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REVIEW

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Interpreting Magnetic Resonance Imaging Findings in Bipolar Disorder

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SUMMARY

The episodic nature of bipolar disorder together with the ostensibly polar extremes of mania and depression have favored the acceptance of a functional model postulating regionally disturbed brain activity returning to normal with time or treatment. Seemingly contrary to that view, anatomical imaging studies have demonstrated abnormalities in brain structure which could reflect neurodegeneration or represent disturbed neuronal development. Resolution may come from an appreciation of adult neurogenesis, especially given the neuroprotective properties of drugs, such as lithium and their effects on brain volume. The brain regions vulnerable to structural changes also show evidence of dysfunction, giving rise to corticolimbic dysregulation interpretations of bipolar disorder. This article reviews the structural and functional magnetic resonance imaging data in bipolar disorder. Its focus is on the interpretation of findings in light of recent developments in the fields of neurobiology and image analysis, with particular attention paid to both the confounding effects of medication and the baseline energy state of the brain.

Introduction

Bipolar disorder is a common psychiatric condition, which presents with a diverse range of symptoms across various domains. Whilst disturbances in mood states are the core feature, disruption of biological rhythms, drives, behavior and cognition are central to its impact on functioning. Diagnosis requires that an individual experiences an episode of distinctly elevated mood—mania in type I and hypomania in type II bipolar disorder. The majority of patients also suffer from periods of depression, with this being a stipulated in the criteria for type II disorder. It is increasingly recognised that depression may represent the greatest burden of the illness [1]. Classically described, those with bipolar disorder are said to have discrete periods of illness from which they return to a normal state. It is widely acknowledged that this pattern may not accurately describe the nature of the condition as dysfunction may be detectable during euthymia. Further, many patients experience chronic illness, mixed presentations, rapid cycling, and/or suboptimal responses to treatment [2].

Defining the nature of bipolar disorder has always been something of a challenge to psychiatry and establishing a neurobiological model of the condition has been beset by problems. The frequently episodic nature of the disorder and the ostensibly polar extremes of mania and depression have, historically, resulted in a functional account being favored over an organic model, disturbed activity within brain regions postulated to return to normal with time or treatment. Underlying the syndromal presentations, derangements in the processes of neural transmission have been proposed, often in a dichotomous manner to mirror the polar nature of the illness; for example, mania has been explored in terms of increased dopaminergic activity, whereas depression discussed in terms of under activity [3]. There is merit to such a stance and much evidence to support the assertions, but factors such as medications, psychosis, physical activity, and stress-axis activation (all of which can span episodes or emerge during both mania and depression), confound the investigation and interpretation of potential neurobiological abnormalities [4].

The brain can be viewed as the source or mediator of normal and abnormal mental states, but may also be considered as an organ vulnerable to the damaging effects of illness. Thus, investigation of the structure of the brain in bipolar disorder may provide insights into the causes and consequences of the condition. Linking evidence from neuropathological, pharmacological, and imaging studies, there is an emerging consensus that affective disorders may well be considered as potential neurodegenerative states [5]. Interest in this area has been further fueled by the findings from

research in the field of cellular plasticity. That the adult mammalian brain has the capacity to recover from insults and generate new neurones is an exciting possibility [6], permitting a more fluid interpretation of the structural abnormalities detected in relapsing and remitting conditions such as bipolar disorder. Accepting structural underpinnings may also provide direction and clarity to the interpretation of functional imaging studies of abnormal mood states. In this overview of the magnetic resonance imaging studies in bipolar disorder, the focus is placed on the interpretation of results in light of recent developments from the fields of neurobiology and image analysis. With this narrative article, we sought to guide informed clinicians to some of the more actively debated topic in the field. The inclusion of studies was, therefore, biased towards exploring a number of specific points but wherever possible, the reader is directed to meta-analyses or systematic reviews covering broader areas.

Brain Strugture in Bipolar Disorder

Overview of Anatomical Imaging Studies

Numerous imaging studies have investigated the brain structure of those with bipolar disorder, using various imaging modalities and analysis techniques. The complexity of investigating bipolar disorder—variable mood states, onset during development, illness progression, medication effects—contributes to the study heterogeneity that hinders effective comparison and conclusions. Nevertheless, data from imaging studies of patients with bipolar disorder have been the subject of meta-analysis by a number of researchers. With the strictest review criteria, right ventricular enlargement appears as the only measure differing between bipolar disorder and healthy controls [7]. Kempton et al. [8], included more studies, finding the greatest effect sizes for ventricular enlargement and white matter hyperintensities, as well as noting greater gray matter volumes in patients on lithium—their review also highlighted that most individual studies are underpowered to detect structural differences. More recently, whole brain and prefronal volume reductions have emerged as significant on review, in addition to the consistent lateral ventricle dilatation [9]. Voxel-based morphometry techniques permit the whole brain to be scrutinized without the need to nominate specific regions of interest, benefiting further from a high degree of automation and reproducibility [10]. In combining the key findings to date, an emerging view supports the implication of corticolimbic structures in bipolar disorder [11].

The prefrontal cortex has been shown to be smaller in those with bipolar disorder compared to healthy subjects, though this is not invariably the case [12]. Considering the prefrontal cortex as a single structural or functional entity is doubtless crude and probably incorrect; comparing specific regions may be of greater value but it is methodologically more challenging. Initially reported by Drevets and subsequently replicated by independent groups, gray matter volume appears to be reduced in the subgenual prefrontal cortex (on the left especially) [13–15]. Gray matter volume reductions across the whole left anterior cingulate cortex have also been reported, though negative studies and contrary findings have been published and recently reviewed [11]. Anatomical variability in this region hinders analysis [16] and illness characteristics are important confounders between studies—grey matter loss, for example, being associated with rapid cycling [17]. The age of the subjects at the time of assessment should also be considered, as the normal maturational reduction in ventral prefrontal cortex that occurs in adolescence may be accelerated in those with bipolar disorder [18,19]. Adolescents with bipolar disorder have also been shown to have smaller amygdala volumes than healthy comparator subjects [20–22]. Conversely, it is widely held that the amygdala volume in adult patient populations is normal or greater than normal [23], though diminutive volumes have been reported [24]. Such variability may be due to difficulties faced when trying to delineate this complex structure, but the effects of medication must be considered since mood stabilisers, such as lithium have been associated with volume increases [23]. For the hippocampus, the consensus view from early imaging studies of bipolar disorder held that its volume was preserved [12], in contrast to the reductions seen in unipolar disorder [25]. Latterly, smaller than normal volumes have been reported [26,27], perhaps conforming to an age-related pattern akin to that seen with the amygdala [28–30]. The hippocampus is prone to the same methodological and pharmacological confounds as the amygdala and, as a potential site of neurogenesis [31], may be susceptible to the effects of stress, relapse, and illness course.

Crudely summarized, corticolimbic dysregulation theories of depression assert that it is associated with ventral paralimbic overactivity and dorsal cortical inactivity [32]; it has been hypothesized that in bipolar disorder, a reduction in the modulating capacity of the prefrontal cortex releases limbic structures from inhibition [33], increasing activity in the amygdala, for example [34]. In proposing neural network dysfunction, subcortical nuclei and their interconnecting tracts may be implicated in addition to cortical regions [33], but the findings from structural image analysis studies offer inconsistent support: the caudate may be of normal [35–38] or increased volume [39,40], with reductions seen in elderly patients [41]; nucleus accumbens volume may be reduced in young patients [21]; the putamen may be normal in euthymia but increased in mania [35,36,38]. The area of the corpus callosum is lower [9], with further evidence of disruption to the integrity of interconnecting tracts comes from the consistent findings of an excess of deep white matter hyperintensities [8], the frontal regions again affected to the greatest degree [42]. Linking once more to the progression or consequences of the illness, the presence of white matter hyperintensities is associated with poor prognosis [43].

Effects of medication on brain structure

The effects of medication on brain structure are likely to be of some significance when discussing bipolar disorder, as various commonly used medications have been shown to alter grey matter globally and regionally [44]. Out with bipolar disorder, marked effects on brain volume, as gauged by MRI, have been observed with agents that influence dopaminergic neurones (a prime candidate system for investigation given its established plasticity and regional specificity). Acute administration of haloperidol reduces the volume of the striatum in a reversible matter, consistent with the pharmacokinetics of the drug [45]. The immediacy of the effect adds an element of complexity to the interpretation of the apparent structural abnormalities in bipolar disorder—addition to the presence or absence of medication, the time since the last dose may require consideration. Although not indicated for the treatment of the affective disorders, L-dopa has been shown

to increase the volume of gray matter in the substantia nigra two hrs within of its administration, assessed using voxel-based morphometry in normal volunteers [46]. Presumably related in some way to an increase in neurotransmitter turnover, this finding is of pertinence to manic presentations—the reported structural abnormalities in the striatum in mania could arguably reflect a disordered hyperdopaminergic functional state rather than disruption to anatomy. Of more direct relevance to bipolar disorder, lithium has been consistently demonstrated to increase gray matter in cross-sectional and longitudinal MRI studies [46–53]. The degree of regional specificity is unclear, but the changes are apparent in prefrontal and limbic areas and appear to develop progressively over several weeks, typically reaching the order of a 3% increase. Larger volume changes have been observed in regions, such as the hippocampus and subgenual areas [52]. Drawing on the established neuroprotective effects of lithium in preclinical models together with magnetic resonance spectroscopy-based demonstrations of increased brain N-acetyl-aspartate (NAA)—a putative marker of neuronal integrity—most authors have attributed the gray matter volume increase to neuroplasticity effects. It has, however, been suggested that a lithium-driven increase in gray matter water content could account for the changes [55], though this could presumably accompany cellular growth and thus support the first proposition. Alternatively, it is possible that drugs, such as lithium, alter the nature of the MRI signal [56], changing the contrast and so causing a misclassification of tissue types with resultant spurious increases in gray matter volume returned. This matter remains unexplored but may be difficult to resolve as the areas prone to misclassification during analysis are those at the boundary of tissue classes [57], namely the hippocampal folds, frontal regions and periventricular areas—the very regions implicated in the process of neurogenesis.

A pragmatic approach would argue that regardless of the mechanism—neurogenesis, hydration, signal artefact, enhanced functioning, toxicity—medication related changes are informing us of the site of action of the drugs, perhaps even the magnitude of their effect at a cellular level. Such information is likely to be of substantial value in understanding the aetiopathogenesis, progression and treatment of bipolar disorder.

Functional Brain Imaging in Bipolar Disorder

Imaging studies investigating the function of the brain in bipolar disorder have been reviewed—differences in imaging modalities, task and rest conditions, mental states, and medication effects are important confounds, the likely effects of which have been discussed elsewhere [58]. Given these confounders, a synthesis of the findings permits only the broadest of conclusions to be reached, the testing of specific hypotheses the remit of individual studies. In general, the areas implicated in structural studies show evidence of dysfunction, though mixed reports abound [59]. On the basis of the findings from studies using the blood-oxygen-level-dependent functional magnetic resonance imaging technique (BOLD fMRI), it has been argued that during emotional and cognitive tasks, mania is predominantly associated with reduced activation in the ventral prefrontal cortex [60–63], whereas in bipolar depression, increased activation is observed [62,64]. Laterality effects may be of some importance, the abnormalities in mania seen within the right hemisphere, depression the left. Pursuing corticolimbic dysregulation, amygdala BOLD fMRI activations at rest and during emotional tasks are typically greater in patients with bipolar disorder compared to controls [64–67]—interestingly, the increase in BOLD signal occurs in both depression and mania.

It would seem reasonable to conclude that the imaging studies support the notion that in mania, frontal inhibition is lost, whereas in depression, the reverse occurs, borne out as a disruption to normal emotional, cognitive, and volitional processes. The certainty in, as well as the direction of the changes in structure and function observed requires discussion in light of the current theories explaining the neurophysiological basis of MRI. With respect to bipolar disorder, two areas warrant attention: the effects of medication and the baseline state of the brain during functional studies (BOLD fMRI in particular).

Medication Effects on Brain Imaging

The effects of medication are often cited as potential confounders, but rarely with more than a general degree of specificity or consideration of mechanisms. fMRI using the BOLD contrast relies on the coupling between neuronal activity and the blood supply to that locality [68–70], a link potentially disrupted by psychotropic medications. With increased neuronal firing, blood flow rises and a state of superabundant perfusion is reached, in which the regional concentration of deoxyhemoglobin is reduced—the loss of the paramagnetic effects of deoxyhemoglobin boosts the signal obtainable from the surrounding water molecules such that BOLD signal increases (activation). Neurovascular coupling is maintained through various mechanisms including feed-forward systems involving gamma-aminobutyric acid (GABA) receptors and associated down-stream pathways. Neuronal firing, in additional to signal conveyance, induces the release of vasoactive substances such as nitric oxide [70]. Neurovascular coupling may be disrupted by the presence of illness and the effects of medication.

The cardiovascular and metabolic dysfunction that often accompanies bipolar disorder would be expected to influence the reactivity of the vascular systems with consequences for the interpretation of the BOLD response [70]. Further, the link between neuronal activity and metabolic demand is contingent upon normal mitochondrial functioning but there is mounting evidence of dysfunction in bipolar disorder [71]. Coupling of blood flow and metabolism is disrupted in unipolar disorder but not bipolar disorder [72] and it interesting to note that mood stabilisers protect against mitochondrial toxicity [73]. Psychoactive drugs may also influence the BOLD signal either by altering neuronal activity (presumably in parallel with their therapeutic effects) or through modulation of the intracellular cascades that govern the response of the local capillary bed. A more inclusive appreciation of a drug's pharmacological profile may, therefore, be required when appraising fMRI data. Sulpiride, for example, appears to have little effect on neurovascular coupling [74] but acetyl-cholinesterase inhibitors may [75], presumably through their effects on nitric oxide turnover [76]. Agents, such as lithium and valproate, with their complex postsynaptic actions (in addition to effects on mitochondria), may require deeper consideration [77,78]. The effects of drugs on neurovascular coupling rather than neuronal firing

is likely to be of some importance to the field of pharmacological imaging (phMRI), but it is uncertain how much of an effect medication has during traditional, task based fMRI [44].

Baseline States and Functional Imaging

Functional imaging has been used to localize higher mental processes to specific brain regions and, in the case of bipolar disorder, discern abnormalities attributable to mania and depression. By and large, studies have compared patient groups to healthy subjects with only a few longitudinal investigations examining the difference between illness states and recovery in the same individuals [79–81]. Most fMRI studies have been task-based, applying a differencing method according to the general linear model (GLM) [82]. That is to say, regional BOLD signal acquired during a task is compared to that acquired during a control condition by simple subtraction; brain areas demonstrating increases in BOLD signal are said to be recruited in the performance of the task, with the intensity of the signal change assumed to be linearly related to the degree of neuronal activity. Greater activation implies more activity, and vice versa.

Various criticisms have been raised against the use of such a model for the interpretation of fMRI data, ranging from explorations of the nonlinearity of the BOLD response to questioning the localization of psychological constructs as functional changes within the complex neural network that the brain is envisaged to be [83,84]. Concern for the correct construction and interpretation of fMRI studies has arisen as the understanding of the neurophysiological basis of the BOLD response has advanced. These are principally medial cortical structures (anterior cingulate cortex, posterior cingulated cortex, and precuneus) and the lateral parietal lobe, now collectively referred to as the default mode regions [86]. The conclusions derived from the explanation of such deactivations may be a special significance to studies of conditions, such as bipolar disorder, a matter which will be considered in the remainder of this article.

Early work using BOLD fMRI focused on signal increases or activations, the idea being that compared to a control condition, the greater demands of a task were met by regional increases in neuronal firing. A strong association between neuronal activity and BOLD activations has been demonstrated [87], there now being a general consensus that activations reflect regional increases in presynaptic activity within neuronal groups. Whilst these groups could be executing or modulatory [68], much of the neurotransmission in the brain is glutamatergic, such that it would seem reasonable to assume fMRI largely gauges excitatory neurotransmission. It has been argued that there was an implicit assumption in the field that the brain was inactive at rest (at least in terms of neuronal firing) and that the BOLD signal activations represented the energy demands of the neurones firing in response to a stimulus or the demands of a task [82]. Within such a model, the observation of deactivations presented something of a problem to interpret—namely that if neurones are inactive at rest, how can some become less active during a task? The immediate solution, then, was to envisage that these areas of the brain were actually active in terms of neuronal firing during the rest condition, and probably to a lesser extent in whatever control condition was used in the experimental design. As a group they were named the default-mode regions and have attracted interest and controversy in equal measure [86,88]—it is not so much their existence that has been debated, but rather the functions ascribable to them. By examining low frequency fluctuations in the BOLD signal (supported by electrophysiological measures), it has been asserted that the regions are functionally connected, comprising a default mode network [89–91]. The validity of this network, whether or not it is a unified or fractionated system [92], and indeed its role is still a matter for debate, though many contest that it mediates processes such as introspection. With regard to the investigation and interpretation of imaging data in patients with bipolar disorder, two important issues arise from these observations: the development of techniques to assess functional connectivity between regions and the importance of the baseline state of the brain from which it is perturbed in the performance of a task.

Functional Connectivity Analysis in Bipolar Disorder

Various analysis techniques exist to study the degree of functional connectivity or synchronization between brain regions, broadly divisible into model-based and model-free strategies [93]. With model-based techniques the fluctuations in BOLD signal over time are extracted from a seed region of interest and cross-correlated with those from other areas; independent component analyses are not constrained by *a priori* nominations of regions, seeking to establish whether connectivity patterns can be gleaned from the signal fluctuations in the brain as a whole.

In bipolar disorder, dysregulation of the resting state signal in the medial prefrontal cortex and hypothalamus has been observed. Compared to healthy individuals, patients with bipolar disorder have a reduction in the spatial extent of the medial prefrontal components of the default mode network, taken to indicate reduced connectivity, as well as an abnormal recruitment of the parietal cortex [94]. In the same study, the frequency of the BOLD signal fluctuations at rest were higher in bipolar disorder than controls, supporting the notion of network dysfunction or, in a more general sense, a perturbation of the baseline condition in those with psychiatric illness. Connectivity studies also support the proposed corticolimbic dysfunction model of affective disorders. In an analysis of multiple regions of interest using resting state data, those with bipolar disorder showed a decreased correlation between the signal profile of the ventral anterior cingulate and that of the amygdala, thalamus, and striatum in comparison to controls [95]. In a subset, the cross-correlation was strengthened by treatment with lithium for a period of 2 months. Similar findings have since been reported in both euthymic and depressed subjects [95], as well as independent replications in more heterogeneous patient groups [96].

Task-Control Differencing fMRI in Bipolar Disorder

BOLD fMRI is not a quantitative technique, inferences about brain function typically being made by examining the localized change in signal over time during a task or stimulus presentation with

respect to a control condition or state of rest. The substantial energy demands of the brain have long been recognized, but it is of some significance that these increase by only a small fraction when moving from rest to the active engagement in a task [84]—resting is a very active state in terms of cellular processes and requirements. Rather than being devoted to cellular "housekeeping tasks," the major draws in terms of energy in the resting state are the events associated with neuronal activity (restoration of ionic gradients and neurotransmitter recycling for example) [87]. Thus, increases in BOLD signal driven through neurovascular coupling may be better thought of as exaggerations or changes in the ever-present neuronal activity—an increment rather than pure initiation [83]. The magnitude of the increment (and so the size of the BOLD signal change) is related to the baseline state of the brain [97]. For a given task or stimulus, BOLD activations will be larger if they arise from a lower baseline energy state [98] and vice versa.

The significance of this observation should not be underestimated. Imagine a BOLD fMRI study, which compares patients with mania to healthy controls in which patients have a lesser degree of BOLD activation when a task condition is compared to a resting situation. The smaller BOLD activation could represent diminished neuronal response/recruitment to the requirements of the task from a baseline that was comparable to the healthy subjects. Alternatively, those with mania may have an abnormally raised baseline and from this higher energy state, reach the same level of neuronal activity as the control subjects—in doing so the increment would be smaller and the BOLD activation reduced. Were this to be the case, the interpretation of a number of imaging studies could potentially be reversed. For instance, the lesser ventral prefrontal cortex activations seen in mania using BOLD fMRI [87] may arise not from a reduction in neuronal activity, but from increased activity at baseline. This would be consistent with the findings of positron emission tomography (PET) studies demonstrating exaggerated anterior cingulate and prefrontal cortex metabolism in mania in some [98], though not all studies [79], and the reduction in studies of the depressed phase [100].

CONCLUDING REMARKS

Magnetic resonance imaging is a powerful technique well suited to the investigation of psychiatric illness, having already provided a wealth of information about important conditions such as bipolar disorder. A degree of caution, however, must be applied when interpreting the studies using this technique.

With anatomical imaging, it is often assumed that volumetric changes reflect tissue neuropathology and whilst such studies could be supported by autopsy examination, this is a rare occurrence. The acute and chronic effects of medication on brain volume, as assessed using MRI, may prove to be a powerful confounder—troublesome to rectify too, since the underlying basis of scan findings has yet to be demonstrated. Until that time, studies involving patients taking lithium (an probably antipsychotic drugs) should be interpreted with care.

Functional imaging studies may also be prone to the effects of medications through various mechanisms, but in practical terms these may translate to a relatively minor consideration for traditional task-based fMRI. Perhaps of more importance is the move to consider the BOLD response not so much as a reflection of neuronal firing, but as a measure of the perturbation in activity and energetics. The sensitivity of the BOLD response to the baseline state of the brain seems likely to emerge as a significant consideration when interpreting fMRI in bipolar disorder—the assumption that a diminutive BOLD response necessarily reflects lesser neuronal activity has already been questioned. Future MRI studies would likely benefit by supplementing BOLD investigations with quantitative perfusion techniques such as arterial spin labelling, or though combination with PET modalities. Should the baseline state of the brain prove to be reliably disrupted by mental illness, bipolar disorder may provide an opportunity to gauge the importance of this effect on the interpretation of BOLD fMRI results, alternating as it can between extreme presentations and quiescence.

Author Contributions

David Cousins developed the concept and draft of the article. Heinz Grunze revised and approved the article.

Conflict of Interest

The authors report no conflicts of interest.

Disclosures

David Cousins received speaker honoraria within the last 12 months from Lilly and Jansen Cilag. Heinz Grunze received consulting fees and speaker honoraria within the last 12 mounths from Astra Zeneca, BMS, Eli Lilly, Gedeon Richter, Merck, Sepracor, Servier and UBC.

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