fMRI comparison between bipolar I and bipolar II disorders

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Abstract

Bipolar disorders are mood disorders characterised by manic (bipolar I disorder,) or hypomanic episodes and major depressive episodes (bipolar II disorder). These have been reworked into the model of "bipolar spectrum disorder", where manic symptom load increases from unipolar depression to bipolar II to bipolar I. In this article we consider the fMRI findings for bipolar I, bipolar II and major depressive disorder (MDD) and conclude that bipolar disorder and MDD do not share the same pattern of neural disturbance. The distinction between bipolar I and bipolar II is less clear, as the data is still preliminary in nature, but the two disorders appear to share a similar pattern of brain activity. This fMRI data suggests that the bipolar spectrum model still requires refining, but provides a useful framework upon which to base future research into affective disorders.

Key words: bipolar disorder, mood disorders, bipolar spectrum, fMRI, neuroimaging

Introduction

Bipolar disorders are a group of affective disorders characterised by the occurrence of manic episodes in the lifetime of the patient. It is a serious condition that can cause significant distress, social and occupational impairment and suicidal tendencies. DSM-IV-TR divides bipoalr disorders into subtypes including bipolar I disorder and bipolar II disorder. bipolar I is defined by one or more manic or mixed episodes. Depressive episodes frequently occur as well. Bipolar II is characterised by at least one hypomanic episode and one or more major depressive episodes. Bipolar disorder has been conceptualised as "bipolar spectrum disorder", with increasing load of manic symptoms from depression to bipolar II to bipolar I (1,2). In this paper we review what functional neuroimaging has contributed to the understanding of the neural differences between these disorders.

Functional magnetic resonance imaging (fMRI) has become increasingly popular in psychiatry. Grossly simplified, it is an MRI technique that measures brain activity by detecting changes in magnetic properties which accompany changes in cerebral blood flow. It uses the principle that changes in blood flow to an area are related to the neuronal activity of that area. The main difference between functional and structural studies is that fMRI can measure changes in brain activity between a control state and an experimental psychological state. The control measurements are subtracted to identify areas sensitive to the processes involved. fMRI is therefore able to identify state and trait disturbances by comparing across mood states and examining at-risk individuals.

The current model of the neural network responsible for emotional processing involves early processing of the emotional stimulus by a limbic-subcortical network, which allocates attention and processes sensory information, followed by regulation of the emotional response by a cortical network, which reappraises the stimulus and inhibits irrelevant information (3). It is thought that disturbances in this network give rise to the abnormal processing seen in affective disorders.

The limbic system

Studies and meta-analyses have consistently shown that in bipolar disorder, the limbic and subcortical structures, specifically the amygdala and parahippocampal gyrus, are overactive (4-7), particularly on the left (5). Although this finding has been widely replicated, some studies have either failed to show hyper-responsiveness of the limbic structures (8-11) or found decreased responsiveness (12,13). The amygdala has been found to be overactive in mixed bipolar I and bipolar II groups in elevation (14)

and euthymia (15) and in bipolar II depression (16). However, Ladouceur et al. (17) found an increase in amygdala activity in bipolar I but not in bipolar disorder not otherwise specified youth, suggesting a different neural basis.

Limbic hyperactivity, especially in the amygdala, is also seen in MDD (18). Lawrence et al. (19), comparing bipolar disorder and MDD, found greater limbic activation in bipolar disorder, which is supported by meta-analysis (6).

The striatum and cortico-basal ganglia network

The striatum and cortico-basal ganglia network has generally been found to be overactive in bipolar disorder (20). Meta-analysis revealed increased activation of the striatum and globus pallidus in response to emotional tasks and decreased activation in response to cognitive tasks (4). Individual studies variably showed increased activity in the striatum (21,22), global pallidus (21) and thalamus (22) in mania. Hyperactivity of these areas has also been found in bipolar I depression (22,23). Studies showed that striatal activity was increased in mixed bipolar I/bipolar II populations (14,23,24) and in bipolar II depression, correlating with depression severity in the latter (25). Increased activation in the left thalamus was also found in bipolar II depression (25).

Striatal underactivity is well described in MDD (20), although overactivity has also been reported (19). Meta-analysis showed striatal hypo-responsiveness, specifically in the left caudate and right putamen (6).

The anterior cingulate cortex (ACC)

A number of studies have suggested that subgenual ACC activity in bipolar disorder depression is characterized by decreased activity on the left and increased activity on the right (3,27,28) and vice versa in mania (29). Other studies have shown a state-related decrease in dorsal ACC activity bilaterally (14,30). However, increased ACC activity has also been reported (28). Meta-analysis revealed decreased left dorsal ACC activity to fearful faces and decreased right dorsal ACC activity to happy faces (6). Increased right dorsal ACC activity has been shown in bipolar II depression (16).

Subgenual ACC activity that was decreased on the left and increased on the right was also seen in MDD (3). Hyperactivity in the right subgenual ACC, also shown on meta-analysis, was particularly increased during acute depressive episodes and normalised with treatment (31). Meta-analysis suggests that the right-sided hyperactivity was more prominent in bipolar disorder, but left-sided pregenual ACC activity was more prominent in MDD (6). One study directly compared MDD and bipolar disorder depression in women and showed increased dorsal ACC activity in MDD (32).

Other cortical areas

Decreased activity in the inferior frontal gyrus, specifically the ventrolateral prefrontal cortex (VLPFC) and part of the orbitofrontal cortex (OFC), has been demonstrated consistently in bipolar disorder (4-7). This ws more marked on the right (5) and has been shown in bipolar depression (9), mania (33) and euthymia (34). Meta-analysis also shows decreased activity in the lingual gyrus (4,6). Disturbances in other cortical areas have been implicated, such as overactivity in the ventromedial prefrontal cortex (VMPFC) in mania (33) and in the dorsomedial prefrontal cortex (DMPFC) in euthymia (15), but these changes were not robustly revealed on meta-analysis (4). Studies examining dorsolateral prefrontal cortex (DLPFC) activity have produced inconsistent findings (4,5). Frontal hypo-responsiveness, especially in the ventral areas, has been shown in mixed bipolar bipolar I/bipolar II depression (23) and bipolar II depression (35), while increased OFC activity has also been demonstrated in bipolar II depression (16).

In contrast with bipolar disorder, VLPFC activity may be increased in MDD (36), although the two disorders appear to have increased VMPFC and DMPFC activity in common (37). DLPFC activity also

seems to be reduced in MDD (3), though these prefrontal disturbances receive limited support from meta-analysis (6).

Conclusion

To summarise the current findings, limbic overactivity has been well demonstrated in both bipolar disorder and MDD, and it is also a possible finding in bipolar II. Striatal activity is also increased in bipolar disorder and possibly bipolar II, but it has been shown consistently to be decreased in MDD. Data examining cortical areas are more preliminary in nature, although at present it seems that the subgenual ACC is underactive on the left and overactive on the right in both bipolar disorder and MDD. VLPFC is thought to be underactive in bipolar disorder but potentially overactive in MDD, while activity in the medial PFC appears to be overactive in both bipolar disorder and MDD. Neuroimaging data in bipolar II is limited, but appears to follow a similar pattern to bipolar I. On the other hand, while MDD shares some common features with bipolar disorder in terms of regional disturbances, there are also some well-documented differences in activity.

There are a number of problems which arise when interpreting these findings. First, it may be premature to form conclusions when there are still many disparities in the data, which is especially preliminary when it comes to BD-II. Second, it is important to consider the limitations of functional neuroimaging. When interpreting fMRI data, we assume that emotional processing can be meaningfully mapped onto brain structures, that it can be manipulated in isolation, that the neural basis can be localised, that the patient groups are controlled for all other factors apart from the diagnosis, and that the same psychological process can be compared across all groups. In view of these assumptions, it is important to not to interpret neuroimaging data in isolation. It would also be instructive to consider the connectivity between structures and how changes in neural activity translate into phenotypes.

Finally, and perhaps most important, the bipolar spectrum model still requires further clarification and validation in terms of the different gradations. The current conceptualisation of the spectrum model is that it describes overlapping clinical manifestations, which are not necessarily products of the same genetic or neural changes. Some studies describe a diagnostic change from unipolar to bipolar depression over time (1), highlighting either the difficulties in nosology and diagnosis or the possibility of a physiological progression from one disorder to the other. The latter would have profound implications for research into impeding the neural changes from unipolar to bipolar depression. Regardless of the implications, it is clear that the bipolar spectrum model needs refining, but it has proven useful as a framework for classifying mood disorders.

GP Comment

What have I learned from this paper?

This article explains that a number of functional neuroimaging changes have been demonstrated in bipolar affective disorder which seem to distinguish it from unipolar depression. Some of these differences raise fundamental questions about the classification of mood disorders. Additional information from functional neuroimaging may help to improve our understanding of the spectrum of bipolar disorder and its relationship to unipolar depression.

Dr Jenny Hopwood, GP Trainee.

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