Resting-state functional connectivity in neuropsychiatric disorders

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Purpose of review

This review considers recent advances in the application of resting-state functional magnetic resonance imaging to the study of neuropsychiatric disorders.

Recent findings

Resting-state functional magnetic resonance imaging is a relatively novel technique that has several potential advantages over task-activation functional magnetic resonance imaging in terms of its clinical applicability. A number of research groups have begun to investigate the use of resting-state functional magnetic resonance imaging in a variety of neuropsychiatric disorders including Alzheimer's disease, depression, and schizophrenia. Although preliminary results have been fairly consistent in some disorders (for example, Alzheimer's disease) they have been less reproducible in others (schizophrenia). Resting-state connectivity has been shown to correlate with behavioral performance and emotional measures. It's potential as a biomarker of disease and an early objective marker of treatment response is genuine but still to be realized.

Summary

Resting-state functional magnetic resonance imaging has made some strides in the clinical realm but significant advances are required before it can be used in a meaningful way at the single-patient level.

Keywords

Alzheimer's, connectivity, default-mode, resting-state

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Introduction

With rare exceptions, functional magnetic resonance imaging (fMRI) has largely failed to fulfill its promise in the clinical realm. The main clinical applications have been in the surgical treatment of epilepsy. Surgical epilepsy centers are beginning to rely more on fMRI for presurgical mapping of motor, language, and memory areas as well as for the detection of epileptic foci using spike-triggered fMRI [1–4]. The general paucity of fMRI applications in other clinical realms can be attributed to one or several limitations of this approach when used in a standard task-activation paradigm. The signal-to-noise ratio (SNR) of fMRI is rather poor so that, for many task-activation paradigms, interpretations are based on data aggregated over 10 or more patients rather than at the single-patient level. Practice effects and habituation can be expected to lessen the sensitivity of serial fMRI as an objective marker of treatment response. Most importantly, the most sick patients – those likely to provide the strongest biological signal – are often too impaired to perform a task correctly in the scanner environment. This results in the lamentable fact that most, if not all, task-activation fMRI studies in patient populations are difficult to generalize beyond the 'high-functioning' 'patients that were able to participate [5,6]. In disorders with prominent cognitive features like autism, schizophrenia, and Alzheimer's disease, this constitutes a substantial limitation.

Resting-state functional connectivity is a relatively novel fMRI approach that has the potential to overcome a number of these limitations. In resting-state fMRI studies, subjects do not have to perform a task. Instead, they are typically asked to rest quietly with their eyes closed for several minutes. Functional connectivity has been defined as 'the temporal correlation of a neurophysiological index measured in different brain areas' [7]. In resting-state fMRI, the neurophysiological index is the blood oxygen level-dependent (BOLD) signal, which exhibits low-frequency spontaneous fluctuations in the resting brain. These spontaneous low-frequency BOLD signal fluctuations show a high degree of temporal correlation across widely separated brain regions, with demonstrable structural connections [8], that constitute plausible functional brain networks. The initial resting-state functional connectivity study by Biswal and colleagues [9] demonstrated that left sensorimotor cortex was joined to the contralateral sensorimotor cortex, the

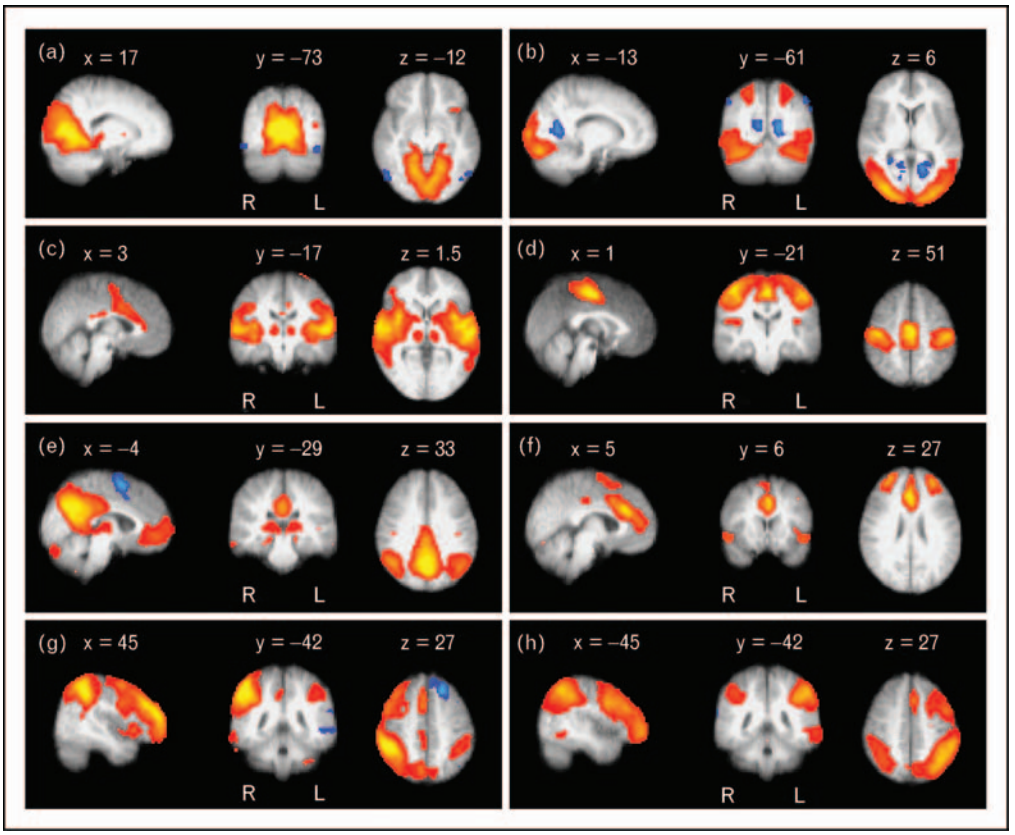
supplementary motor area and premotor regions in a sensorimotor network. Since that landmark paper, there have been dozens of studies that have outlined a set of canonical resting-state networks (RSNs) corresponding to critical brain functions including movement, vision, audition, language, episodic memory, executive function, and salience detection [10,11–15,16•] among others. Linking RSNs to their putative functions is invariably based on inference, as by definition, the subjects are not performing a task when the RSNs are identified. This inference is relatively straightforward for the primary motor and sensory RSNs in which case it is safe to assume, for example, that an RSN that includes the bilaterally primary auditory cortices is involved in audition. Inferring function in the other RSNs believed to be linked to higher order cognitive processing is, perhaps, more tenuous. The default-mode network has been linked to episodic memory, for example, because it includes regions activated by episodic memory retrieval tasks (the posterior cingulate/retrosplenial cortex and hippocampus) and because it is disrupted in Alzheimer's disease, the quintessential disorder of episodic memory [8,17].

Two main approaches have been used to characterize functional connectivity in these various RSNs: independent component analysis (ICA) and region-of-interest (ROI) analysis. The pros and cons of each approach are nicely summarized in a recent review by Fox and Raichle [18••]. The ROI analysis requires the a-priori selection of a region whose spontaneous BOLD signal fluctuations over several minutes of rest provide a waveform, which is used to search the brain for other regions whose BOLD signal fluctuations are significantly correlated. Voxel values in this case reflect the degree to which a given voxel is correlated with the ROI. ICA provides a means of detecting and separating several distinct RSNs at once, based mainly on their independent spatial patterns. Voxel values in ICA reflect the degree to which a given voxel's timeseries is correlated with the mean timeseries of that particular RSN [10,19]. Figure 1 provides an example of some of the several different RSNs that can be detected in resting-state data using ICA. At least two issues related to ICA need some further work. First, the number and spatial pattern of RSNs that are identified with ICA will vary depending on the number of components generated. Determining the 'optimal' number of components, therefore, constitutes a critical early step that varies across studies and laboratories [10,20••]. Second, once the components have been generated, deciding which components are noise-related and which constitute genuine RSNs is also critical. To avoid the potential for investigator bias inherent in visual inspection, our group and others have favored using an automated approach based on each component's spatial correlation to a standard template of an RSN [17,21]. Both ROI and ICA approaches have been used in investigating RSNs in the neuropsychiatric disorders reviewed below. The most common analysis, whether using an ICA or an ROI approach, is to compare the patient group connectivity map to the control group connectivity map using a two-sample *t*-test. Secondary analyses in the patient sample, exploring within-group correlations between a disease measure and RSN connectivity, for example, are often included as well.

Alzheimer's disease and other dementias

Among the early forays of resting-state fMRI into the clinical realm, Alzheimer's disease has received the most attention. Li and colleagues [22] examined resting-state functional connectivity between the left and right hippocampus in nine healthy controls, 10 patients with Alzheimer's disease, and five patients with mild cognitive impairment (MCI) and found a parametric reduction in connectivity from controls to MCI to Alzheimer's disease. They did not generate a broader map of hippocampal connectivity to other regions but focused only on the pair-wise correlations between the bilateral hippocampi. Subsequently, our group used ICA to examine functional connectivity in a specific RSN known as the default-mode network (DMN) [17]. The DMN (Fig. 1e) is made up of several regions, including the posterior cingulate cortex, the posterolateral parietal cortices, and the medial temporal lobes/hippocampi that are known from PET studies to be targeted early in the course of Alzheimer's disease [23,24]. We reported reduced connectivity within the DMN, not at rest but during a simple button-pressing task, in a group of 13 Alzheimer's disease patients and 13 controls. Using a simple classification algorithm, reflecting how well a single subject's DMN map was spatially correlated with a standard template of the DMN, we correctly classified 11 of 13 Alzheimer's disease patients and 10 of 13 controls. This finding has been extended now into MCI by Sorg *et al.* [20••], who have reported reduced DMN connectivity in a group of 24 MCI patients compared with controls. Recent work from the group in Beijing has shown that ROI-based approaches also demonstrate reduced connectivity in DMN regions such as the hippocampus [25] and posterior cingulate cortex [26]. An intriguing property of the DMN generally, and perhaps the posterior cingulate within the DMN more precisely, is that it is anticorrelated with several key regions such as the frontoinsular cortex and the dorsolateral prefrontal cortex found in other RSNs [12–14]. Both the study by Sorg *et al.* [20••] and the 2007 study by Wang *et al.* [27] suggest that Alzheimer's disease and MCI disrupt not only positive correlations with the DMN and posterior cingulate but also anticorrelations, and that the combined use of disrupted positive and negative correlations may be more useful in classifying Alzheimer's disease than using positive correlations alone.

Figure 1 Independent component analysis applied to resting-state data can identify several resting-state networks related to critical functions



Presumed functions related to the eight maps above are primary vision (a), higher order visual processing (b), hearing (c), touch and movement (d), memory (default-mode network) (e), salience processing (f), and executive control (g and h). For further details, please see Beckmann *et al.* [10].

Although most early work has focused on this connection between Alzheimer's disease and the DMN, preliminary work from Seeley and colleagues [28,29] suggests that other networks may show specific susceptibility to other neurogenerative diseases. Their work has focused particularly on an RSN (Fig. 1f) anchored in the dorsal anterior cingulate (dACC) and frontoinsular regions – the salience network – implicated in monitoring or generating autonomic responses or both to salient stimuli [16•]. This salience network appears to be particularly vulnerable to degeneration in frontotemporal dementia (FTD) [28–30]. This group has hypothesized that in addition to the FTD–salience and Alzheimer's disease–DMN connections there may be several additional specific links between neurodegenerative disorders and these canonical RSNs [28].

Depression

Anand and colleagues [31] were the first to report resting-state connectivity results in depression. They adopted a hypothesis-driven, ROI-based approach to examine resting-state connectivity between the dACC (Brodmann's area (BA) 24) and three other regions: medial thalamus, amygdala, and the pallidostriatum. At baseline they found that the dACC showed reduced connectivity with the three other regions in the 15 depressed patients compared with the 15 controls [31]. This was associated with an increased limbic activation in the depressed group to negative pictures, raising the possibility that reduced connectivity between the dACC and limbic regions resulted in a loss of cortical control over limbic responsivity. The patients were treated for 6 weeks with sertraline and rescanned along with the unmedicated healthy controls. The general trend was for dACC connectivity to increase in the depressed group (now 12 patients) and decrease in the control group (now 11 subjects). This effect was significant, however, only for the dACC to medial thalamic connection [32]. There were no significant correlations between depression change score and resting-state functional connectivity. This pair of studies has some important limitations – only four axial slices were obtained for the resting-state data which may be why connectivity maps were not shown, global scaling was not performed, and the ROIs were chosen anatomically – but represent the first and, as yet, only attempt to demonstrate changes in resting-state connectivity following treatment.

Our group has recently published an ICA-based paper [33•] examining DMN connectivity in a group of 28 depressed patients compared with 21 controls. Unlike our Alzheimer's disease study in which there was diffuse reduced DMN connectivity in the patient group, here we found no regions of reduced DMN connectivity in the depressed patients. Rather, the depressed group should increased DMN connectivity in several regions including the thalamus and subgenual cingulate (BA 25). The latter region has become a focus of intense research following the work of Mayberg *et al.* [34] showing that patients with refractory depression have increased glucose metabolism in the subgenual cingulate and respond to deep brain stimulation targeting this region. Of all the regions in our study that demonstrated increased DMN connectivity, only the subgenual region correlated with the duration of the current depressive episode; that is, the longer someone was ill, the greater their subgenual connectivity within the DMN.

Schizophrenia

Numerous studies using various approaches [35,36] have suggested that schizophrenia is best characterized as a disconnection syndrome. Recent work using resting-state functional connectivity has, thus far at least, not lent any consistent evidence to support this long-standing hypothesis. Most of the work in schizophrenia has focused on the DMN. The group in Beijing has reported that schizophrenia generally increases connectivity within the DMN [37], whereas Bluhm and colleages [38] reported just the opposite. Building on the finding that certain RSNs are inversely correlated with one another [14], several groups have examined inverse correlations between RSNs in schizophrenia. Here again, however, the results have not been consistent across studies. The Beijing group generally found significantly increased inverse correlations between the DMN and other RSNs in schizophrenia [37], whereas Bluhm and colleagues [38] found that schizophrenia had no significant effect on the inverse correlations between the DMN and other RSNs. A third group, using ICA, has reported a general trend toward increased connectivity between RSNs in schizophrenia [39]. Even within the Beijing group's series of resting-state papers on (largely overlapping) schizophrenia samples it is hard to reconcile the findings. The focused ROI-based approach [37] reports that schizophrenia generally increases connectivity within the DMN and between the DMN and other RSNs, whereas two additional studies, using about 100 ROIs to gauge whole-brain connectivity, suggest that resting-state connectivity is generally reduced in schizophrenia [40,41].

Development and attention-deficit/hyperactivity disorder

Two studies have examined the presence of RSNs in infants and young children. Kiviniemi and colleagues [42] demonstrated resting-state connectivity in the visual network (Fig. 1a) in a group of young children between the ages of 5 months and 5 years. This study was important also in that it demonstrated that sensory RSNs could be identified under sedation (in this case with thiopental). The ability to identify these RSNs under sedation is critical from a practical standpoint given that many severely affected clinical populations will require some level of sedation. Recent work on monkeys sedated with isoflurane [43••] and humans sedated with midazolam [44] has confirmed that even putative cognitive RSNs such as the DMN can be identified under mild-to-moderate sedation. Fransson and colleagues [45•] pushed these findings further forward in development to show that basic sensory and sensorimotor RSNs (Fig. 1a, c, and d) are detectable in premature infants scanned (under chloral hydrate) at a gestational age of 39–42 weeks. They did not detect any evidence at this stage of development for more cognitive RSNs like the DMN.

Resting-state connectivity abnormalities in attention-deficit/hyperactivity disorder (ADHD) have been reported in multiple publications by the group in Beijing but, again, on largely overlapping samples. I was not able to distill a consistent theme from the four related papers [46–49]. Castellanos and colleagues [50•] have recently reported that ADHD is associated with reduced connectivity within the DMN. They also demonstrated that the inverse correlations between the DMN and the dACC were reduced in ADHD.

Miscellaneous: aging, multiple sclerosis, pain

Several other conditions or disorders of interest to neuropsychiatry have been subjected to resting-state analyses though none have, as yet, been studied by more than one group. Using ICA, Damoiseaux and colleagues [21] have shown that normal aging is associated with reduced connectivity in the DMN (but not in several other RSNs) and that reduced connectivity was correlated with reduced performance on a test of executive function. Although not strictly a resting-state analysis, a second group has shown that healthy aging is associated with reduced DMN connectivity [51] and, again, that connectivity and cognitive performance were correlated. Multiple sclerosis patients were shown to have reduced connectivity in a motor RSN [52]. Recent research from our group found that the salience network (Fig. 1f) showed abnormally increased connectivity in patients with chronic pain, whereas connectivity in the DMN

(Fig. 1e) and visual network (Fig. 1a) did not differ from controls [53]. Further, within the chronic pain patients, pain severity correlated with connectivity in the salience network. (See also article by Guye *et al.* in this issue on structural and functional connectivity.)

Methodological considerations: near-rest, control networks, and noise

Although the purist's interpretation of resting-state connectivity implies a prolonged period of task-free rest, a number of studies have examined RSN connectivity in less than pure rest conditions. As mentioned above, our paper examining DMN connectivity in Alzheimer's disease used data from a simple button-pressing task [17]. The group at Washington University has recently published two studies examining resting-state connectivity in childhood by cutting and pasting blocks of rest from within a longer cognitive task [54,55]. Using a similar approach, one group has reported reduced DMN connectivity in patients with autism [56]. Another approach involves regressing task-related activation out of a time-series and examining RSN connectivity using the residual signal. Using this method, He and colleagues [57] demonstrated that functional connectivity in post-stroke neglect patients correlates with the degree of impairment and might be helpful in predicting recovery. A similar approach was used to demonstrate reduced DMN connectivity in healthy aging [51]. The main question here is whether and to what degree 'impure' resting-state connectivity reflects pure resting-state connectivity. The effect of having just performed a task block (ruminating on any errors, for example) or anticipating the next task block may alter RSN connectivity and would not be present in pure resting-state scans. One group has examined some of these potential effects, comparing 'pure' rest to these alternate approaches, and found that there is a significant loss of connectivity strength when using the residual signal from event-related tasks and to a lesser degree when using the signal from extracted blocks of rest [58]. Decreased 'resting' connectivity strength in these task settings may be related to the loss of some low-frequency signal or to task performance factors (e.g. subjects not truly resting but reflecting on the just completed task or anticipating the upcoming task) or both. These connectivity changes between 'pure' rest and 'impure' rest may be particularly critical if they differ between patients and controls in which case group-level differences might not be attributable to differences in connectivity *per se* but in how connectivity is altered by task performance.

A second methodological issue pertains to the need and, encouragingly, the trend to include some type of internal control. Thresholds for significance can differ widely across groups and software platforms making it difficult to compare studies. The inclusion of one or more RSNs that are not expected to differ between groups (and then shown not to differ), for example, can provide some confidence that reported differences in RSN connectivity between two groups are meaningful, have some expected anatomic specificity, and are not related to confounds such as differential exposure to psychoactive medications [20••,53]. Including a patient control group (for example, non-Alzheimer's disease dementia patients in an Alzheimer's disease study) will also be increasingly important to demonstrate disease-specificity when reporting abnormal RSN connectivity.

Finally, several groups have demonstrated that noise, from both physiologic and scanner sources, can contaminate the low-frequency signal in which RSN correlations are detected [59–61]. Temporal filtering can help reduce these artifacts to some degree though aliased signal from the cardiac and respiratory cycles and low-frequency alterations in respiratory volume can still pose a problem. Another approach to remove the diffuse effects of some of these noise sources is to covary out the global signal [12,59]. ICA may be helpful in isolating some noise sources as distinct independent components [10]. In the ideal setting cardiac and respiratory signals are measured in the scanner so that their various associated noise sources can be isolated and removed [61].

Conclusion

Resting-state fMRI has the potential to greatly increase the clinical utility of fMRI. Consistent findings in disorders such as Alzheimer's disease are encouraging but tempered by less consistent findings in disorders such as schizophrenia. The field can expect an improved understanding of the underlying physiology that generates these low-frequency BOLD signal fluctuations from multimodal approaches such as simultaneous fMRI and electroencephalography (EEG) [62] and from continued work in nonhuman primates [43••,63]. Continued improvements in SNR will be driven by methods to enhance the signal, with longer timeseries and high-field scanning, for example, as well as methods to reduce noise, by isolating and removing artifactual signals. Ultimately, a better understanding of the physiology combined with improvements in SNR may allow us to make meaningful interpretations of resting-state connectivity at the single patient level.

Acknowledgements

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