Journal of Affective Disorders 206 (2016) 280–286

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Functional alterations of fronto-limbic circuit and default mode network systems in first-episode, drug-naïve patients with major depressive disorder: A meta-analysis of resting-state fMRI data

Xue Zhong, Weidan Pu, Shuqiao Yao *

Medical Psychological Institute, Second Xiangya Hospital of Central South University, Changsha, Hunan 410011, China

ARTICLE INFO

Article history:
Received 13 June 2016
Received in revised form
2 September 2016
Accepted 8 September 2016
Available online 13 September 2016

Keywords:
First-episode
Drug-naïve major depressive disorder
Resting-state fMRI
Meta-analysis

ABSTRACT

Background: The neurobiological mechanisms of depression are increasingly being explored through resting-state brain imaging studies. However, resting-state fMRI findings have varied, perhaps because of differences between study populations, which included the disorder course and medication use. The aim of our study was to integrate studies of resting-state fMRI and explore the alterations of abnormal brain activity in first-episode, drug-naïve patients with major depressive disorder.

Methods: Relevant imaging reports in English were searched, retrieved, selected and subjected to analysis by activation likelihood estimation, a coordinate-based meta-analysis technique (final sample, 31 studies). Coordinates extracted from the original reports were assigned to two categories based on effect directionality.

Results: Compared with healthy controls, the first-episode, medication-naïve major depressive disorder patients showed decreased brain activity in the dorsolateral prefrontal cortex, superior temporal gyrus, posterior precuneus, and posterior cingulate, as well as in visual areas within the occipital lobe, lingual gyrus, and fusiform gyrus, and increased activity in the putamen and anterior precuneus.

Limitations: Not every study that has reported relevant data met the inclusion criteria.

Conclusion: Resting-state functional alterations were located mainly in the fronto-limbic system, including the dorsolateral prefrontal cortex and putamen, and in the default mode network, namely the precuneus and superior/middle temporal gyrus. Abnormal functional alterations of the fronto-limbic circuit and default mode network may be characteristic of first-episode, drug-naïve major depressive disorder patients.

1. Introduction

Major depressive disorder (MDD) is a common psychiatric disorder, characterized by a depressed or irritable mood, anhedonia, and feelings of guilt and worthlessness (Association, 1994). The World Health Organization projected that, by 2020, the disease burden of MDD would be second only to that of coronary heart disease, causing substantial personal and social problems (Sliz and Hayley, 2012). Despite continued growth of the interest in and literature addressing MDD, the findings have been inconsistent and the underlying neurobiological mechanisms of MDD remain elusive.

The inconsistency of previous studies may due to large part to the heterogeneity of clinical populations, including wide variations in exposure to antidepressants and clinical stage (e.g., first-episode vs. recurrent). For example, Anand's study demonstrated that after 6 weeks of sertraline treatment, the lower baseline low-frequency blood oxygen level-dependent fluctuations of cortico-limbic circuit in patients with MDD was significantly increased (Anand et al., 2005b). Similarly, a recent study (Wang et al., 2015) showed that after 8 weeks of escitalopram treatment, the decreased functional connectivity strength between bilateral dorsomedial prefrontal cortex in MDD patients was significantly increased. All those findings prove that antidepressants medication could alter the human brain functional organization in depressed patients.

Additionally, different resting-state data analytic methods used to identify functional abnormalities in MDD may also yielded inconsistent results. Generally, the analytical approaches for resting-state fMRI can be divided into two categories (Song et al., 2011).

Abbreviations: MDD, major depressive disorder; HCs, healthy controls; DMN, default mode network; ReHo, regional homogeneity; MNI, Montreal Neurologic Institute; DLPFC, dorsolateral prefrontal cortex; ALFF, amplitude of low frequency fluctuation; fALFF, fractional amplitude of low-frequency fluctuations; ICA, independent component analysis; FCD, functional connectivity density; FC, functional connectivity; VMHC, voxel-mirrored homotopic connectivity

* Corresponding author.
E-mail address: shuqiaoyao@163.com (S. Yao).

http://dx.doi.org/10.1016/j.jad.2016.09.005
0165-0327/

One analytical approach is based on depicting local features of spontaneous BOLD signal. The other category of analytical methods is measuring the functional relationship between distinct brain regions, which usually referred to as functional connectivity (FC). Those two methods of data analysis may reflect different aspects of neurophysiological mechanisms underlying MDD, hence yield different effects on the results.

Although some inconsistency exists between study results, numerous fMRI studies conducting with MDD patients over the last two decades have provided consistent insights into the functional alterations associated with this disorder. In accordance with Mayberg's classical neurobiological model (Mayberg, 1997, 2003), MDD has been regarded as a disorder involving fronto-limbic circuit dysregulation of several key regions, including the prefrontal cortex, cingulate cortex, amygdala, and striatum (Anand et al., 2009, 2005; Seminowicz et al., 2004; Sheline et al., 2010). Consistent with this model, patients with MDD were observed to have decreased frontal cortex function and increased limbic system function (Mayberg et al., 1999). Converging evidence has demonstrated that fronto-limbic circuit regulates mood, cognition, and behavior (Liu et al., 2010). For instance, the fronto-limbic circuit plays an important role in regulating mood and affect as it's centrally involved in integrating exteroceptive and interoceptive inputs (Mayberg, 1997; Price and Drevets, 2010), which therefore correlated with the altered processing on stimulus salience and emotional valences in MDD patients (Hamilton et al., 2012; Liao et al., 2012; Zhang et al., 2016). Furthermore, dysfunction of this circuit are also responsible for the failure to sustain engagement in rewarding behavior of MDD patients (van Tol et al., 2013). Importantly, recent resting-state fMRI studies have found that both functional connectivity and spontaneous BOLD signal of brain were abnormal alterations in the frontal-limbic circuit in first-episode, drug-naïve MDD patients (Guo et al., 2015a, 2015b; Lai and Wu, 2015; Liu et al., 2013), suggesting that the fronto-limbic circuit is directly involved in the initial neurophysiological pathogenesis of MDD, independent of medication use or clinical course.

Recently, an intrinsic brain network known as the default mode network (DMN) has been given considerable attention in the MDD resting-state fMRI literature (Raichle et al., 2001). The DMN, composed mainly of the medial prefrontal cortex, posterior cingulate cortex, and precuneus (Broyd et al., 2009), has been associated with self-referential processing (Gusnard et al., 2001) and autobiographical memory (Buckner et al., 2008). Functional impairment of the DMN has been reported to be associated with rumination (Hamilton et al., 2015) and autobiographical memory deficits (Sumner et al., 2010), which are prominent clinical features of MDD. Interestingly, together with fronto-limbic circuit, the DMN has been found to be impaired consistently in first-episode, drug-naïve MDD patients (Guo et al., 2014a, 2014b; Lai and Wu, 2014; Peng et al., 2015; Zhu et al., 2012). These findings suggest that the DMN may also be a fundamental neurosubstrate in MDD, independent of clinical course and medication use.

Limiting MDD study cohorts to drug-naive patients with short illness duration minimizes the influence of confounding factors, thereby enabling robust evidence for potential therapeutic targets to be obtained. Notably, a recent meta-analysis showed altered regional homogeneity (ReHo) in one node of DMN in MDD patients (Iwabuchi et al., 2015). However, their study only included 10 fMRI studies (total of 225 patients) and just focus on the ReHo alterations. Additionally, only 6 of 10 studies recruited drug-naïve MDD patients.

In the present study, we explored resting-state brain functional alterations in first-episode, drug-naive patients with MDD employing a meta-analysis approach. The meta-analysis integrated existed researches about resting-state fMRI and provided comprehensive spatial information about locations of altered FC or regional brain activity in patients with MDD. Given the existing evidence indicating that functional abnormalities in fronto-limbic and DMN regions may be independent of clinical course and medication use (Wang et al., 2012a, 2012b), we hypothesized that functional alterations within these circuits would be observed in first-episode, drug naïve MDD patients. Activation likelihood estimation was used to consolidate spatial information about spontaneous brain activity.

2. Materials and methods

2.1. Data used for meta-analysis

Our search included literature published on or before March 15th, 2016 that was indexed in Pubmed, Web of Science, ScienceDirect, PsychoINFO, and/or EMBASE. Articles were searched with the following key words: “depression”, “major depressive disorder”, “first-episode”, “medication naive”, “drug naive”, “treatment naive”, “fMRI”, and “resting-state”. Articles in the reference lists of the search-selected articles were also considered and obtained if relevant.

The compiled articles were reviewed on the basis of strict inclusion and exclusion criteria. To qualify for inclusion in the meta-analysis, papers were required to: (a) compare differences between first-episode, medication-naïve patients with MDD and healthy controls (HCs); (b) to employ resting-state fMRI; (c) to provide detailed localization of altered brain regions in Talairach or Montreal Neurologic Institute (MNI) coordinates. We excluded studies that included primarily subjects not satisfying the criteria of MDD (i.e. bipolar depression and subthreshold depression) or included subjects with DSM-IV Axis I comorbid disorders (e.g. panic disorder). Studies that included evaluation of a treatment or participants who were <18 years old or >65 years old were excluded. Where multiple studies were present from the same authors, they were analyzed to ascertain whether they had involved different samples and only included if this appeared to be the case. Based on these criteria, a total of 31studies were determined to be suitable for inclusion. These studies reported on 457 individuals with MDD and 451 HCs. The study identification, selection progression and all the included studies were showed in Fig. 1 and Table 1. Additionally, there were 6 ROI-based studies in all 31 selected studies. As Margulies et al. suggested that the original seed coordinates in ROI-based analysis were less strictly to reflect the spatial location of potentially associated alterations (Margulies et al., 2010), we calculated the meta-analysis both with and without the 6 ROI-based analysis studies.

2.2. Meta-analysis using ALE

The meta-analysis was performed with GingerALE software (http://brainmap.org/ale) in MNI space (Eickhoff et al., 2012, 2009). Reported maxima coordinates were extracted and, if reported in Talairach space, converted to MNI space by tal2icbm (Laird et al., 2010; Lancaster et al., 2007).

Coordinates were assigned to two categories based on directionality of findings to avoid clearly opposed findings in the original studies. Groups 1 and 2 were comprised of cohorts in which the studies indicated decreased and increased spontaneous neural activity in MDD subjects relative to HCs, respectively. Coordinates in groups 1 and 2 were assigned to 20 and 16 presumably independent subjects groups, respectively. Coordinates were masked using the less conservative standard mask in Ginger ALE. Study-specific smoothing with a Gaussian kernel (group 1: FWHM median $=8.86$ mm, range 8.61–9.01 mm, group 2: FWHM median