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Review

A systematic literature review of resting state network—functional MRI in bipolar disorder

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ABSTRACT

Background: Several studies using functional magnetic resonance imaging (fMRI) in bipolar disorder (BD) have been performed in the last decade. Some of them have applied novel neuroimaging techniques such as resting-state functional connectivity magnetic resonance imaging (rs-fcMRI).
Methods: We reviewed the top-quality rs-fcMRI studies in BD available in the PubMed and Embase databases up to November, 2012 to identify brain activation networks and research techniques that may benefit future research.
Results: We present and discuss the methods and findings of eight articles. Most of these studies used the regions-of-interest (ROI) and independent component analysis (ICA) methods, and some used approaches such as amplitude of low-frequency fluctuation (ALFF), restricted global brain connectivity (rGBC) and regional homogeneity (ReHO). The largest differences in their results were found in the connectivity of the medial prefrontal cortex (mPFC) and the anterior cingulated cortex with limbic-striatal structures, and in spatial extent in ReHo when studying the default mode network (DMN).
Limitations: The heterogeneity of the analytical methods used to explore the resting-state network (RSN) and the characteristics of the sample of each study limit the conclusions.
Conclusions: Despite the variation among the results of the reviewed papers, they all support the cortico-limbic hypothesis and suggest that connectivity can be more complex and that intra-regional disturbances should also be studied. Recommendations for future studies include consideration of intra-regional disturbances, better control of confounding factors, use of larger scale methods, and a consensus regarding how to approach the study of resting-state networks and interpret the results obtained.
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1. Introduction

Bipolar disorder (BD) is a chronic and fluctuating disease, considered one of the most disabling psychiatric conditions (Miret et al., in press; Murray and Lopez, 1997). There are still many questions concerning the pathophysiology of BD during affective episodes or in the euthymic phase, but new functional magnetic resonance imaging (fMRI) methods can help us better understand the underlying neurobiology of BD (Phillips and Vieta, 2007) and possibly define endophenotypes of the disorder (Pan et al., 2009). In the last years, the number of neurofunctional studies in BD has increased and new data have been obtained using the BOLD fMRI signal (Liu et al., 2012a; Sepede et al., 2012; Townsend et al., 2010).

Directed-task studies have been widely used which rely on neuropsychological paradigms and assess brain activation while patients are carrying out a specific task related with the main cognitive domains such as working memory or executive function (Clark and Sahakian, 2008; Gruber et al., 2010; Kaladjian et al., 2009; Keener and Phillips, 2007; Lagopoulos and Malhi, 2007; Liu et al., 2012a; Monks et al., 2004; Vargas Upegui et al., 2011; Wessa et al., 2007). The results of these studies lack consistency due to differences in the neurofunctional paradigms and in the inclusion criteria used—particularly regarding history of drug dependence—and to the lack of control of confounding factors (Keener and Phillips, 2007; Liu et al., 2012a; Monks et al., 2004; Wessa et al., 2007).

All the studies consistently report prefrontal dysfunction in BD patients compared to healthy controls, specifically in the dorsolateral region, obtained with the Stroop test and working memory tasks. However, dysfunction is also reported in other areas which vary in each article, including the frontopolar region (BA 10), the anterior cingulated cortex and the parietal and ventral prefrontal cortices (Liu et al., 2012a; Monks et al., 2004; Vargas Upegui et al., 2011; Wessa et al., 2007). These findings throw some light on the neurobiology of BD and on the neuronal circuits involved in mood regulation (Clark and Sahakian, 2008; Kaladjian et al., 2009; Lagopoulos et al., 2007), but they have limited applicability, because the studies were restricted to the brain areas activated for specific neuropsychological functions and therefore do not support generalizations about the global functioning of the brain (Keener and Phillips, 2007).

The basal activity of the brain unrelated to cognitive performance was initially considered low frequency noise (Proal et al., 2011). However, several recent studies have shown that such fluctuations have a particular intrinsic organization and may represent a functional connectivity network of the brain (Van den Heuvel and Pol, 2011). On this basis, studies have been undertaken to explore brain's functional connectivity networks in resting state in patients with psychiatric disorders. To that end, patients are assigned no cognitive task and only instructed to rest quietly but awake with their eyes closed during the fMRI scan (Williamson and Allman, 2012). The results of these studies have been at least eight main brain networks including the primary motor network, the extra-striate visual network, the default mode network (DMN), the parietal–frontal network and other cortico-limbic networks (Van den Heuvel and Pol, 2011).

A recent meta-analysis of resting-state functional-MRI in Major Depressive Disorder reviewed 16 studies related with resting-state networks (RSN) which discuss both the role of the cortico-limbic mood regulating circuit (MRC) in Major Depression (Wang et al., 2012) and the challenge of improving the methodological issues in future studies. In schizophrenia and schizoaffective disorder some authors have even proposed hypotheses about neural mechanisms underlying hallucinations and insight, based on DMN studies (Madre et al., 2013; Northoff and Qin, 2011).

Regarding RSN studies in BD, several have been published in the last 5 years, but to date there is no systematic review of their findings (Anand et al., 2009; Anticevic et al., 2012; Calhoun et al., 2008; Chepenik et al., 2010; Liu et al., 2012a, 2012b). The main objective of this article is to review the available literature related to RSN in adult BD patients, evaluate its quality and suggest potential pathways and methods for future research.

2. Methods

2.1. Literature research

A systematic literature search was conducted in accordance with the PRISMA statement, to select publications pertaining to the use of resting state fMRI in BD (Moher et al., 2009). The search was conducted in two electronic databases: the National Library of Medicine's Medline database (PubMed) and Embase. They were consulted using specific search terms which belonged to two constructs, namely (1) bipolar disorder and (2) resting state network. In PubMed we performed an advanced search strategy using the following Mesh terms, alone or in combination: resting state network, default mode network, functional, connectivity, bipolar disorder, affective disorder, and fMRI. The search in Embase was conducted in a similar manner. After removing all duplicate articles, all the records were grouped in a final database which was supplemented by cross-reference entries. No language, publication status, or date restrictions were imposed to the systematic search.

2.2. Eligibility criteria

The papers retrieved from the search were screened first by title and abstract and then by the following criteria:

1. The study population was aged 18 and over.
2. The study population included patients diagnosed with lifetime bipolar disorder by a psychiatrist according to DSM or ICD criterion.
3. The studies included a healthy control comparison group comprised of subjects with no axes I and II disorder diagnoses.
4. Assessment with resting state fMRI was conducted for both BD patients and healthy controls.
5. The results were presented clearly and the changes in the brain networks described accurately.

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