Systematic Review of an Emerging Trend in China: Resting-State Functional Connectivity in Major Depressive Disorder

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Major depressive disorder continues to challenge medical and psychological resources worldwide. A marked surge has occurred recently in China in neuroimaging studies of major depressive disorder. Those studies represent an emerging trend in neuropsychiatry in that such research has previously been extremely rare in China. The present article provides a systematic review of reports published in English by research institutes in China on resting-state functional connectivity studied by MRI in depressed subjects and healthy control subjects. Particular attention is given to whether the information may advance effective diagnosis and treatment options for patients with major depressive disorder.

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One interesting feature of brain imaging in China concerns the clinical condition of depressed subjects that participate in research projects. In many cases, they are severely depressed but have never received treatment during their first episode of major depressive disorder that may have lasted up to several months. The fact that such treatment-naïve individuals can be found for research projects in China, despite the adversity of their depressive condition, was accounted for recently by Wang et al.[1] They explained that a large number of patients with mental diseases in China remain unidentified until their disorder becomes particularly severe. In fact, 90% of persons with mood disorders requiring treatment never receive any type of professional help before turning up at major mental health centers.[2] Those conditions in China have made it possible to perform large studies of first-episode treatment-naive patients with severe mood disorders that have lasted for several months. Such a population of subjects with major depressive disorder is unique in providing favorable conditions for studying possible links between brain function and psychopathology.

China continues to expand in terms of neuroscience research. Of particular interest for this review is a recent surge in the use of MRI with mood disorders in China. That surge is evidenced by the fact that only six studies from China had been published in English on functional connectivity in mood disorders prior to April 2012,[3] whereas more than 30 reports are included in the present account (Table 1). My interest in studies carried out on mood disorders in China stems primarily from a recent collaboration that alerted me to uncertainties in such findings.[4] The present review concerns studies published in English on functional connectivity in the brain of depressed subjects by groups in China, with particular interest in the potential impact of such research for effective diagnosis and treatment options for patients with neuropsychiatric disorders.

METHODS

Literature Search

Reports cited in this article were retrieved on June 20, 2013 using PubMed and keywords "resting state fMRI major depression." Abstracts of the retrieved articles were examined to find studies carried out in China. Reference lists of those articles were searched for further reports of interest. Four criteria were used for inclusion of reports in this review (Figure 1): (1) the research must have been carried out in China alone, (2) the report must contain an adequate description of experimental methods including appropriate diagnostic procedures, (3) the report must provide an adequate presentation of statistical methods and empirical results, and (4) the study must include a nondepressed, healthy control group for comparison with individuals that have a history of major depressive disorder.

Main Features of Resting-State Neuroimaging

Recent advances in the acquisition and analysis of resting-state MRI data have provided a means of assessing functional connectivity in the human brain.[5] Originally, Raichle et al. used positron emission tomography (PET) to study oxygen

metabolism in the normal adult human brain and noted an unexpected decrease in oxygen metabolism in some brain regions when subjects changed from a resting condition to a more active condition, in which they processed visual stimuli.[6] They coined the term "default mode network" to encompass brain regions that had higher levels of oxygen metabolism while at rest than while actively engaged in a cognitive task. They stated that the default mode network, consisting primarily of regions of the medial parietal cortex (i.e., precuneus and posterior cingulate), bilateral inferior parietal cortex, ventromedial frontal cortex, and cerebellum may be intimately involved in cognitive functions.[7] Since then, possible relationships between brain function in the resting state and psychic disorders have inspired studies of major depressive disorder, and numerous networks have been described.[8–11]

Resting-state MRI requires only that subjects remain as motionless as possible while they lay on their back within the confines of the scanner. They are instructed to relax and not to think of anything in particular.[12,13] Subjects are told to keep their eyes opened in some studies, whereas in other studies they are instructed to keep their eyes closed. Subjects are fitted with earplugs to reduce the penetrating noise generated by the scanner, and their head is held in place by padding inside a sturdy mask-like head holder that contains signal detection equipment. Although the time needed for resting-state MRI is usually less than 10 minutes, subjects may spend more than 30 minutes in the scanner for the technicians to properly carry out all procedures.

MR scanners use rapid fluctuations in electromagnetic fields to induce changes in the orientation of electrons spinning about atoms in the body. For an MRI scan of the brain, an echo-planar scanning sequence is typically used for recording the temporal level of oxygen in the bloodstream throughout the brain, a parameter known as the blood-oxygen-level-dependent (BOLD) response.[14–16] The software provided by the MR scanner records a digital time series of BOLD signals emanating from millions of individual cubic units, known as voxels, in the brain.[17,18] Thus, MRI data are time series of the frequency and amplitude of oscillations in the BOLD signal that occurred in the brain of the subject in the MR scanner during the recording session. It is important to keep in mind that the BOLD signal is only an indirect indicator of hemodynamic events in the brain and that the relationship of the BOLD signal to neuronal activity remains unsettled.[19] Recent studies show that variables affecting cerebral blood flow, such as respiration rate, caffeine, and psychotropic drugs,[20–22] require close attention in comparisons of BOLD signal activations between subjects with neuropsychiatric disorders and healthy control subjects.

Main Features of Resting-State Functional Connectivity MRI

Analysis of data from studies of resting-state functional connectivity MRI (rs-fcMRI) produces a correlation matrix for BOLD signals arising from pairs of individual voxels in the brain.[23,24] Voxel pairs that have a relatively high correlation coefficient for the time course of their BOLD signals are said to show functional connectivity.[24–26] Correlation coefficients for depressed subjects are compared with those for healthy subjects to determine whether functional connectivity differs markedly between the two groups.

Analysis of resting-state MRI data can be data-driven or model-driven.[5,13] Data-driven analyses make few assumptions concerning the characteristics of the BOLD signal and regarding whether they must be similar between brain regions. Data-driven functional MRI (fMRI) analyses can often detect short-lived variations in BOLD signals that may identify unexpected functional links between brain regions.[27] In contrast, model-driven analyses assume that the defining characteristics of the BOLD signal are known and that they are identical for all brain regions. For those who are unfamiliar with the methods that are currently used for data analysis of rs-fcMRI recordings, here is a brief account of their main principles.

Main Principles of rs-fcMRI Data Analysis

Regional homogeneity (ReHo) is a data-driven approach that assumes that the time series of BOLD signals for a given voxel is temporally similar to that of its neighbors.[13] The outcome of ReHo analysis of fMRI data are an array of ranked correlations describing the synchrony of BOLD signals emanating from adjacent voxels or clusters of voxels. Higher correlations of BOLD signals among adjacent regions in one group of subjects than in another group reflects greater ReHo that is commonly interpreted as an indication of more functional connectivity. One advantage of ReHo for analysis of fMRI recordings is claimed to be disclosure of unexpected regional functional connectivity, because the method has no a priori requirement for intraregional hypotheses.[13] ReHo has become increasingly popular in studies of resting-state fMRI in China and elsewhere.[28] Recent work in China shows, however, that the outcome of ReHo depends heavily on the selection of experimental procedures.[29] Analysis of fMRI data according to ReHo is carried out by a nonparametric statistical procedure known as Kendall's coefficient of concordance (KCC), which normalizes the data and assigns a value to the time series of an individual voxel with respect to its nearest neighbors ranging from 0 (no similarity) to 1 (identical). Thus, ReHo provides a qualitative, ranked index of the similarity of fluctuations of BOLD signals (i.e., synchrony) among adjacent voxels within the brain. ReHo uses only the correlation between the ranks of BOLD time series to assess functional connectivity.

Coherence-based regional homogeneity takes the frequency distribution of BOLD signals into account for estimating the degree of similarity between voxels.[30]

Seed-based analysis of resting-state fMRI data is a model-driven approach that requires selection of a region of interest in the brain as a starting point for generating correlation matrices based on BOLD signals in the region of interest compared with other regions.[7,31]

Voxel-mirrored homotopic connectivity (homotopic means "same place") is a computer-based procedure that uses data from resting-state fMRI to explore correlations between BOLD signals from identical sites on opposite sides of the brain.[32–34]

TABLE 1. Summary of Resting-State MRI Studies of Functional Connectivity in Subjects With Major Depressive Disorder and Healthy Control Subjects in China[a]

Data Analysis	MDD>HC	MDD<HC	Reference
First-episode, treatment-naïve depressed subjects			
ReHo		Left middle temporal gyrus genotype-dependent	92
ReHo	No differences	No differences	93
Seed-based anterior cingulate cortex and thalamus	Left parahippocampus, parietal lobe and frontal lobe	Right parietal lobe and cingulate gyrus	45
Seed-based left posterior cingulate cortex	Bilateral dorsolateral prefrontal cortex and inferior parietal lobe	Medial prefrontal cortex / orbitofrontal cortex	46
VMHC		Medial prefrontal cortex and posterior cingulate cortex / precuneus	47
ALFF	Fusiform gyri and anterior and posterior lobes of the cerebellum	Left inferior temporal gyrus and right inferior parietal lobe	1
ALFF	Left superior occipital gyrus and cuneus	Right cerebellum posterior lobe, left parahippocampal gyrus and right middle frontal gyrus	39
ALFF	Right dorsolateral frontal cortex, bilateral inferior frontal gyrus and orbital frontal region	Left insula, bilateral caudate and left hippocampus	43
Network analysis	Left hippocampus and right parahippocampal gyrus	Left superior orbitofrontal cortex and left medial frontal cortex	48
Graph analysis	Anterior cingulate cortex, dorsolateral, medial and inferior prefrontal cortex, insula, amgydala and superior and middle temporal gyri		44
Depressed outpatients			
ReHo	Insula, cerebellum anterior lobe, middle frontal gyrus, superior temporal gyrus, lentiform nucleus, precentral gyrus and postcentral gyrus	Interior frontal gyrus, inferior parietal lobule and posterior lobe of the cerebellum	50
ReHo and ROI analysis	Bilateral anterior cingulate cortex, medial prefrontal cortex, right insula and right parahippocampalgyrus	Left posterior fusiform gyrus, inferior frontal area, inferior parietal lobule and caudate	51
ReHo		Right orbitofrontal cortex, fusiform gyrus, ventral anterior cingulate gyrus, posterior cingulate gyrus. Left dorsal anterior cingulated gyrus and lentiform nucleus	55
ReHo	Right inferior temporal gyrus	Left posterior lobe of the cerebellum, right fusiform gyrus, left parahippocampal gyrus and right postcentral gyrus	56
ReHo		Left thalamus, left temporal lobe, bilateral occipital lobe and left posterior lobe of the cerebellum	94
Seed-based cerebellar regions	Regions of the cerebellum, left middle frontal cortex and poles of the temporal cortex	Regions of the cerebellum, posterior cingulate cortex, ventromedial prefrontal cortex, superior frontal gyri, left orbitalfrontal gyrus and hippocampus	12
Seed-based right dorsolateral prefrontal cortex	Right dorsolateral prefrontal cortex, left anterior cingulate cortex, left parahippocampal gyrus, thalamus and precentral gyrus	Right dorsolateral prefrontal cortex and right parietal lobe	52
Seed-based left and right hippocampus		Left and right hippocampus, middle frontal gyrus, inferior parietal lobe and cerebellum	53
Seed-based left and right amygdala		Amygdala and left ventral prefrontal cortex	54
Seed-based 16 ROIs		Left thalamus and right cingulate cortex; right insula and precuneus	57

continued

TABLE 1, *continued*

Data Analysis	MDD>HC	MDD<HC	Reference
ALFF	Right dorsomedial frontal gyrus and right precuneus	Bilateral lingual gyri	49
Treatment-resistant, depressed subjects			
ReHo	Left superior temporal gyrus, anterior and posterior lobe of the cerebellum, right cerebellar tonsil and bilateral fusiform gyrus	Left insula, superior temporal gyrus, inferior frontal gyrus, lingual gyrus and anterior lobe of the cerebellum	95
Seed-based 16 ROIs		Precuneus, left middle frontal gyrus and cingulate cortex	57
Seed-based gray matter volume of right middle temporal gyrus and right caudate nucleus	Right precuneus, middle temporal gyrus, bilateral superior frontal gyrus and left middle frontal gyrus	Right cuneus	63
Elderly depressed subjects			
ReHo	Left anterior insula, right posterior insula and right dorsolateral prefrontal cortex	Right orbitofrontal cortex, left middle frontal gyrus, left dorsolateral prefrontal, left inferior temporal gyrus and left postcentral gyrus	67
ReHo	Superior frontal gyrus, postcentral gyrus and putamen	Superior and middle frontal and temporal gyri, postcentral gyrus, fusiform gyrus and precuneus	68
Cohe-ReHo	Left posterior lobe of the cerebellum, left superior temporal gyrus, bilateral supplementary motor area and right postcentral gyrus	Left caudate nucleus, right anterior cingulate gyrus, left dorsolateral prefrontal cortex, right angular gyrus, bilateral medial prefrontal cortex and right precuneus	64
Seed-based posterior cingulate cortex	Posterior cingulate cortex and temporal cortex	Posterior cingulate cortex and frontal cortex	65
Suicidal, traumatized, or somatically ill depressed subjects			
ALFF	Parahippocampal gyrus, anterior cingular gyrus and angular gyrus of the parietal lobe		69
ALFF	Anterior and posterior lobes of the cerebellum	Right dorsolateral prefrontal cortex, ventromedial prefrontal cortex, superior frontal cortex, right middle temporal gyrus and rostral anterior cingulate cortex	71
Graph analysis		Prefrontal cortex and anterior cingulate gyrus	70

[a] ALFF: Amplitude of low frequency fluctuations; Cohe-ReHo: coherence-based regional homogeneity; HC: health control subjects; MDD: major depressive disorder; ReHo: regional homogeneity; ROI: region of interest; VMHC: voxel-mirrored homotopic connectivity.

Because ReHo and seed-based analyses of resting-state fMRI recordings fail to indicate the direction and the mutual throughput of functional connectivity, voxel-mirrored homotopic connectivity was developed to address these issues.[23,35]

Amplitude of low frequency fluctuations (ALFF) takes the amplitude of brain activity as measured by BOLD signals in resting-state fMRI into account.[36,37] In ALFF, the power spectrum of BOLD signals in the low-frequency range is used for calculating correlations to estimate the degree of functional connectivity among voxels.

Fractional ALFF is the procedure in which ALFF values for each voxel are divided by the global ALFF mean to normalize the data prior to statistical comparisons.[38,39]

Network analysis is a computational procedure that views the brain as a whole in search of dynamic, functional networks.[40]

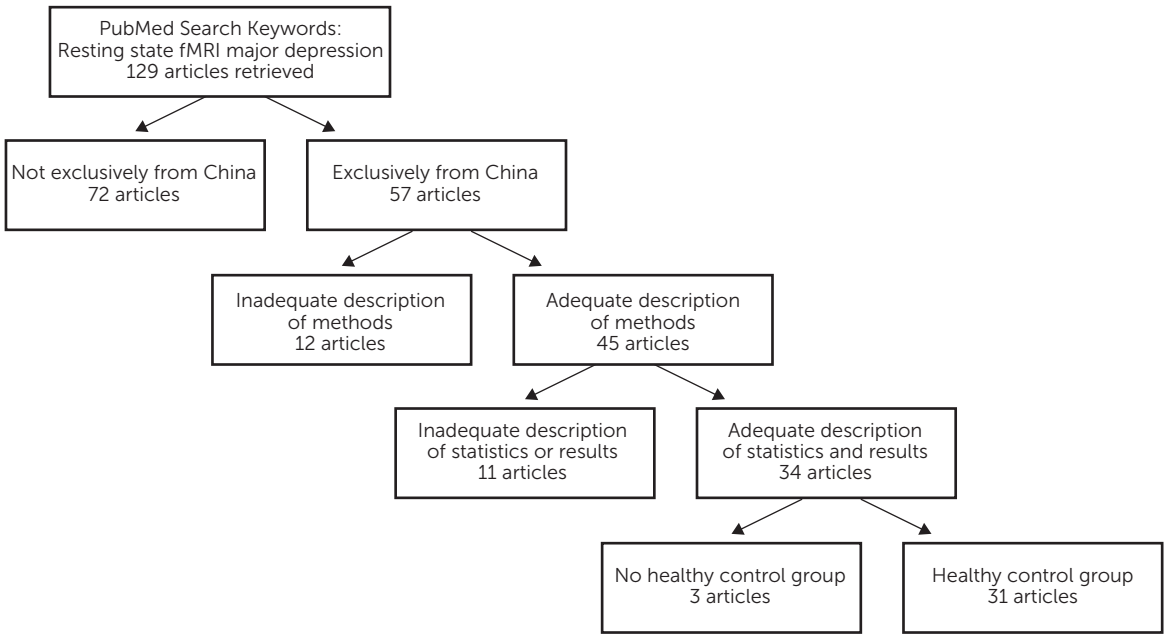
Graph analysis, on the other hand, is a computational procedure that views the human brain as consisting mainly of dense clusters of local connectivity with relatively few long-range connections between any pair of neurons or brain regions.[41] In graph theory, the likelihood that a particular region is a node in a network is defined by the number of nodes with strong correlations with the target node.[42] Graph analysis uses correlation coefficients to determine the degree of connectedness of nodes identified on the basis of whole-brain BOLD recordings.

RESULTS

First-Episode, Treatment-Naïve Depressed Subjects

Ten studies were found that have been carried out in China and published in English on rs-fcMRI in first-episode, treatment-naïve depressed subjects (Table 1). These studies are unique in providing information on potential disturbances in pristine cases of severe and untreated major depressive disorder. If

FIGURE 1. Flux Diagram Showing the Criteria for Selection of Articles for Review



consistent differences were to be found by rs-fcMRI between such subjects and healthy control subjects, then the methodology would provide invaluable information on cerebral function of great clinical utility. Sadly, these studies failed to provide consistent findings. Thus, four studies noted greater functional connectivity in regions of the frontal cortex of first-episode, treatment-naïve depressed subjects than healthy control subjects,[43–46] whereas three other studies found lesser functional connectivity in frontal regions of depressed subjects than in healthy control subjects.[39,47,48]

The regions of the parietal and temporal lobes, as well as the hippocampus, have also received marked attention in studies carried out in China on first-episode, treatment-naïve depressed subjects and healthy control subjects, but they too have failed to reveal consistent patterns of differences in rs-fcMRI findings between the two groups (Table 1). For example, greater functional connectivity was noted in the brain of first-episode, treatment-naïve depressed subjects than in healthy control subjects in parietal and temporal regions in five studies,[39,44–46,48] but three other studies obtained opposite results.[1,43,47]

Depressed Outpatients

Eleven studies were identified that used rs-MRI to study the functional connection in the brain of depressed subjects that were outpatients at psychiatric facilities in China (Table 1). Some of these outpatients may have been both in their first episode and treatment naïve, but no information was provided on that in the published reports. Five studies noted greater functional connectivity in frontal and prefrontal regions of depressed subjects than in healthy control subjects,[12,49–52] but opposite findings were described in five other reports.[12,52–55] Regions of the posterior cingulate, precureus, and temporal cortex were found to have greater functional connectivity in depressed subjects than in healthy control subjects in four studies,[12,49,50,56] but the situation was reversed in six other reports.[51–53,55,57,58] Functional connectivity in subcortical regions such as the thalamus, caudate, insula, and hippocampus also failed to differentiate consistently between depressed outpatients and healthy control subjects in this series of studies.

Treatment-Resistant Depressed Subjects

Three studies were noted on rs-fcMRI in treatment-resistant depression, which is currently a major challenge in clinical practice (Table 1).[59,60] Over the years, much attention has been given to whether consistent disturbances in brain function characterize treatment-resistant depression, in hope of finding effective cures.[61,62] Of the studies on rs-fcMRI that have been carried out in China in treatment-resistant depressed subjects and healthy control subjects, no consistent findings have been obtained. For instance, functional connectivity was greater in the precuneus and middle frontal region of treatment-resistant depressed subjects than in healthy control subjects in one study,[63] whereas opposite findings were noted in another report.[57] It is, however, too soon to say whether further studies can disclose reliable features of functional connectivity that govern treatment-resistant depression.

Elderly Depressed Subjects

Four studies were found that compared functional connectivity in the brain of elderly depressed subjects with that in age-matched healthy control subjects (Table 1). Two of the studies noted greater functional activity in temporal cortex of elderly depressed subjects than in elderly healthy control subjects,[64,65] whereas opposite findings were reported in the other two studies.[66–68] Thus, no general

conclusion can be drawn on the direction of differences in functional connectivity that may characterize brain function in elderly depressed subjects versus age-matched healthy control subjects.

Suicidal, Traumatized, or Somatically Ill Depressed Subjects

A few recent studies have been carried out in China on functional connectivity in the brain of healthy control subjects versus depressed patients who were suicidal, traumatized in childhood, or afflicted by Parkinson's disease (Table 1). Greater functional connectivity was noted in the anterior cingulate cortex of depressed suicidal subjects than in healthy control subjects,[69] whereas lesser functional connectivity was found in the anterior cingulate cortex of depressed subjects traumatized in childhood and in depressed subjects with Parkinson's disease than in healthy control subjects.[70,71]

DISCUSSION

The main conclusion to be drawn from studies reviewed here on rs-fcMRI in depressed subjects and healthy control subjects in China is that consistent differences failed to appear for functional connectivity between the two groups. This conclusion coincides with the failure of other neuroimaging modalities to identify biomarkers that are specific for major depression disorder.[72–74]

One of the factors that may contribute to the failure of traditional research designs to identify reliable biomarkers of major depressive disorder concerns the heterogeneity of the disease.[75,76] Future studies of major depressive disorder may, therefore, require stratifying the disorder by longitudinal designs that assess brain function in relation to temporal variations in symptoms.[73] Another factor that may contribute to the failure of rs-fMRI to show consistent differences between depressed subjects and health control subjects relates to the diversity of techniques used for processing the BOLD signal.[77–81] Most data-processing procedures used for rs-fcMRI rest on correlation analysis, which is notorious for both false-positive findings and failing to demonstrate causal relationships.[82,83] Novel research designs in which rs-fcMRI recordings are carried out repeatedly to estimate test–retest reliability[84] in individual subjects in varying mood states may aid in identifying reliable relationships between mood state and functional connectivity in the brain. A third factor that may affect the outcome of studies on rs-fMRI in major depressive disorder relates to confirmation bias.[85–87] Over the years, neuroscience research has become an increasingly competitive field with an engrained "publish or perish" atmosphere. That situation may tend to cause researchers to use ever-increasing computing power plus a never-ending array of procedures for data analysis to achieve statistically significant findings that correspond with current notions on relationships between resting-state brain activity and psychic depression. Conformation bias may be limited by requiring preregistration of research project protocols and electronic submission of empirical data at public websites,[87] so that others can determine whether their procedures can replicate the outcome of the original study.[88,89]

For those interested in converting results from brain imaging studies in major depressive disorder into useful clinical guidelines, there is still a long way to go for rs-fcMRI. The failure of traditional research on rs-fcMRI to disclose reliable links in depressed subjects between symptoms and brain function has stimulated interest in alternative research strategies.[73,90] Detailed clinical assessment and neuroimaging of individual depressed subjects over time may serve to stratify subjects with major depressive disorder into evidence-based categories on the basis of syndrome subtypes. Neuroimaging studies may then aid in the selection of effective antidepressant treatment regimens.[91] Although longitudinal studies may require more subjects and more staff than are typically included in traditional cross-sectional research projects on rs-fcMRI, the use of mobile MRI units with highly trained technicians in major cities may facilitate the task. Such revisions of experimental designs in resting-state studies of functional connectivity in major depressive disorder in China as elsewhere may eventually provide information of clinical utility.

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