Molecular Psychiatry (2002) 7, S64–S70

www.nature.com/mp

ORIGINAL RESEARCH ARTICLE

Can brain-imaging studies provide a 'mood stabilizer signature?'

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Brain-imaging investigations have attempted to characterize the neurobiological basis of bipolar disorder. Preliminary studies have also focused on *in vivo* brain correlates of treatment response with antidepressants, mood stabilizers and other psychotropic medications. A MEDLINE® literature search was conducted dating back to 1966. Selected *in vivo* brain-imaging studies that examined neurobiological correlates of treatment response in mood disorder patients were identified. Discrete anatomical abnormalities in subregions of the prefrontal cortex, medial temporal lobe and cerebellum have been identified in bipolar patients. Functional imaging studies suggested abnormalities in particular brain circuits encompassing these same brain regions and the striatum. However, functional imaging correlates of treatment response with lithium or other mood stabilizers have not yet been characterized. Neurochemical studies suggested a reduction in N-acetyl aspartate levels in prefrontal cortex and abnormalities in membrane phospholipids in frontal and temporal lobes. Preliminary findings suggest that lithium may increase the gray matter content and N-acetyl aspartate levels in various cortical regions, which could reflect its putative neurotrophic effects. Few *in vivo* receptor-imaging studies have examined brain correlates of treatment response in bipolar patients. The available studies suggest anatomical, neurochemical and functional brain abnormalities in bipolar patients. However, *in vivo* brain correlates of treatment response with mood stabilizers in bipolar patients have not yet been well characterized.
Molecular Psychiatry (2002) **7,** S64–S70. DOI: 10.1038/sj/mp/4001020

Keywords: bipolar disorder; mood disorders; neuroimaging; magnetic resonance imaging; magnetic resonance spectroscopy; positron emission tomography

Introduction

Developments in brain-imaging methods have brought new possibilities for *in vivo* studies of the human brain, allowing anatomical, neurochemical and functional investigations with unprecedented resolution. Over the past decade, a growing number of studies have examined possible brain mechanisms involved in mood disorders.[1,2] In several morphometric magnetic resonance imaging (MRI) studies, particular brain regions, such as subregions of the prefrontal cortex (PFC), medial temporal lobe, striatum and cerebellum were found to be abnormal. These regions participate in brain neuroanatomic circuits involved in mood regulation.[3,4] In particular, they participate in two interrelated brain circuits, a limbic-thalamic-cortical circuit, and a limbic-striatal-pallidal-thalamic circuit, which comprise critical brain regions possibly implicated in the pathophysiology of mood disorders. Subsequent investigations have examined the functional and neurochemical substrates of abnormalities in these brain regions, with magnetic resonance spectroscopy (MRS), functional magnetic resonance imaging (fMRI), single photon emission computerized tomography (SPECT) and positron emission tomography (PET). Such studies hold considerable promise to elucidate the brain mechanisms involved in mood disorders. Recently, potential *in vivo* brain correlates of treatment response with psychotropic drugs utilized in the treatment of mood disorders have been examined in human studies. For example, preliminary brain imaging studies have examined *in vivo* correlates of treatment response with antidepressant medications[5] and mood stabilizers.[6]

In this article, we review the published brain-imaging findings in bipolar disorder, with a particular focus on available studies that attempted to characterize the *in vivo* brain correlates of treatment response with mood stabilizers. We summarize emerging findings and suggest possible strategies for future investigations.

Materials and methods

A MEDLINE® search for the period from 1966 to May 2001 was conducted, and was complemented by a manual search of bibliographic cross-referencing. All *in vivo* human studies that utilized brain-imaging tools

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to investigate the mechanisms of action of mood stabilizers in the treatment of bipolar patients were identified. Papers were selected for inclusion in this review according to their perceived importance and potential interest to this emerging field of investigation.

Results

Morphometric studies

Several MRI studies that examined subregions of the frontal lobe have suggested abnormalities in bipolar patients. Sax *et al*[7] found decreased PFC volumes in manic patients, and Drevets *et al*[8] found decreased gray matter volume in subgenual PFC in unipolar familial mood disorder and bipolar subjects. The findings of abnormalities in the subgenual PFC have recently been partly replicated, with a report of reduced subgenual PFC in the left side in familial unipolar subjects.[9] Abnormalities in subgenual PFC were further confirmed in neuropathological studies, which demonstrated decreased glia, without corresponding loss in neuronal size.[10] Rakjowska *et al*[11] recently examined the dorso-lateral PFC (DLPFC) in a postmortem brain study, and found reduced neuronal size and density, and reduced glial density in bipolar patients. These findings are in line with our recent findings of reduced gray matter content in this brain region in unmedicated bipolar patients,[12] and suggest that this brain region may be an important site of dysfunction in bipolar disorder and related to the pathophysiology of the illness. Interestingly, in this study, the gray matter values in the DLPFC of lithium-treated bipolar patients were very similar to those values for healthy controls, suggesting that lithium may have potential effects of preventing or reversing such gray matter abnormalities in bipolar patients.

There is considerable disagreement in the literature regarding anatomical changes in medial temporal lobe structures in bipolar patients, which are probably due, to a large extent, to various imaging methods utilized, as well as difficulties in anatomical delineation of these structures. The most recent studies used higher-resolution scans and improved anatomical methods, and may have detected changes missed in earlier ones. Two independent studies found increased amygdala volumes in bipolar patients compared with healthy controls.[13,14] These findings were recently replicated by our group, with findings of enlarged left amygdala in bipolar patients.[15] In bipolar individuals, one study found decreased right hippocampal volume,[16] while others did not find significant differences in hippocampal area or volume.[14,15,17] In unipolar individuals, most studies to date have found decreased hippocampal volumes,[1] which may be mediated by dysfunction in the hypothalamic-pituitary-adrenal axis.

In unipolar disorder, smaller caudate and putamen volumes were reported, while most studies in bipolar patients did not find abnormalities in these structures.[3,18] These findings indicate that anatomical abnormalities in striatum may be a distinctive feature of unipolar disorder not present in bipolar disorder.

Anatomical abnormalities in cerebellum were found in bipolar and unipolar subjects in several studies, with increased rates of vermis atrophy, and decreased cerebellar size.[3] Atrophy in V3 vermal area was found in multiple-episode, compared with first-episode, bipolar patients, suggesting a neurodegenerative process.[19] As the cerebellum has important anatomical projections to brain stem and limbic regions, cerebellar abnormalities could possibly result in abnormalities in catecholamines, as well as interfere with functioning of limbic and cortical structures.

Recently, Moore *et al*[20] reported that bipolar patients (n = 10) treated with lithium for a 4-week period had increased gray matter content, by an average of 3%, in various cortical regions. Our group recently compared the total brain gray matter volumes in a group of unmedicated bipolar patients, lithium-treated patients and healthy controls in a cross-sectional study, and did not find significant differences, suggesting that, for the whole brain, no significant changes in gray matter volumes are present, and that no potentially protective effects of lithium on total gray matter brain volumes can be detected in this patient population.[21] These findings suggest that any potential effects of lithium on neuroprotection could be more specific to certain key brain regions, eg, the DLPFC, or subgenual PFC, which are regions that could be anatomically and functionally abnormal in this disorder.

Functional studies

To date, the functional studies involving mood disorder subjects have been largely SPECT and PET studies, at resting state. PET studies with [^{15}O]-water and [^{18}F]-FDG, which examined cerebral blood flow and glucose metabolism, respectively, found evidence of hypofrontality in unipolar and bipolar individuals. Two groups of investigators have reported functional abnormalities in depressed patients in anterior cingulate, in Brodmann areas 24[8] and 25.[22] Decreased blood flow and glucose metabolism in subgenual PFC of familial unipolar and bipolar mood disorder patients were reported.[8] Mayberg *et al*[23] found that depressed patients who responded to a 6-week trial with fluoxetine had a different pattern of brain activation compared with non-responders, with decreased activation in limbic and striatal regions, and increased activation in brain stem and dorsal cortical regions. However, further independent replication of these findings, as well as characterization of these changes longitudinally as related to mood state, is still needed. Evidence for functional deficit in medial PFC related to neuropsychological dysfunction was found in mood disorder patients,[24] as well as blunted left cingulate activation at the Stroop test, which is an attentional task.[25] Recently, preliminary fMRI evidence of dysfunction in rostral and orbital PFC regions has been reported.[26] In conclusion, available functional findings suggest involvement of abnormalities in PFC in bipolar and unipolar disorders, suggesting that this is an important site of dysfunction involved in the pathophysiology of these illnesses.

There has been a report of increased blood flow in left amygdala in familial pure depressed subjects in a PET [^{15}O]-water study,[27] which is conflicting with other available findings.[4] Additionally, decreased blood flow and glucose metabolism in basal ganglia, particularly caudate, have been reported in several studies.[4] These reports have largely involved depressed unipolar subjects, but a few also involved bipolar individuals.

In conclusion, the available functional imaging studies have generally not examined longitudinally the same patients in various mood states. Investigations have been conducted primarily in the depressed state, and only a few studies included manics and euthymic, or remitted, patients. Therefore, it is not clear at this point whether reported changes are trait or state related, and to what extent they relate to use of psychotropic medications. Longitudinal studies involving drug-free individuals in various mood states are clearly warranted.

In vivo neurochemical studies

MRS studies Developments in the methods for *in vivo* MRS brain studies have started to be applied in investigations of mood disorders.[28] N-acetyl aspartate (NAA), which is a marker of neuronal viability and/or function, and can be quantitated with *in vivo* ^{1}H MRS, appears to be decreased in particular brain regions in mood disorder subjects, suggesting abnormal neuronal processes regionally. Decreased levels of NAA in the dorsolateral PFC of bipolar patients were reported.[29] Further studies should investigate NAA abnormalities in other brain regions involved in mood regulation in bipolar and unipolar patients, both while unmedicated and after treatment. Recently, Moore *at al*[6] reported interesting findings in a study that involved a group of bipolar patients and healthy controls. These authors found increased NAA levels in various cortical regions, as a result of lithium treatment. Vis-à-vis recently reported lithium effects increasing production of neurotrophic factors such as bcl-2, these findings may represent direct *in vivo* evidence of putative neuroprotective effects of lithium. A recent study compared NAA levels in frontal lobe in psychotic patients being treated with typical and atypical antipsychotics.[30] The patients on atypical antipsychotics had significantly higher NAA levels in anterior cingulate than the ones on typical antipsychotics, suggesting that the atypical medications may prevent or reverse potential insult in particular brain regions, and potentially confer neuroprotection. However, in a preliminary study,[31] another group of investigators treated rats with olanzapine, and the only detectable effect was a small reduction of NAA/PCr-Cr after 7 days of olanzapine administration. This study involved a voxel placed in the center of the animals' brains, and negative findings may be related to region specificity. Also, if neuroprotective effects are present, perhaps more prolonged administration of the drug is required, in contrast with the 7-day period utilized in this study. Therefore, there are preliminary suggestions that atypical antipsychotics could have specific neuroprotective effects in the human brain, and these interesting possibilities remain to be specifically investigated in future studies as related to the mechanisms of action of mood stabilizers and other medications utilized in the treatment of bipolar disorder.

Choline is an important cell membrane component, and has important functions in membrane turnover and function. The choline peak, as visualized by MRS, comprises various choline-containing molecules, including a small fraction that is free choline. Increased choline peak in basal ganglia has been reported in bipolar disorder subjects.[28] Moore *et al*[32] found increased Cho/PCr-Cr ratios in right anterior cingulate in bipolar patients. Steingard *et al*[33] reported increased Cho/PCr-Cr ratios in depressed adolescents in orbito-frontal cortex. In another study, Renshaw *et al*[34] reported significantly reduced Cho/PCr-Cr ratios in the basal ganglia of depressed unipolar subjects, which was more pronounced in subjects who responded to fluoxetine treatment. In bipolar patients, the increase in choline-containing molecules in basal ganglia reported in some studies does not appear to be related to lithium treatment, as it is also present in drug-free individuals. Additional studies in unmedicated patients, and improved methodology to quantitate free choline in MRS studies, when available, will be important to further clarify the potential relevance of such abnormalities.

A hyperglutamatergic state in some of the key brain regions involved in mood regulation, eg, the PFC, may be possibly implicated in the pathophysiology of mood disorders. Considering findings of hypometabolism[4] and decreased glia and neurons in this brain region,[11] the hypothesis of a hyperglutamatergic state being involved in pathophysiology is plausible. Increased glutamate levels could be neurotoxic and could explain available brain imaging and postmortem findings for this brain region. A recent *in vivo* MRS study in unipolar depressed subjects reported increased glutamine and glutamate (glx peak) in this brain region.[35] In a group of depressed bipolar adolescents, a bilateral increase in glx in frontal cortex, as well as basal ganglia, has recently been reported.[36] These preliminary findings suggest that glutamatergic abnormalities may be involved in neurotoxicity that is potentially responsible for specific brain insults present in this disorder. The ^{1}H MRS method utilized in these studies did not allow optimal resolution of glutamate, glutamine and the underlying glutamate and γ-amino butyric acid (GABA) resonance, but further studies are underway utilizing MRS methods that would allow this distinction.

Brain GABA levels can be measured with *in vivo* ^{1}H MRS. Decreased GABA levels were reported in occipital cortex in drug-free, depressed, unipolar subjects.[37] These interesting preliminary findings suggest the involvement of GABAergic brain mechanisms in the pathophysiology of mood disorders. However, they still require independent replication and examination of other brain regions potentially involved in the pathophysiology of unipolar and bipolar disorders.

Myo-inositol is a substrate for recycling of inositol phospholipids in the phosphoinositol intracellular pathway, and has an important role in brain signal transduction pathways. Abnormalities in the phosphoinositol pathway have been implicated in the pathophysiology of bipolar disorder, and lithium is known to have important effects in this pathway, which may be critical for its therapeutic actions. Myo-inositol levels in the right frontal lobe, as detectable by ^{1}H MRS, were significantly decreased after 4 weeks of lithium treatment in bipolar patients.[38] These findings have recently been replicated in a sample of bipolar adolescents, where bilateral reductions in myo-inositol levels in anterior cingulate were reported.[39] Future studies that will attempt to clarify the role of abnormalities in the PI pathway in the pathophysiology of bipolar disorder are clearly warranted.

^{31}P MRS allows *in vivo* examination of neuronal membrane processes and aspects of neuronal metabolism. Kato *et al*[40,41] found increased levels of phosphomonoesters (PME) in the manic and depressed states, and decreased PME in the euthymic state, while Deicken *et al*[42,43] found decreased PME in the frontal and temporal lobes in euthymic bipolar patients. As patients in these studies were mostly on lithium or off lithium for short periods of time, increased levels of PME could reflect medication effects. PMEs are precursors of membrane phospholipid metabolism, while PDEs are breakdown products. Abnormalities in PMEs could be consistent with increased membrane anabolism in the frontal and temporal lobes in bipolar disorder in the manic and depressed phases, and decreased in the euthymic state. ^{31}P MRS studies also suggested decreased pH in the frontal lobe of lithium-treated and drug-free, euthymic, bipolar subjects, and in areas of increased white matter hyperintensity, decreased pH and increased PDE have been reported.[44] Decreased pH and increased white matter hyperintensity may be non-specific abnormalities related to various brain insults.

^{7}Li MRS has been applied for investigations in lithium-treated bipolar patients.[45] Preliminary studies characterized the kinetics of lithium in the brain.[46] A relationship between brain and serum lithium concentrations ranging from 0.4–0.8 has been found in most studies. There are preliminary suggestions that ^{7}Li MRS could have therapeutic relevance.[45] Future studies should examine whether lithium concentrations in brain tissue have clinical relevance in the acute and maintenance treatment of bipolar patients.

Radiotracer receptor studies New imaging methods have allowed *in vivo* examinations of the serotonergic system in mood disorder patients. Decreased density of serotonin transporters (5HTT) in midbrain may be present in drug-free, depressed, unipolar subjects.[47] However, the radiotracer used in this study, ^{123}I-beta CIT (Methyl 3 beta- (4-[^{125}I]iodophenyl)tropane-2 beta-carboxylate)), does not allow the examination of 5HTT levels in cortical regions. No studies have examined 5HTT levels in bipolar individuals. New PET radiotracers, such as [^{11}C]-McN5652, have made the examination of 5HTT levels in cortical regions feasible, and can now be applied for studies in bipolar and unipolar populations. Increased $5HT_{2A}$ binding in frontal cortex of patients treated with selective serotonin reuptake inhibitors compared with drug-free depressed patients was reported in a PET [^{18}F] setoperone study.[48] Another PET [^{18}F]-setoperone study[49] did not reveal abnormalities in $5HT_{2A}$ cortical levels, except for decreased binding in frontal cortex in a small sample of depressed subjects ($n = 7$). After clomipramine treatment and improvement in depressive symptoms, specific cortical binding decreased, which suggests $5HT_{2A}$ receptor occupancy or down-regulation. Normal density of $5HT_{2A}$ receptors in unipolar patients was found in a recent PET [^{18}F] setoperone study,[50] while another study[51] reported decreased $5HT_{2A}$ binding across several regions, including frontal, temporal, parietal and occipital cortices in unmedicated depressed subjects. Biver *et al*[52] reported decreased [^{18}F] altanserin binding in right posterolateral, orbito-frontal and anterior insular cortex in drug-free unipolar depression, suggesting decreased $5HT_{2A}$ receptor levels. In conclusion, the available results are somewhat conflicting and are in disagreement with postmortem findings, which showed increased $5HT_{2A}$ cortical levels in suicide and in mood disorders. Finally, the effects of serotonergic drugs in the *in vivo* cortical levels of $5HT_{2A}$ receptors in depressed subjects are not clear, but there are suggestions that $5HT_{2A}$ cortical levels could decrease after antidepressant treatment. The $5HT_{1A}$ receptor system has been investigated with the PET tracer [^{11}C]-carbonyl-WAY 100635 in human studies. Drevets *et al*[53] reported decreased $5HT_{1A}$ receptor levels in mesiotemporal cortex, hippocampus, pregenual anterior cingulate and lateral orbito-cortex in a small sample of depressed, familial, unipolar and bipolar individuals. Recently, Sargent *et al*[54] reported decreased binding potential in frontal, temporal and limbic cortex in selective serotonin reuptake inhibitor-treated and unmedicated, depressed, unipolar patients. With availability of appropriate *in vivo* methodology for studies of $5HT_{2A}$ and $5HT_{1A}$ receptors, and 5HTT, future studies will allow further characterization of the potential role of a serotonergic dysfunction in the pathophysiology of mood disorders, and the precise role of serotonergic modulation in the mechanisms of action of treatments for these conditions.

Abnormalities in the dopaminergic system may be present in mood disorder subjects. A N-[[^{11}C]]methyl-spiperone ([[^{11}C]]NMSP) PET study[55] found increased binding potential in striatum of neuroleptic-naive or neuroleptic-free psychotic patients compared with non-psychotic bipolar patients and healthy individuals. These findings indicate increased striatal D_2 receptor levels, and are similar to findings in schizophrenic patients. In a recent study, Anand *et al*[56] did not find abnormalities in D_2 striatal baseline level in euthymic, lithium-treated, bipolar patients. In this study, these patients did not have abnormalities in amphetamine-induced dopamine release. These findings suggest that such abnormalities in dopaminergic transmission may be characteristic of psychotic patients. In conclusion, few *in vivo* brain-imaging studies have examined D_2 receptors in bipolar patients. There is suggestion from one study that neuroleptic-free or neuroleptic-naive, psychotic, bipolar individuals have increased levels of D_2 receptor in striatum. Future investigations should also examine the levels of D_2 receptors in extra-striatal regions, with radiotracers such as the SPECT tracer [^{123}I]-epidepride or the PET tracer [^{18}F]-fallypride which allow such studies. The SPECT tracer [^{123}I]-beta CIT also allows imaging of dopamine transporters in striatum, and investigations in unipolar patients have produced negative results.[47] Nonetheless, no available studies have examined dopamine transporters in medication-free bipolar individuals. Recently, alpha-methyl-paratyrosine and [^{123}I]-IBZM or [^{11}C]-raclopride have been used to study baseline dopamine levels. These investigations are of great interest, considering findings of increased dopamine release in schizophrenics, which may be a marker of psychotic states.[57] In conclusion, very few *in vivo* imaging studies have examined the dopaminergic system in bipolar patients, but there are suggestions of dysfunction. Studies in drug-free patients in various mood states are greatly needed to attempt to clarify the involvement of the dopaminergic system in the pathophysiology of mood disorders.

Lastly, fMRI—in conjunction with specific pharmacological paradigms—has not been utilized for *in vivo* human neurochemical studies in this field. There is, however, clearly a very interesting potential for utilization of these modalities in studies in this area, and it is likely that we will start seeing them in the near future.

Discussion

Bipolar and unipolar mood disorders appear related to anatomical, neurochemical and functional abnormalities in particular neuroanatomic brain circuits involved in mood regulation. Specifically, the PFC, medial temporal lobe, striatum and cerebellum are regions that seem to be affected. High-resolution MRI studies have started to characterize the neuroanatomy of these disorders. A new generation of fMRI studies is attempting to characterize the brain dysfunction involved in modulation of particular brain functions, eg, components of affective regulation, attention, and memory, in mood disorder patients. Recent investigations have also examined *in vivo* neurochemical abnormalities in this patient population. The availability of improved brain imaging SPECT and PET tracers for $5HT_{1A}$, $5HT_{2A}$, D_1 and extra-striatal D_2 receptors, 5HTT, and the feasibility of imaging neurotransmitter release and baseline levels, will allow comprehensive investigations of *in vivo* brain neurochemistry in bipolar and unipolar patients, and substantial progress in this area may become possible. Furthermore, *in vivo* brain investigations of signal transduction processes with methods from MRS or PET have been proposed, but these tools still do not have appropriate resolution to accurately examine intracellular brain signal transduction mechanisms. Finally, future investigations that would specifically characterize the time course of brain abnormalities, as related to treatment response with mood stabilizers in this patient population, are very much warranted. Important areas in which future studies are expected to focus include D_2 and $5HT_{2A}$ receptor levels, D_1 receptor levels, 5HTT levels, glutamate, glutamine, and GABA-ergic abnormalities, NAA, gray matter regional content, myo-inositol modulation, and regional activation or metabolic brain changes.

In conclusion, the field of *in vivo* brain-imaging investigations in mood disorders is still in its infancy. The published studies in this area have largely involved small patient samples, or samples where a substantial proportion of these patients were on psychotropic medications that could have confounded the results, and to a great extent have yielded conflicting findings. The available findings come largely from cross-sectional studies, and there is still a clear need for independent replication of most published results. Furthermore, there is a great need for studies that will examine longitudinally the influence of mood and medication effects on *in vivo* brain-imaging abnormalities. Such studies are likely to be of major relevance for the identification of surrogate markers for potential utilization in clinical trials in mood disorders. It is expected that *in vivo* brain imaging could potentially become a very useful tool in the screening of new therapeutic compounds that could be potentially useful as mood stabilizers, if specific and reliable neuroimaging targets can be identified, and be utilized as effective tools to aid in drug development.

Acknowledgements

This work was partially supported by grants MH 01736, MH 29618 and MH 30915 from NIMH, the Theodore and Vada Stanley Foundation, and the National Alliance for Research in Schizophrenia and Affective Disorders (NARSAD). Dr Soares was the 1999–2001 NARSAD Selo Investigator.

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