D. & Menon, V. Default-mode activity during a passive sensory task: uncoupled from deactivation but impacting activation. J. Cogn. Neurosci. 16, 1484–1492 (2004).
124. Kokkonen, S. M. et al. Preoperative localization of the sensorimotor area using independent component analysis of resting-state fMRI. Magn. Reson. Imaging 27, 733–740 (2009).
125. Liu, H. et al. Task-free presurgical mapping using functional magnetic resonance imaging intrinsic activity. J. Neurosurg. 111, 746–754 (2009).
126. Shimony, J. S. et al. Resting-state spontaneous fluctuations in brain activity: a new paradigm for presurgical planning using fMRI. Acad. Radiol. 16, 578–583 (2009).
127. Hampson, M., Peterson, B. S., Skudlarski, P., Gatenby, J. C. & Gore, J. C. Detection of functional connectivity using temporal correlations in MR images. Hum. Brain Mapp. 15, 247–262 (2002).
128. Sanai, N., Mirzadeh, Z. & Berger, M. S. Functional outcome after language mapping for glioma resection. N. Engl. J. Med. 358, 18–27 (2008).
129. Quigley, M. et al. Effect of focal and nonfocal cerebral lesions on functional connectivity studied with MR imaging. AJNR Am. J. Neuroradiol. 22, 294–300 (2001).
130. Quigley, M. et al. Role of the corpus callosum in functional connectivity. AJNR Am. J. Neuroradiol. 24, 208–212 (2003).
131. Buzsaki, G., Kaila, K. & Raichle, M. Inhibition and brain work. Neuron 56, 771–783 (2007).
132. Le Bihan, D. Looking into the functional architecture of the brain with diffusion MRI. Nat. Rev. Neurosci. 4, 469–480 (2003).
133. Greicius, M. D., Supekar, K., Menon, V. & Dougherty, R. F. Resting-state functional connectivity reflects structural connectivity in the default mode network. Cereb. Cortex 19, 72–78 (2009).
134. Zhang, D., Snyder, A. Z., Shimony, J. S., Fox, M. D. & Raichle, M. E. Noninvasive functional and structural connectivity mapping of the human thalamocortical system. Cereb. Cortex doi:10.1093/cercor/bhp182.
135. Sporns, O., Tononi, G. & Kotter, R. The human connectome: A structural description of the human brain. PLoS Comput. Biol. 1, e42 (2005).
136. Habas, C. et al. Distinct cerebellar contributions to intrinsic connectivity networks. J. Neurosci. 29, 8586–8594 (2009).
137. Krienen, F. M. & Buckner, R. L. Segregated fronto-cerebellar circuits revealed by intrinsic functional connectivity. Cereb. Cortex 19, 2485–2497 (2009).
138. Behrens, T. E., Berg, H. J., Jbabdi, S., Rushworth, M. F. & Woolrich, M. W. Probabilistic diffusion tractography with multiple fibre orientations: what can we gain? Neuroimage 34, 144–155 (2007).
139. Hagmann, P. et al. Understanding diffusion MR imaging techniques: from scalar diffusion-weighted imaging to diffusion tensor imaging and beyond. Radiographics 26 (Suppl. 1), S205–S223 (2006).
140. van den Heuvel, M., Mandl, R., Luigjes, J. & Hulshoff Pol, H. Microstructural organization of the cingulum tract and the level of default mode functional connectivity. J. Neurosci. 28, 10844–10851 (2008).
141. Lowe, M. J. et al. Resting state sensorimotor functional connectivity in multiple sclerosis inversely correlates with transcallosal motor pathway transverse diffusivity. Hum. Brain Mapp. 29, 818–827 (2008).
142. Raichle, M. E. Two views of brain function. Trends Cogn. Sci. (in press).
143. Popa, D., Popescu, A. T. & Pare, D. Contrasting activity profile of two distributed cortical networks as a function of attentional demands. J. Neurosci. 29, 1191–1201 (2009).
144. Raichle, M. E. A brief history of human brain mapping. Trends Neurosci. 32, 118–126 (2009).
145. Bar, M. The proactive brain: using analogies and associations to generate predictions. Trends Cogn. Sci. 11, 280–289 (2007).
146. Albert, N. B., Robertson, E. M. & Miall, R. C. The resting human brain and motor learning. Curr. Biol. 19, 1023–1027 (2009).
147. Schroeder, C. E. & Lakatos, P. Low-frequency neuronal oscillations as instruments of sensory selection. Trends Neurosci. 32, 9–18 (2009).
148. Leopold, D. A., Murayama, Y. & Logothetis, N. K. Very slow activity fluctuations in monkey visual cortex: implications for functional brain imaging. Cereb. Cortex 13, 422–433 (2003).
149. Boly, M. et al. Baseline brain activity fluctuations predict somatosensory perception in humans. Proc. Natl Acad. Sci. USA 104, 12187–12192 (2007).
150. Hesselmann, G., Kell, C. A., Eger, E. & Kleinschmidt, A. Spontaneous local variations in ongoing neural activity bias perceptual decisions. Proc. Natl Acad. Sci. USA 105, 10984–10989 (2008).
151. Fox, M. D., Snyder, A. Z., Vincent, J. L. & Raichle, M. E. Intrinsic fluctuations within cortical systems account for intertrial variability in human behavior. Neuron 56, 171–184 (2007).
152. Shulman, G. L. et al. Common blood flow changes across visual tasks: II. decreases in cerebral cortex. J. Cogn. Neurosci. 9, 648–663 (1997).
153. Gusnard, D. A. & Raichle, M. E. Searching for a baseline: functional imaging and the resting human brain. Nat. Rev. Neurosci. 2, 685–694 (2001).
154. Buckner, R. L., Andrews-Hanna, J. R. & Schacter, D. L. The brain's default network: anatomy, function, and relevance to disease. Ann. NY Acad. Sci. 1124, 1–38 (2008).
155. Graph network stereogram movie [online], ftp://imaging.wustl.edu/pub/raichlab/NRN/ (2009).
156. Murphy, K., Birn, R. M., Handwerker, D. A., Jones, T. B. & Bandettini, P. A. The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? Neuroimage 44, 893–905 (2009).
157. Weissenbacher, A. et al. Correlations and anticorrelations in resting-state functional connectivity MRI: a quantitative comparison of preprocessing strategies. Neuroimage 47, 1408–1416 (2009).
158. Kay, K. N., Naselaris, T., Prenger, R. J. & Gallant, J. L. Identifying natural images from human brain activity. Nature 452, 352–355 (2008).
159. Mitchell, T. M. et al. Predicting human brain activity associated with the meanings of nouns. Science 320, 1191–1195 (2008).
160. Haynes, J. D. & Rees, G. Decoding mental states from brain activity in humans. Nat. Rev. Neurosci. 7, 523–534 (2006).
161. Norman, K. A., Polyn, S. M., Detre, G. J. & Haxby, J. V. Beyond mind-reading: multi-voxel pattern analysis of fMRI data. Trends Cogn. Sci. 10, 424–430 (2006).

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Supplementary information

Supplementary information is linked to the online version of the paper at www.nature.com/nrneurol