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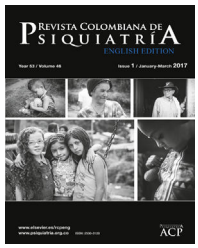

Review Article

Resting-state functional nuclear magnetic resonance imaging in patients with bipolar disorder: Beyond euthymia☆

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ABSTRACT

Introduction: Functional nuclear magnetic resonance imaging in the resting state (R-fMRI) allows the identification of complete functional connectivity networks and the possible neuronal correlations of psychiatric disorders. The literature on R-fMRI and bipolar disorder (BD) will be reviewed, emphasising the findings in the phases of mania, hypomania and depression.

Methods: It is a narrative review of the literature in which articles were searched in PubMed and Embase, with the key words in English "bipolar disorder" AND "resting state", without limit on the date of publication.

Results: The studies of BD patients in the mania and hypomania phases who underwent R-fMRI show concordant results in terms of decreased functional cerebral connectivity between the amygdala and some cortical regions, which indicates that this functional connection would have some implication in the normal affect regulation. Patients in the depressive phase show a decrease in functional brain connectivity, but as there are several anatomical structures involved and neural networks reported in the studies, it is not possible to compare them.

Conclusions: There is a decrease in functional connectivity in patients with BD, but current evidence does not allow establishing specific changes in specific functional brain connectivity networks. However, there are already some findings that show correlation with the patients' symptoms.

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Resonancia magnética nuclear funcional en estado de reposo en pacientes con trastorno bipolar: más allá de la eutimia

Palabras clave:
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R E S U M E N

Introducción: La resonancia magnética funcional en estado de reposo (RMf-ER) permite identificar redes de conectividad funcional completas y los posibles correlatos neuronales de trastornos psiquiátricos. Se revisa la literatura sobre RMf-ER y trastorno bipolar (TB) haciendo énfasis en los hallazgos en las fases de manía, hipomanía y depresión.
Métodos: Es una revisión narrativa de la literatura en la que se buscaron artículos en PubMed y EMBASE con las palabras clave en inglés "bipolar disorder" AND "resting state", sin límite en la fecha de publicación.
Resultados: Los estudios de pacientes con TB en fases de manía e hipomanía sometidos a RMf-ER muestran resultados concordantes en cuanto a la disminución de la conectividad funcional cerebral entre la amígdala y algunas regiones corticales, lo cual indica que esta conexión funcional tendría alguna implicación en la regulación normal del afecto. Los pacientes en fase depresiva muestran disminución en la conectividad funcional cerebral, pero como son varias las estructuras anatómicas implicadas y las redes neuronales reportadas en los estudios, no es posible compararlos.
Conclusiones: Hay disminución en la conectividad funcional en los pacientes con TB, pero la evidencia actual no permite establecer cambios específicos en redes de conectividad funcional cerebral puntuales. Sin embargo, ya hay algunos hallazgos que muestran correlación con la clínica de los pacientes.

Introduction

Bipolar disorder (BD) is a disabling condition that is recurrent and mainly affects mood[1–3]. It has become a public health problem in recent years, generating high costs for healthcare systems[3]. Despite its episodic characteristics, with partial or total remission of symptoms, there are generally residual, chronic manifestations that notably affect the functionality of individuals who suffer from it[1–4].

The aetiology of BD remains uncertain, but a large number of studies focusing on neuroimaging, peripheral markers and genetics have provided insights into the pathophysiological processes underlying the disorder[5]. Neuroimaging findings have shown decreased grey matter and abnormal activation of some subcortical regions in response to emotional stimuli[5]. It has been suggested that these findings could be biomarkers of BD. For example, brain activation patterns were found in functional images that could predict a conversion to BD in high-risk individuals, clarify differential diagnoses or guide the selection of the most appropriate treatment[6].

One possible functional imaging biomarker is resting-state functional magnetic resonance imaging (R-fMRI), which allows delineation of complete functional connectivity networks or circuits and possible neural correlates in psychiatric diseases[7]. With this modality, background brain activity, also called intrinsic or spontaneous activity, can be assessed, i.e. that which is not related to the execution of cognitive tasks and was previously considered to be random low-frequency noise, and so excluded from the studies[7].

Many published studies on R-fMRI and BD have provided information valuable in identifying neural networks that could be associated with the pathophysiology of the disorder, its prognosis or response to treatment[7–9]. Some of those studies report data on R-fMRI findings during phases of mania or hypomania and depression, and our review focuses on these.

Methods

This is a narrative review of the literature. We carried out a search of PubMed and EMBASE using the keywords "bipolar disorder" AND "resting state", with no limit on publication date. In total, the search yielded 309 results, out of which we discarded articles not in English or Spanish, not related to BD and R-fMRI, or which only described the findings in euthymia. Ultimately, 11 articles were included that met these requirements.

R-fMRI in BD

R-fMRI is an emerging brain imaging method that facilitates the study of functional integration of neural networks at rest, i.e. when no cognitive or sensorimotor task is imposed[10]. There are two models of approach to studying the R-fMRI technique. The first is based on seeds or voxel (region of interest [ROI])[7,10], in which there is already a prior evidence-based hypothesis about the brain areas that may be related to a specific phenomenon and the analysis is focussed precisely in these regions and their connections. The second model is the independent component analysis (ICA), which analy-

ses the different findings reported in all brain connections by mathematical methods and spatio-temporal variables and is particularly useful when the regions involved in a specific function or functional connectivity are not known[7,10].

It has been possible to measure the functional activity of the brain from blood oxygenation level-dependent (BOLD) signal changes[7]. In recent years, valuable information has been obtained in this field of study through the use of the BOLD signal[9].

Information from many published studies on R-fMRI and BD has helped to identify neural networks that may be associated with the pathophysiology of the disorder, its prognosis or response to treatment[7–9]. One such study, published in 2014 by Vargas et al., described eight activation networks identified in euthymic patients with BD-I. Of these networks, they selected four in which, according to the literature, a greater relationship with patient affective processing has been found: the default mode network (DMN) (medial temporal lobe, medial prefrontal cortex, posterior cingulate, precuneus and medial, lateral and inferior parietal cortex); temporolimbic (temporal lobe, parahippocampal gyrus, limbic lobe, hippocampus and amygdala), frontal and salience network (anterior cingulate and anterior insula).[8]

Intrinsic brain activity has led to greater agreement between studies in terms of findings. In R-fMRI studies, the brain areas most discussed are the medial prefrontal cortex, the pregenual anterior cingulate cortex, the mediodorsal thalamus, the amygdala and the parietal cortex[9].

Findings in mania and hypomania

In 2008, Wang et al.[11] compared six patients with mania or hypomania, five patients with bipolar depression and 15 with unipolar depression, with 15 healthy controls. They found that compared to healthy controls, patients with BD had reduced connectivity bilaterally between the pregenual anterior cingulate cortex, amygdala, thalamus and striatum. They also found that functional corticolimbic connectivity was decreased in patients with mania or hypomania compared to healthy controls.

In 2010, Chepenik et al.[12] compared five patients with mania or hypomania, two patients with depressive episode with BD-I and eight euthymic patients with ten healthy controls to assess the functional connectivity between the amygdala and the ventral prefrontal cortex. They found that there was a significant and inverse relationship between the left ventral prefrontal cortex and amygdala activity in healthy controls; this relationship decreases in patients with BD. They also found that there was a high interhemispheric correlation in patients with BD between the activity of the bilateral ventral prefrontal cortices and the right ventral striatum.

In 2011, Chai et al.[13] compared 39 patients with mania and 20 patients diagnosed with schizophrenia having a psychotic episode with 15 healthy controls. In the group of patients with BD, they found a positive correlation between the medial prefrontal cortex and the left insula and between the medial prefrontal cortex and the right ventrolateral prefrontal cortex. This was not the case in the group of patients with schizophrenia and healthy controls, who showed no correlation and a negative correlation, respectively.

In 2015, Li et al.[14] compared 18 patients with mania and ten patients with bipolar depression with 28 healthy controls. They found that patients with mania had decreased functional connectivity between the bilateral amygdala and the bilateral caudate/putamen. They also found decreased functional connectivity between the right amygdala and the left inferior orbitofrontal gyrus and the left amygdala and the right inferior orbitofrontal gyrus, the right lingual gyrus and the posterior part of the right lobe of the cerebellum.

In 2016, Altinay et al.[15] compared 30 patients with BD-II having depressive episodes, 30 patients with hypomania and 30 healthy controls, to identify similarities and differences in functional connectivity of the striatum. They found an increase in functional connectivity between the right dorsal caudate and the midbrain around the substantia nigra in the group of patients with hypomania.

That same year, Spielberg et al.[16] compared 30 patients with BD having manic or hypomanic episodes and 30 patients with BD having depressive episodes with 30 healthy controls. They found that the patients with BD had greater connectivity in a network in which the right amygdala had the highest number of differential links, indicating that the amygdala has a strong influence on generalised network processing.

In 2017, Wei et al.[17] compared 16 patients having a first depressive episode and 13 patients having a first manic episode, all in the context of BD, with 30 healthy controls. These authors found that patients in a manic episode had a lesser functional connectivity between the amygdala and the right orbitofrontal cortex, suggesting that hemispheric lateralisation influences the first affective episode.

Findings in depression

In 2012, Liu et al.[18] compared 26 patients with BD in depressive phase with 26 healthy controls measuring the amplitude of low-frequency fluctuations (ALFF) in the BOLD signal in R-fMRI. They found that in patients with BD, there was decreased ALFF in the left postcentral gyrus, left parahippocampal gyrus and cerebellum and increased ALFF in the left insula, right caudate, temporal gyrus, posterior lobe of the cerebellum and frontal lobe.

In another similar study, Xu et al.[19] reported that the areas with increased ALFF were the prefrontal cortex, medial frontal cortex, insula and putamen, and the only area reported with decreased ALFF was the lingual gyrus.

Li et al.[14] compared ten patients with BD having a depressive episode with 28 healthy controls. Compared to the healthy controls, they found that the patients with BD had decreased functional connectivity between the right amygdala and the bilateral caudate/putamen, and also between the right amygdala and the left inferior orbitofrontal gyrus, the posterior lobe of the cerebellum and the right hippocampus. For the left amygdala, although the findings were similar, there were also significant additional data: compared to healthy controls, patients with depression had a reduction in the functional connectivity between the left amygdala and the bilateral caudate/putamen, the right inferior orbitofrontal gyrus, the right lingual gyrus and the posterior part of the right lobe of the cerebellum.

In 2015, Wang et al.[20] compared 40 patients with BD-II having a depressive episode and 37 patients having a depressive episode with no history of BD with 40 healthy controls, in order to identify any interhemispheric functional differences. They found that the voxel-mirrored homotopic connectivity (VMHC) values in the lingual gyrus and the anterior and posterior lobes of the cerebellum were lower in the group of patients with BD-II. That same year, Wang et al.[11] compared 30 patients with BD-II having a depressive episode and having had no treatment in the previous five months with 41 healthy controls. They found that the VMHC values in the medial prefrontal cortex and the inferior temporal gyrus were lower in the group of patients with BD-II than in the control group.

In 2016, Wang et al.[21] compared 37 patients with BD-II on no treatment having a depressive episode with 37 healthy controls. They found that, compared to healthy controls, patients with BD-II having a depressive episode showed a significant decrease in functional connectivity strength values in the DMN and the right supramarginal, angular, right superior frontal and right superior parietal gyri. Furthermore, they found that these patients had increased functional connectivity strength values in the bilateral temporal pole, left anterior cingulate cortex, left superior temporal gyrus, right lingual gyrus and left anterior lobe of the cerebellum.

Altinay et al.[15] compared 30 patients with BD-II having depressive episodes and 30 patients with hypomania criteria with 30 healthy controls, to assess the functional connectivity of the striatum. They found that the group of patients with depressive episodes had an increase in functional connectivity between the left ventral rostral putamen and the precentral and postcentral frontal gyrus, as well as between the left ventral rostral putamen and the left superior temporal gyrus.

In 2017, Wei et al.[17] compared 16 patients with a first depressive episode and diagnosis of BD and 30 healthy controls. Their patients having a depressive episode had lower resting-state functional connectivity between the amygdala and the left orbitofrontal cortex.

Discussion

Very few studies have been carried out with R-fMRI in patients with BD, as the brain imaging method has only recently been introduced. However, it has very quickly broadened the horizons of functional research in neuroscience in general and psychiatry in particular[7]. In this narrative review, the literature search showed that most of the studies in this field have been carried out in patients in the euthymic phase, while there are limited studies in patients in phases of mania/hypomania or depression. The main reasons for this are the technical and methodological limitations involved in taking a decompensated patient to an MRI scanner[9]. We should also clarify that the studies included in this review have small sample sizes, explained by the complexity of R-fMRI, which requires specialised interpretation, and its high costs[4,7].

It is striking that those studies that did include patients in phases of mania and hypomania[11,12,14,17] agree that there is a decrease in brain functional connectivity between the amygdala and some cortical regions, such as the ventral prefrontal cortex and the orbitofrontal cortices, indicating that this connection may have some involvement in normal regulation or downregulation of affect. These same studies mention other structures associated with this decrease in functional connectivity, such as the striatum and the thalamus. Only Wang et al.[11] report decreased functional connectivity in the corticolimbic network. In contrast, only three studies reported increased functional brain connectivity in these patients[13,15,16], but their findings do not concur.

With regard to patients in the depressive phase, in general a decrease in brain functional connectivity is the rule, but the studies report on multiple different anatomical structures and networks, so the findings cannot be compared. Interestingly, Wang et al.[21] reported a decrease in functional connectivity in the DMN, previously mentioned by Vargas et al.[8] as one of the networks related to affective processing in patients with BD.

The evidence available to date does not allow us to definitively point to specific changes in functional brain connectivity in all patients with BD in the manic/hypomanic or depressive phases. It is possible that the study findings represent a trait marker, i.e. they are invariant in all patients with the disorder and independent of exacerbation status. It is therefore important to continue working in this field of research, as they may be related to aetiopathogenesis and might be more useful for the study of pathophysiology, early detection and aetiology. It is also possible that the changes in the R-fMRI are a consequence of the chronic nature of the disorder or an effect of the episodes, due to compensatory, adaptive or directly physiopathogenic changes.

Conclusions

Although recent, the introduction of R-fMRI into research as a brain imaging method has revealed possible functional brain connectivity changes that may occur in BD patients. From the evidence currently available, we cannot confirm these specific changes in precise networks, but there are already some findings showing a correlation with patients' clinical symptoms. Functional neuroimaging is a developing field of research, which, without any doubt, is going to bring many benefits to psychiatry.

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Conflicts of interest

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