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Review article

Resting state networks in major depressive disorder

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ABSTRACT

Resting state functional magnetic resonance imaging (fMRI) examines the spontaneous low frequency neural activity of the brain to reveal networks of correlated neural activity. A number of different methodologies, each with its own advantages and disadvantages, have been used to examine networks of neural activity that may be related to clinical presentation. Major depressive disorder (MDD) research has largely focused on the default mode network (DMN), which is most active at rest and may relate to negative rumination. However, other networks can be discerned in the resting state such as salience and affective and cognitive control networks, all of which may be relevant to MDD psychopathology. This article reviews the rapidly increasing literature on resting state networks. A number of state- and trait-dependent abnormalities have been reported in MDD in a wide variety of regions including the cerebellum, lingual gyrus, anterior cingulate cortex (ACC), middle frontal gyrus (MFG), dorsolateral prefrontal cortex (dlPFC), amygdala and insula. Current and chronic medication is often a potential confound. Few trials have examined the immediate or delayed effects of antidepressants on resting state networks. This article presents a novel approach to the analysis of drug effects, the identification of signatures of efficacy, and thus for drug development.

Contents

Abbreviations: AMYG, amygdala; AN, affective network; ant, anterior; ACC, anterior cingulate cortex; BD, bipolar disorder; BPD, bipolar depression; b/l, bilateral; CES-D, Center for Epidemiologic Studies Depression Scale; Cohe-ReHo, coherence based regional homogeneity; cMDD, current major depressive disorder; Cr, creatinine; FnC, functional connectivity; fALFF, fractional amplitude of low frequency fluctuations; ALFF, amplitude of low frequency fluctuations; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; FG, fusiform gyrus; IFG, inferior frontal gyrus; ITG, inferior temporal gyrus; Glx, glutamate+glutamine; HAM-D, Hamilton Depression Rating Scale; HC, healthy controls; hx, history; INS, insula; IPL, inferior parietal lobule; LG, lingual gyrus; MDD, major depressive disorder; MFG, middle frontal gyrus; mFG, medial frontal gyrus; MMSE, mini mental state examination; mOFC, medial orbitofrontal cortex; MR, magnetic resonance; MRS, magnetic resonance spectroscopy; MTG, middle temporal gyrus; PCC, post cingulate cortex; PHG, parahippocampal gyrus; post, posterior; OCC, occipital cortex; rACC, rostral anterior cingulate cortex; rMDD, remitted major depressive disorder; ROI, region of interest; ReHo, regional homogeneity; sibsMDD, healthy siblings of MDD patients; SFG, superior frontal gyrus; SPL, superior parietal lobule; STG, superior temporal gyrus; T, Tesla; THAL, thalamus; trMDD, treatment resistant major depressive disorder; TR, Repetition time; tx, treatment; vlPFC, ventrolateral prefrontal cortex; VMHC, Voxel-mirrored homotopic connectivity; vmPFC, ventromedial prefrontal cortex; vACC, ventral anterior cingulate cortex; vPFC, ventral prefrontal cortex

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1. Resting state networks

The resting state refers to regional neural activity of the brain when humans or animals are awake and alert but not actively involved in any activity that requires attention or a goal-directed action (Raichle et al., 2001, Broyd et al., 2009). Resting state functional magnetic resonance imaging (fMRI) studies of major depressive disorder (MDD) have focused on several distinct networks containing brain regions that have been shown to have correlated oscillating blood oxygenation level dependent (BOLD) signals. Veer et al. (2010) identified a total of 13 functionally relevant resting state networks (RSNs) from a study of 19 recovered depressive patients and 19 healthy controls. The 13 functionally relevant RSNs were the following: (1) primary visual, (2) lateral visual, (3) medial visual, (4) sensory-motor, (5) right lateral, (6) left lateral, (7) precuneus, (8) ventral stream, (9) medial temporal, (10) salience, (11) task positive, (12) auditory, and (13) default mode (Veer et al., 2010), all of which have previously been demonstrated in healthy volunteers (Damoiseaux et al., 2006).

Resting state networks are most frequently assessed first by identifying regions that show correlated activity of over time against a region of interest (ROI; seed-based correlation) or that emerge from independent components analysis (ICA). ICA is able to extract from the BOLD time series a number of spatially independent components that can be interpreted as a network showing similar BOLD activity levels (Rosazza and Minati, 2011). The degree to which the component is present is expressed as a power function. Direct comparisons of the different analytic methodologies have identified similar networks (Bluhm et al., 2008). An alternative method of regional homogeneity (ReHo) analyses the differences in neural activity between one voxel and its nearest neighbours. It assumes that the haemodynamic characteristics of the neighbouring voxels will be similar and also that a cluster of voxels will demonstrate synchronised activity (Liang et al., 2013). Abnormal ReHo is therefore likely to be related to temporal changes in BOLD signal (Zang et al., 2004). Other measures include Uddin and colleagues' "network homogeneity", where voxels are compared with all other voxels in the brain network (Uddin et al., 2008), "integrated local correlation" (Deshpande et al., 2009) and Greicius et al.'s (2004) "goodness of fit" model (Greicius et al., 2004). New techniques for the analysis of the resting state have also emerged. These include analysing the fractional amplitude of low frequency fluctuations (fALFF) or the amplitude of low frequency fluctuations (ALFF) and voxel-mirrored homotopic connectivity. Fractional ALFF is the fractional component of the low frequency range of the ALFF, which is close to the spontaneous resting neural activity (Zou et al., 2008).

There are strengths and weaknesses with each of these methods. ICA is a model-free, data-driven approach. However, the number of components to be generated in ICA during the analysis will affect the number of spatially distinct networks detected. Components can be functional networks or physiologically linked regions but may also be imaging artefacts. It is also difficult to compare components between groups and participants (Uddin et al., 2008). In the ROI-based method, seed placement can be somewhat arbitrary, affecting the patterns of functional connectivity observed (Uddin et al., 2008). Furthermore, the ROI-based method is more susceptible to contamination from other non-neural low frequency fluctuations when compared with the ICA-based approach (Greicius et al., 2007). Kuhn and Gallinat have also commented that the seed-voxel-based analysis approach is highly dependent on the positioning of the seed voxel and may therefore produce inconsistent results (Kuhn and Gallinat, 2011).

The newer method of network homogeneity is better suited to examining longer range connectivity and group differences in pathology since it allows comparison of one voxel with all the other voxels in a particular network. However, the network of interest needs to be identified and well characterised before analysis. This makes network homogeneity less useful in paediatric populations (Uddin et al., 2008) as there is the potential to miss differences between networks that might otherwise be demonstrated. Greicius et al.'s (2004) "goodness of fit" model suffers from similar problems because the data are matched to a spatial template that is selected before analysis. They attempted to alleviate this by examining the four "best-fit" components. These are then matched using an automated process followed by the examination of the differences between them (Greicius et al., 2004).

The advantage of regional homogeneity (ReHo) is the model-free nature of the method which allows discovery of unpredicted BOLD response. However, regional homogeneity can be affected by the level of spatial smoothing, cluster size and volume examined (Zang et al., 2004). This method was reported to be insensitive to phase variability, such as random noise across the time series, leading to an improvement in sensitivity to detect differences in spontaneous neural activity (Guo et al., 2012a). Integrated local correlation was introduced to alleviate the problems of ReHo. ReHo uses only the neighbouring voxels, whereas in integrated local correlation the integration of the spatial correlation function for each voxel is used. Integrated local correlation is also reported to be unaffected by fluctuations from cardiac and respiratory cycles except around large blood vessels (Deshpande et al., 2009).

Functional connectivity (FnC) provides information about the correlation between a set of pre-specified brain regions. As FnC is not data-driven, it does not demonstrate changes in specific brain regions and will not identify the part of the network that is dysfunctional (Zang et al., 2007; Zou et al., 2008). ALFF allows detection of spontaneous BOLD signal changes without these challenges. However, greater regional ALFF is especially prevalent around large blood vessels and cisternal areas (Zang et al., 2007; Zou et al., 2008) due to physiological noise. To improve the approach, Zou et al. (2008) used the ratio of the power of the low frequency range (0.01–0.08 Hz) to the whole frequency range (0–0.25 Hz), termed fractional ALFF (fALFF).

2. Default mode and salience networks

Raichle et al. first coined the phrase "default mode" to describe correlated brain activity in its resting state (Raichle et al., 2001). The default mode network (DMN), one of several resting state networks of brain regions that show high levels of functional connectivity in the resting brain, includes the posterior cingulate cortex (PCC)/precuneus, medial prefrontal cortex (mPFC), ventral anterior cingulate cortex (vACC), and lateral and inferior parietal cortex. Because the network is most active at rest, it has been associated with self-referential processing (Bluhm et al., 2008). Different components have been emphasised by different authors. For example, Franco et al. (2009) emphasised the ACC (Brodmann area (BA) 11/32), dorsolateral and superior frontal gyrus (BA 8/9/10), inferior frontal cortex (BA 47), PCC (BA 23/31), posterior parietal lobule (BA 7/39/40), inferior temporal gyrus (BA 19/37) and parahippocampal gyrus (BA 30/36) (Franco et al., 2009). The most consistently defined parts of the DMN are the precuneus/PCC and the mPFC. The PCC is believed to be related to the monitoring of internal and external environments (Raichle et al., 2001), whilst the mPFC is thought to be involved in social cognition and observing the psychological states of self and others. The DMN therefore interfaces task performance and emotion (Simpson et al., 2001). Self-referential tasks have demonstrated increased response in the dorsomedial prefrontal cortex (dmPFC) whilst reduced response was observed in the ventral mPFC when affective stimuli were presented (Gusnard et al., 2001).