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Review

A systematic review of resting-state functional-MRI studies in major depression

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ABSTRACT

Background: To evaluate the literature pertaining to the use of resting-state functional magnetic resonance imaging (fMRI) in Major Depression (MD).
Methods: A search for papers published in English was conducted using MedLine, Embase, PsycINFO, OvidSP, and ScienceDirect with the following words: resting state, depression, MRI, affective, and default-mode.
Results: The findings from 16 resting-state fMRI studies on MD are tabulated. Some common findings are discussed in further detail.
Conclusion: The use of resting-state fMRI in MD research has yielded a number of significant findings that provide the basis for understanding the pathophysiology of depressive symptoms. Of particular note and deserving of further research are the roles of the cortico-limbic mood regulating circuit (MRC) and the interaction between task-positive and task-negative networks in MD. There is increasing interest in the use of resting-state fMRI in the study of psychiatric conditions, and continued improvement in technique and methodology will prove valuable in future research.

Contents

1. Introduction

Disturbances of mood and affect are among the most prevalent of all behavioural disorders. Major Depression (MD) is especially common, occurring in about 15% of the population. A 2008 report from the World Health Organisation (WHO) indicated that MD was the foremost contributor to the global burden of disease, as measured by years of health lost to disability (Daly, 2009). MD is a recurrent disorder, affecting adolescents and adults alike. However, despite its prevalence the mechanisms that underpin the disorder remain poorly understood. The diagnosis of a major depressive episode is based not only on the presence of a persistent negative mood state but also on a range of associated disturbances including attention, motivation, psychomotor speed, as well as sleep, appetite and libido. The involvement across such a broad range of functional domains stands as a testament to the disorder's complexity and may, in part,

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explain the observed variability across imaging studies. To date, the most consistent findings in MD include decreased frontal lobe function (primarily involving the medial prefrontal cortex; MPFC) and increased limbic system activity (including the amygdala). To a lesser extent, abnormalities have also been reported in paralimbic (cingulate) and subcortical (thalamus) structures but as distinct from most of the lesion literature, imaging studies describe bilateral rather than left-lateralization abnormalities. The identified neural substrates and their associated networks are highly connected via feedback loops with complementary networks primarily responsible for identifying non-emotional aspects of information, which include the MPFC (Gallagher and Chiba, 1996). It has been postulated that MD may evolve from a failure in the coordinated interaction between these cortico-limbic pathways. Within this theoretical framework, the dorsal compartment, which includes the neocortical and superior limbic elements, is postulated to regulate attention and cognitive features of depression (such as apathy and impaired attention) and the ventral compartment, composed of the limbic, paralimbic and subcortical regions is hypothesised to mediate vegetative and somatic aspects of the illness (including sleep, appetite and endocrine disturbances). Within this dorsal-ventral segregation, the MPFC and the amygdala are considered the critical neural substrates in the modulation of mood and together form the primary emotion specific neural network.

The past decade has seen significant advances in neuroimaging techniques allowing the non-invasive investigation of the brain's functional domains. With the aid of these sophisticated brain-imaging techniques, it is possible to study these domains in greater detail and glean their interrelationships. One such technique is functional magnetic resonance imaging (fMRI), which is an established imaging modality specific for studying brain activity and neuronal network connectivity. Its utility lies with contrasting functional differences between healthy control populations and patients with a variety of psychiatric conditions including schizophrenia, bipolar disorder (BD) and MD to name a few. To date, the vast majority of fMRI studies have employed stimulus driven paradigms where the imaging signal is time-locked to cognitive or sensorimotor tasks. These studies have primarily focused on interpreting the activation of different brain regions that are stimulated by task performance. More recently in the case of MD, there is a confluence of evidence that suggests depressive symptoms may evolve as a consequence of aberrations within discrete brain networks (rather than in isolated brain regions), which modulate function. To this end, fMRI has more recently been employed in a "stimulus-free" manner such as in the case of resting-state fMRI, to investigate changes in brain networks and their connectivity. Resting-state fMRI is a relatively new modality that potentially overcomes several key limitations of task-stimulated fMRI studies. Typically, resting-state fMRI is conducted while the subject is in a continuous state of rest (e.g. lying still with eyes closed). This allows the inclusion of subjects, suffering from a severe episode of the psychiatric condition, who may be incapable of performing cognitive tasks at a satisfactory level (Greicius, 2008). An important advantage of this is that a more direct comparison can be made between groups, including differences between patient groups of different conditions as well as subjects at varying stages of disease severity and development (Fox and Raichle, 2007).

Presently, the literature on resting state fMRI studies on MD points to a lack of consistency in the approaches to data collection, analysis and, subsequently, interpretation of the findings. As a consequence, this has led to a number of contradictory findings and the lack of an overall consensus on the interpretation of these changes. The aim of this review was to examine the methods and results of the currently available resting-state fMRI studies on MD and to discuss the relevant themes and future considerations.

2. Methods

A search for papers published in English was conducted via MedLine, Embase, PsycINFO, OvidSP, and ScienceDirect using terms composed of varying combinations of the following keywords: resting state, depression, MRI, affective, and default-mode. A total of 21 articles met the criteria as being resting-state fMRI studies in MD. Of these, 5 articles were excluded for the following reasons (the study): (i) did not use subjects who had been diagnosed with MD; (ii) used subjects with remitted depression: (iii) used arterial spin labelled (ASL) perfusion fMRI (Duhameau et al., 2010), which rendered comparison difficult; and (iv) used resting-state fMRI in the context of the graph theory of the brain (Bullmore and Bassett, 2011), which complicated interpretation of the results. In the end, 16 articles on resting-state fMRI studies in MD were examined in greater detail. However, due to the variable use of terminologies, it is possible that some relevant articles may have been overlooked.

3. Results

3.1. Methods of resting-state fMRI analysis

In the study of MD, resting-state fMRI is a relatively new approach that has been gaining momentum in recent years. There are a number of different strategies that can be adopted when conducting resting-state fMRI studies. Two of the most popular approaches are termed region-of-interest (ROI) analysis (Fox and Raichle, 2007) and independent component analysis (ICA) (Greicius et al., 2007). In a ROI analysis, a seed region is selected *a priori* and the subsequent functional connectivity map is extracted from the temporal correlations between the ROI and all other brain regions (Greicius, 2008). On the other hand, the ICA approach proceeds without an *a priori* selection of a seed region, but rather the data for the entire brain is decomposed into a set number of components, each of which is depicted as a functional map (Cole et al., 2010). The respective merits and shortcomings of ROI analysis and ICA are still widely debated (Cole et al., 2010; Fox and Raichle, 2007). The general trend currently seems to be that ROI analysis is favoured in resting-state fMRI studies due to its comparative ease of interpretation (Zhou et al., 2010). Defining the temporal correlation with a specific brain region to be the basis for direct comparison between any number of other regions allows for a relatively straightforward approach to interpreting the data (Cole et al., 2010). On the other hand, the requirement for seed-selection introduces potential biases in evaluating the findings and precludes identifying unexpected areas of interest. In that regard, ICA is superior to the ROI approach, as it does away with spatial assumptions and allows for simultaneous comparisons of activities in disparate resting-state networks. However, it does have its own shortcomings. In ICA, the number of components to be generated in the analysis will largely affect the number of connectivity patterns that can be derived; the process of determining the optimal number of components to be generated is a largely arbitrary one, and could vary greatly from study to study (Greicius, 2008). Developing meaningful ways to synthesise findings obtained by the different analytical procedures will be a key challenge in the field going forward. Of the 16 studies included in this review, 10 had used the seed ROI analysis approach (Table 1). Only one paper had employed the ICA method, which may represent a significant opportunity for more research groups to use the ICA approach to provide further insights, as the ICA presents different advantages from the ROI analysis. The remaining 5 studies had chosen a method called Regional Homogeneity (ReHo), which was first described in detail by Zang et al. (Zang et al., 2004). In a ReHo analysis, the time series of a given voxel is compared to those of its nearest voxels, and thus a temporal activation map of the whole brain is observed (Peng et al., 2011). The ReHo method of analysis is

Table 1
Tabulation of the resting state fmri studies reviewed.

Study	Subjects	Principal Findings	Interpretation
Anand et al. (2005a)	15 patients with MD (mean age 28); 15 healthy controls (mean age 28)	Decreased connectivity in MD group between ACC-left medial thalamus, ACC-right medial thalamus, ACC-left pallidostriatum.	Decreased cortico-limbic connectivity implies decreased ACC regulation over limbic areas, which could mediate emotional dysregulation
Anand et al. (2007)	12 patients with MD (mean age 30); 11 healthy controls (mean age 29)	Decreased corticolimbic connectivity in MD group. Treatment with Sertraline induced increase in corticolimbic connectivity in MD group.	Treatment in MD patients induced increased regulation of ACC over limbic regions.
Anand et al. (2009)	11 patients with BD (mean age 33); 6 BD patients with manic episode (mean age 34); 5 BD patients with depression episode (mean age 32); 15 patients with unipolar MD (mean age 29); 15 healthy controls	Decreased connectivity between pgACC-right amygdala, pgACC-left dorsomedial thalamus, pgACC-right dorsomedial thalamus in unipolar MD group and BD groups compared to control. No significant differences between patient groups.	Decrease in corticolimbic connectivity is greater in BD than in MD, which suggests decreased corticolimbic mood regulation in BD compared to MD. BD as a more severe mood disorder than MD.
Bluhm et al. (2009)	14 patients with early MD (mean age 23.5); 15 healthy controls (mean age 21.9)	Decreased precuneus/PCC-bilateral caudate connectivity in MD group.	Decreased precuneus/PCC-caudate connectivity could indicate discrepancy in reward-processing networks and account for lack of motivation and anhedonia. Patients could have different functional profile depending on duration of illness.
Cullen et al. (2009)	Focus on adolescent age subjects. 12 patients with MD (mean age 16.5); 14 healthy controls (mean age 16.8)	Decreased functional connectivity between sgACC and supragenual ACC, right medial frontal cortex, left superior and inferior frontal cortex, left superior temporal cortex, insular cortex. No clinical correlations between connectivity and symptom severity.	SgACC as central component of altered brain networks in MD. Decreased cortical-subcortical connectivity leads to emotional dysregulation. Decreased insular cortex connectivity accounts for somatic complaints, negative bias in interpreting interpersonal feedback.
Greicius et al. (2007)	28 patients with MD (mean age: 38.5); 20 healthy controls (mean age: 35.4)	MD patients showed increased functional connectivity in sgACC, thalamus, orbitofrontal cortex, precuneus. Length of current depression episode correlated positively with functional connectivity in sgACC.	Cross-modality confirmation of PET studies that showed increased activation of sgACC and thalamus in MD patients. Correlation between refractoriness and functional connectivity could point to guided therapy.
Guo et al. (2011)	24 patients with treatment-resistant depression (TRD) (mean age: 27.9); 19 healthy controls (mean age: 24.4)	Widespread decreased and increased ReHo in MD group.	TRD patients display abnormal neural activity in multiple brain regions. Cerebellar involvement a surprising find. Possibility of cerebellar involvement in emotional regulation.
Horn et al. (2010)	18 patients with MD (mean age: 39.2) (10 severe, 8 mild); 22 healthy controls (mean age: 34.1)	Metabolite levels in pgACC negatively correlates with severity of depression. Only in MD group, functional connectivity between pgACC and anterior insula is linearly correlated with Glx/Cr ratio in pgACC.	Impaired pgACC function accounts for MD symptoms such as ruminating thoughts. Glutaminergic modulation of abnormal fMRI responses. Altered metabolite levels correlate to severity of depressive symptoms.
Kenny et al. (2010)	Focus on late-life depression. 16 patients with MD (mean age: 76.4); 17 healthy controls (mean age: 75.7)	Increased hCN connectivity with a number of brain areas. Peak connectivity for left hCN with bilateral thalamus, bilateral precuneus, left precentral gyrus. Right hCN connectivity with bilateral cingulate, L precentral gyrus.	Abnormal functional connectivity in mood-regulating circuits contribute to symptoms.
Liu et al., (2010)	15 patients with MD (mean age: 29.1), 15 first-degree relatives of MD patients (mean age: 37.9); 15 healthy controls (mean age: 30.2)	Significant ReHo differences between 3 groups in right insula, left cerebellum, left postcentral gyrus. Numerous other differences between MD and control, MD and relatives, relatives and control.	Abnormalities shared by patients and relatives may be useful for diagnosing MD. Cerebellar involvement in emotional processing is a recent idea, still unclear.
Lui et al. (2011)	32 nonrefractory MD patients (mean age: 32); 28 refractory MD patients (mean age: 33); 48 healthy controls (mean age: 35)	Both MD groups showed reduced connectivity within prefrontal-limbic-thalamic areas. Nonrefractory group showed reduced connectivity in ACC, prefrontal cortex, hippocampus, insula, amygdala. Refractory group showed reduced connectivity in prefrontal and thalamic areas. Nonrefractory compared to refractory showed reduced connectivity in left amygdala-ACC-right insula-precuneus region.	Nonrefractory MD and refractory MD are characterised by distinct functional abnormalities.
Peng et al. (2011)	16 patients with MD (mean age: 34.1); 16 healthy controls (mean age: 33.7)	Decreased ReHo in left thalamus, left temporal lobe, left cerebellar posterior lobe, and the bilateral occipital lobe in MD group.	Abnormal spontaneous activity in the left thalamus, left temporal lobe, left cerebellar posterior lobe, and the bilateral occipital lobe in MD as a reference for distinct brain activity signatures in resting state fMRI.
Sheline et al. (2010)	18 patients with MD (mean age: 35.9); 17 healthy controls (mean age: 30.9)	Increased functional connectivity in bilateral DMPFC region in MD group. Functional connectivity in dorsal nexus positively correlated with HAMD scores.	Functional abnormality in dorsal nexus underlies emotional dysregulation.
Wu et al. (2011)	22 nonrefractory MDD patients (mean age: 35); 22 refractory MDD patients (mean age: 35); 26 healthy controls (mean age: 33)	Both MD groups showed high ReHo within temporo-limbic structures and low ReHo in frontal, parietal, posterior fusiform cortices, caudate. Refractory showed more ReHo alterations than nonrefractory. Correlation between ReHo alterations and clinical severity.	ReHo could be used as clinical tool to monitor persistent MD.
Yao et al. (2009)	22 patients with MDD (mean age: 38.2); 22 healthy controls (mean age: 38.8)	MD group showed decreased ReHo in numerous regions. Symptom domains such as anxiety severity, cognitive disturbance, retardation severity, sleep disturbance, and hopelessness	Extensive distribution of functional abnormalities in depression. Some symptom domains are separately mediated by separate abnormalities.

Table 1 (*continued*)

Study	Subjects	Principal Findings	Interpretation
		showed distinct correlations with ReHo in implicated regions.	
Zhou et al. (2010)	18 patients with MDD (mean age: 38.9); 20 healthy controls (mean age: 40.6)	MD group showed increased positive or negative functional connectivity in group-common and group-specific intrinsic regions. Length of current episode correlated positively with functional connectivity between R inferior frontal gyrus and L middle frontal gyrus.	Abnormally increased neural sources recruitment in regions known to be related to emotion, attention, and memory could provide neural basis for the negative bias observed in MD.

useful in identifying functional clusters within the brain, activities of which could be modulated by various conditions (Qiu et al., 2011). Because of its dependence on the synchronous activities of neighbouring voxels, the ReHo analysis is limited in its usefulness for representing functional connections between spatially distant structures. This is an aspect in which both ROI analysis and ICA are superior. However, the methodologies involved in ReHo analysis have been largely consistent across different studies, and it shows promise toward supplementing ROI analysis and ICA studies by illuminating key structures that might be missed due to the inherent biases in the latter approaches. As of now, there is very little discussion in the field that make comparisons between ReHo and the other types of analyses, and this is another area that warrants closer inspection.

3.2. Resting-state fMRI studies in major depression

The majority of resting-state fMRI studies in MD have their theoretical basis in anatomical, positron emission tomography (PET), and activation fMRI studies that have come before them. In terms of discrete structures, along with the MPFC and the amygdala, there is additional interest in the role of the anterior cingulate cortex (ACC) and the hippocampus, both of which have been shown to have anatomical and functional abnormalities in MD. Specifically, activation fMRI studies have found elevated activity in the ACC in MD patients, which is thought to be evidence of abnormal processing of environmental stimuli in MD (Ebmeier et al., 2006). Meta-analyses have pointed to a reduction in hippocampal size in MD patients, suggesting its possible use as a diagnostic neurobiomarker for MD (Cole et al., 2011; Kempton et al., 2011). When considering functional connectivity networks in the depressed brain, the default-mode network (DMN) (Broyd et al., 2009) and the prefrontal-amygdalar-pallidostriatal-mediothalamic mood regulating circuit (MRC) are frequently cited as regions of abnormal synchrony (Anand et al., 2005a).

In a series of related studies (Anand et al., 2007; Anand et al., 2009; Anand et al., 2005a), Anand et al. placed the ROI in the cortico-limbic MRC. In the first experiment, which was a direct resting-state fMRI comparison between depressed patients and healthy controls, the MD group was found to have decreased functional connectivity between the ACC and three structures: the amygdala, the pallidostriatum, and the medial thalamus, suggesting a decreased regulatory effect of the ACC over the mood-regulating limbic areas. Notably, anti-depressant treatment (i.e. sertraline) increased resting-state functional connectivity in the depressed group, but not in the control group. A third study introduced comparisons with BD patient groups in various stages of their mood disorder. Both depressed and BD patients exhibited decreased cortico-limbic connectivity compared to healthy controls, but the difference was more pronounced in BD patients. Taken together, the work by Anand et al. suggests a possible mechanism of cortico-limbic mood dysregulation in MD and other mood disorders.

A number of other studies followed with similar explorations of mood-regulating networks. Cullen et al. found that depressed adolescents showed decreased functional connectivity between the subgenual anterior cingulate cortex (sgACC) and a number of cortical areas, including the right medial frontal cortex, the left superior and inferior frontal cortices, left superior temporal cortex, and the insula cortex (Cullen et al., 2009). These findings implicate the sgACC as being a central component in the abnormalities that characterise brain networks in MD. The insula and its role in interoception suggests that abnormalities pertaining to the insula cortex could underlie several affective symptoms such as somatic complaints and negative bias in interpreting interpersonal feedback (Fitzgerald et al., 2008). Lui et al. extended the findings of Anand et al. (Anand et al., 2007; Anand et al., 2009; Anand et al., 2005a) and Cullen et al. (Cullen et al., 2009) by showing bilaterally reduced functional connectivity within the prefrontal-limbic-thalamic areas, in particular in regions subserved by the left amygdala-ACC and the right insula-precuneus region, in depressed patients (Lui et al., 2011).

Bluhm et al. investigated the hypothesis that DMN abnormalities mediate depression with a ROI analysis in the precuneus and the PCC. The depressed group displayed bilaterally significantly reduced precuneus and PCC connectivity with the caudate (Bluhm et al., 2009). This finding indicates aberrant functioning within the striatum, which contains the caudate nucleus and is involved in the processing of reward stimuli (Haruno et al., 2004). Possibly, discrepancies in the reward-processing network are involved in anhedonia and lack of motivation, both of which are prominent features of MD. In a separate study, a sample of late-life depression (LLD) patients showed widespread increased connectivity between the head of the caudate nucleus (hCN) and various brain regions thought to be integral to the DMN (Kenny et al., 2010). The main function of the DMN is believed to be self-referential thought and attention-orienting (Broyd et al., 2009). Thus, the increased connectivity in this network in depressed patients suggests that abnormalities in self-referential thought and attentional shifts contribute to MD. Kenny et al. has also emphasised that affective disorders are more likely due to aberrations at the circuit level rather than at a localised brain region (Kenny et al., 2010).

Another research group sought to further delineate the brain circuits that are relevant to MD by examining seed regions in the task-positive network (TPN), thought to activate during attentional tasks, and the task-negative network (TNN), which activates during self-reflective tasks (Zhou et al., 2010). Depressed patients exhibited widespread increased connectivity in both networks compared to healthy controls. Zhou et al. hypothesised that the increased functional connectivity within the TPN may serve to relate previous negative experiences into negative expectations, whereas that in the TNN may play a role in enhancing negative memories. Involvement of both the TPN and the TNN suggests a concurrence of negative attentional bias and negative memory bias in MD. Keeping the focus on identifiable functional networks in the brain, Sheline et al., 2010 found that MD patients showed increased connectivity between the

dorsomedial prefrontal cortex (DMPFC) and the precuneus, the dorsolateral prefrontal cortex (DLPFC), and the subgenual ACC, which are regions involved in the DMN, the cognitive control network (CCN), and the affective network (AN) respectively. In the same study, there were positive correlations between DMPFC connectivity and Hamilton Depression Rating Scale (HAMD) scores, lending support to the claim by Anand et al. that abnormal associations between the DMPFC and various brain networks contribute to some of the dysfunctions seen in MD.

Greicius et al. provided the only ICA-driven resting-state fMRI study in the present sample of studies (Greicius et al., 2007). Increased functional connectivity in the sgACC, the thalamus, the orbitofrontal cortex, and the precuneus were all significant. All of these regions have been previously implicated in ROI studies, suggesting that abnormal connectivity in these regions are a robust feature in the depressed brain. In addition, functional connectivity in the sgACC was positively correlated with measures of disease refractoriness (Greicius et al., 2007).

Horn et al. extended findings in neuroanatomical connectivity with an added focus on metabolic involvement as measured using proton magnetic resonance spectroscopy (^{1}H –MRS) (Horn et al., 2010). Resting-state fMRI showed severely depressed patients to have increased connectivity between the pregenual anterior cingulate cortex (pgACC) and the left anterior insula. This connectivity was negatively correlated with the glutamine:creatine ratio in the pgACC, but only in the depressed groups. HAMD scores were positively correlated with functional connectivity and negatively correlated with the glutamine:creatine ratio in the pgACC. Therefore, abnormal functional connectivity in MD is likely to be accompanied by abnormal metabolic activity in these same brain regions.

Several research groups have independently produced findings from resting-state ReHo studies. A wide range of increased and decreased ReHo has been found in depressed subjects in structures implicated in other resting-state fMRI studies, including the ACC, the insula, the thalamus, the MPFC, the hippocampus, the caudate, and the precuneus (Guo et al., 2011; Liu et al., 2010; Peng et al., 2011; Wu et al., 2011; Yao et al., 2009). Multiple studies found ReHo differences in the fusiform gyrus and the cerebellum (Guo et al., 2011; Liu et al., 2010; Wu et al., 2011). The fusiform gyrus is widely purported to be the processing centre of facial stimuli and its abnormal activity has been associated with symptoms of depression (Demenescu et al., 2011). The cerebellum has been previously identified as relevant to depression (Fitzgerald et al., 2008), but its role in emotional dysregulation remains poorly understood.

4. Discussion

The use of resting-state fMRI in MD research is relatively new, however, the number of published studies continues to steadily increase, signifying an intensifying interest in the technique among researchers. The literature thus far has uncovered a wide array of brain regions that exhibit group differences between depressed subjects and healthy controls. Therefore, the perceived value and importance of resting-state fMRI research in MD are likely to continue to grow. Neuroimaging studies of MD typify an increasingly popular view that functional abnormalities in neural networks, rather than those in discrete brain structures, underlie the pathophysiology of psychiatric conditions.

One of the most robust patterns that have emerged in the literature is that of the abnormal involvement of the cortico-limbic MRC in MD. Structures in the limbic area that have shown abnormal activation in depressed patients include the medial thalamus, thought to be involved in emotional perception, and the amygdala, which plays a key role in the neural response to negative stimuli (Anand et al., 2005a). Cortical regions such as the ACC are thought to have a regulatory role over the limbic structures that process emotional stimuli (Anand et al., 2005b). A breakdown in this circuitry could potentially explain the development of depressive characteristics such as negative bias in interpersonal feedback and somatic complaints (Cullen et al., 2009). Indeed, a number of different research groups have found abnormal functional connectivity incorporating the ACC and limbic structures (Anand et al., 2005a, b; Cullen et al., 2009; Horn et al., 2010; Liu et al., 2010), suggesting its importance as a biomarker for MD. The notion of a dysregulation in the neural network that subserves mood perception being attributable to symptomatic mood disturbances offers an elegant model for understanding the pathophysiology of affective disorders, and is supported by the current evidence from resting-state fMRI studies. Furthermore, there is evidence to suggest that anti-depressant treatment has reciprocal effects on this functional network (Anand et al., 2007). In the study by Sheline et al., 2010, the network incorporating the subgenual and pregenual cingulate and the amygdala is called the affective network and was found to show increased activity in MD patients. It is speculated that this network is involved in appetite, libido, and sleep, the disruption of any of which can be a hallmark symptom of MD (Sheline et al., 2010). However, additional studies with larger, homogenous cohorts are needed to better delineate this relationship.

The DMN is one of the more commonly recognised resting-state networks in the brain, containing structures such as the MPFC, the PCC, the precuneus, and the medial, lateral, and inferior parietal cortices (Broyd et al., 2009). From the current body of research, all of these regions have been demonstrated to have abnormal resting functional connectivity in depressed patients. This strongly suggests pervasive involvement of DMN abnormalities in MD. However, there is yet to be a clear interpretive model for attributing increases (or decreases) in DMN functional connectivity to definable functional deficits. Often, increased and decreased resting connectivity were found together in the same network and in the same subject groups. Of particular interest in this context is the role of the DMPFC, which was found to have increased connectivity with the DMN (Sheline et al., 2010). To better understand how DMN abnormalities modulate the pathophysiology of MD, there is a need for continued cross-referencing with activation fMRI studies to further elucidate the functional neuroanatomy of resting-state networks.

The literature suggests there is evidence of increased connectivity in the TPN in depressed patients (Zhou et al., 2010), which must be considered in conjunction with the DMN, which is generally considered to be a TNN (Broyd et al., 2009). An increasingly popular interpretive approach is to consider the anti-correlations between the TPN and the TNN as components of the same functional network, with the view that temporally anti-correlated activities of the two networks are as, if not more, functionally important as their independent activities (Broyd et al., 2009). This temporal anti-correlation between the TPN and the TNN is indeed increased in depressed subjects compared to healthy controls, suggesting that the excessive competition between mental activities subserved by the two networks could underlie some of the symptoms of MD (Zhou et al., 2010). The involvement of TPN and TNN as elicited by Zhou et al. is reinforced by Sheline et al. who found increased activity of the cognitive control network and the affective network. Therefore, the role of TPN and TNN, possibly in relation to connectivity with the DMPFC (Sheline et al., 2010), is an area that warrants further investigation. Moreover, resting-state research in MD could be better served by expanding the focus onto other resting-state networks that have been identified, including the visual and auditory networks (Broyd et al., 2009).

There is growing evidence from neuroimaging studies that the cerebellum, long considered to be mainly sensorimotor in its function, plays a role in the emotional and cognitive processing of negative stimuli (Schraa-Tam et al., 2011). Several resting-state fMRI studies have now identified cerebellar abnormalities in MD (Guo et al., 2011; Liu et al., 2010; Peng et al., 2011). However, these were ReHo studies, which are sensitive to the temporal homogeneity in local clusters but are not designed for detecting connections between spatially distant regions, which makes it difficult to expand these findings into an understanding of resting-state networks (Cole et al., 2010). In order to consider the cerebellum in the context of functional networks and to better understand its role in MD, ROI analyses and ICA would need to be conducted to complement these ReHo findings.

Several studies examined resting-state fMRI in MD in the context of stages of development (Cullen et al., 2009; Kenny et al., 2010) and of resistance to treatment (Guo et al., 2011; Lui et al., 2011; Wu et al., 2011). Resting-state fMRI studies on adolescent depression or geriatric depression are presently too few in number and lack between-group comparisons. On the other hand, group differences in functional connectivity and ReHo were present between refractory and non-refractory MD patients. Any significant insight into these issues would require more studies of this type and the replication of current findings.

One of the most cited limitations in resting-state fMRI studies is the need to correct for physiological artifacts due to respiration and cardiac activity. With the current fMRI technology, low-frequency noise from the cardiac and respiratory cycle alters the results of resting-state fMRI. The ICA method, due to its post-hoc component analysis, is better equipped to extract the physiological noise than the ROI analysis method (Guo et al., 2011). Nonetheless, improved familiarity with the technique and advancement in image acquisition technology will offer generalised benefits to the field.

The variance in medication history and clinical characteristics among subjects is possibly a significant confounding factor. Depression patients inevitably have a markedly different medication history from healthy controls. Accordingly, interpretations of such data, which may contain a medication confound, needs to be conducted in a conservative manner. Group comparisons between medicated and drug-naïve depression is one possible approach to dealing with the vexed issue of medication. MD is often comorbid with symptoms of other psychiatric conditions such as anxiety, and often presents with considerable diversity in symptomatology (Cullen et al., 2009). As such, it is difficult to establish clear correlations between specific findings and MD. Striving to recruit larger, more homogenous cohorts of patients will help alleviate the confounding effects related to both medication and clinical presentation.

Presently, there is no established consensus on how to best compare and synthesise findings from studies that employ different analytical approaches. This article has described studies that employed ROI, ICA, and ReHo analysis, each of which produced, for the most part, corroborating results, however, in a few instances, contradictory findings also. The ROI analysis has been favoured because its ease in interpreting outcomes. This is reflected in the extant literature, synthesised in this article, where the majority of the studies had successfully undertaken an ROI approach. Taken as a group thus far, the main usefulness of ROI studies in MD appears to be in forming the basis for a direct study-to-study comparison. The relatively fixed nature of the ROI method readily lends itself to reproducibility of studies across groups and is particularly amenable to longitudinally designed studies. A good example of the advantages of the ROI approach is reflected by the series of experiments by Anand et al., 2005, 2007, and 2009, whereby repeated use of ROI analyses focusing on the ACC and limbic structures consistently demonstrated a robust pattern of abnormalities across groups of MD patients. Despite this, the ROI approach alone does not take full advantage of the power of resting-state fMRI approach in studying MD. Increased application of the ICA and ReHo methods needs to be encouraged with the aim that a more complete picture of the functional neuroanatomy of MD can be constructed. The similarity between the ICA and ReHo methods lies in their lack of *a priori* constraints, thus affording the opportunity to discover previously unconsidered abnormalities of and relationships between discrete structures. In this regard, ReHo studies have proven useful in pointing out the potentially significant involvement of the cerebellum and the fusiform gyrus in MD. However, the emphasis moving forward might be better placed in the use of ICA, as it comes with the added benefit over ReHo of eliciting functional connectivity maps, and therefore the ability to describe resting-state networks. While meaningful conclusions can certainly be drawn from individual ICA studies, they are likely to prove most valuable as a launching point for more focused ROI studies, which then leads to direct synthesis and comparisons of findings. In general, resting-state fMRI studies of psychiatric populations would benefit greatly from collaborative efforts between research groups aimed at constructing a viable foundation for analysis and comparison.

5. Conclusion

Resting-state fMRI is a valuable neuroimaging modality for studying MD. Numerous research groups have pursued this avenue with promising results, and interest is still growing. The current evidence largely suggests abnormal resting functional connectivity in the cortico-limbic MRC and the DMN to be contributing to the pathophysiology of MD. Continued efforts to study resting-state fMRI in MD, in conjunction with other neuroimaging modalities, will advance our understanding of the involvement of neural networks in disease processes. Resting-state fMRI is a versatile technique that can be applied to study other resting-state networks in the brain, to compare functional differences between different stages of disease development, and to explore treatment possibilities. Technological advancement, larger and more homogenous cohorts, and an established model for comparisons between different analysis methods are worthwhile considerations for future studies.

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Conflict of interest

The authors of this manuscript do not have any conflicts of interests to disclose.

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