Medication Effects in Neuroimaging Studies of Bipolar Disorder

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Abstract

Objective—Neuroimaging studies are promising components for a new diagnostic framework for bipolar disorder, but a major issue is the potential confound of psychotropic medication upon experimental measures. Withdrawing all individuals from medication and examining only unmedicated individuals may be clinically unfeasible, and examining only unmedicated individuals may render findings less generalizable.

Method—The authors review structural and functional neuroimaging studies of medicated and unmedicated patients with bipolar disorder to discern the possible confounding effect of medication.

Results—Findings from studies identified on MEDLINE that included medicated individuals with bipolar disorder indicated either no significant effect or ameliorative effects of psychotropic medications on abnormal structural and functional neuroimaging measures relevant to pathophysiologic mechanisms of the disorder. Different strategies for assessing medication effects are compared.

Conclusions—Neuroimaging studies of bipolar disorder ideally should recruit both unmedicated and medicated individuals. Individuals who are unable to tolerate medication withdrawal likely have more severe illness and are especially informative for research examining biomarkers of illness and treatment response.

The research agenda for DSM-V emphasizes the need for translating basic and clinical neuroscience research findings into a new classification system for psychiatric disorders based upon pathophysiologic and etiological processes (1,2). It also supports the recent call for such research to help create "rational treatment advances" in disorders such as bipolar depression (3) and the National Institute of Mental Health recommendation for the need to translate basic science discoveries into biomarkers, diagnostic tests, and new treatments for individuals with psychiatric disorders. Biological evidence of pathophysiologic processes can help meet critical challenges in psychiatric research by aiding the construction of diagnostic and treatment response groupings. This is particularly relevant to bipolar disorder, which is frequently either misdiagnosed or diagnosed late, often as unipolar depression in individuals without a clear previous history of manic episodes (4).

Studies employing neuroimaging techniques, and functional neuroimaging techniques in particular, provide direct measures of neural system abnormalities that may be associated with different domains of pathology in bipolar disorder (2). These domains include abnormal emotion regulation and impaired cognitive control. A major issue for studies of psychiatric populations, however, is the potential confound of psychotropic medication upon

neuroimaging measures. It remains unclear how different psychotropic medications affect neuroimaging measures, such as the proxy measures of blood flow used in functional magnetic resonance imaging (fMRI). This is especially problematic for studies of bipolar populations, in which the majority of individuals, particularly individuals with bipolar disorder type 1, may be receiving psychotropic medication.

Restricting Study to Unmedicated Individuals With Bipolar Disorder: Advantages and Disadvantages

Restricting study to medication-naive individuals with bipolar disorder is one strategy to avoid any potential confound of medication upon neuroimaging measures. This strategy would likely limit recruitment to small numbers of participants who may not be representative of the chronically ill bipolar populations managed in most clinical settings. The inclusion of only unmedicated individuals in neuroimaging studies in bipolar disorder necessarily involves withdrawing individuals from psychotropic medication, since maintenance treatment is usually required to decrease the probability of a relapse because of the recurrent nature of the disorder. For the individuals who are able to tolerate medication withdrawal and washout, there are clear benefits. These include not only the potential of identifying biomarkers of bipolar illness but also the opportunity provided by medication washout to identify biomarkers that may predict individual response to subsequent treatments without confounds of current psychotropic medication. There are other justifications for implementing medication withdrawal and washout. The process may decrease copharmacy, whose rational use is hampered by a lack of systematic research on its safety and efficacy (5). Furthermore, there are instances in which psychiatric symptoms or physical side effects improve upon discontinuation of ongoing medications.

There are two difficulties inherent in medication withdrawal. First, withdrawing individuals from medication may increase the probability of relapse for individuals in remission and a worsening of clinical status for individuals experiencing an acute episode (6). This may therefore make medication withdrawal clinically unfeasible for some individuals with bipolar disorder. A related problem is that the medication withdrawal period may need to be long to include both withdrawal itself and a subsequent medication-free washout period to ensure the absence of potential withdrawal phenomena that may confound neuroimaging measures. This may further increase the risk of relapse or a worsening of symptoms in individuals with bipolar disorder. It takes five half-lives to eliminate 97% and six half-lives to eliminate 98% of residual drug (7). For medications with a long half-life, this translates into a washout period of several months. The clinical setting in which the washout and withdrawal are performed clearly plays an important role in the evaluation of the risk-benefit ratio of the procedure, and careful examination of the history of each individual is necessary to determine the level of risk and potential complications that the procedure would entail.

A second potential difficulty with medication withdrawal and washout is that it may carry the risk of selection of a subpopulation that is not representative of the bipolar population as a whole. Individuals with a history of severe manic or psychotic episodes, individuals with co-morbid anxiety disorders, and those with a high suicide risk or a high risk of dangerous behaviors may be underrepresented in subpopulations that are able to tolerate the washout procedure and remain medication free. Conversely, individuals with less severe symptoms are likely to be overrepresented in these subpopulations. For the development of new treatments for bipolar disorder, the most at-need group includes individuals with correctly diagnosed bipolar disorder yet who are poorly responsive or nonresponsive to existing treatments. These individuals with bipolar disorder are likely to be medicated and, as discussed above, may be unable to tolerate medication withdrawal. Biomarkers of bipolar illness and treatment response identified from neuroimaging studies of unmedicated individuals only may not, therefore, be

generalizable to medicated groups. This limitation may reduce the usefulness of any putative investigations.

Some neuroimaging studies have been able to recruit unmedicated individuals with bipolar disorder type II (8), small numbers of unmedicated individuals with bipolar disorder type 1 (9), or unmedicated individuals in a first episode (10) or with pediatric bipolar disorder (11). Recruitment of large numbers of unmedicated individuals with bipolar disorder type 1 remains difficult, however. Indeed, the actual proportion of individuals with bipolar disorder type 1 excluded from neuroimaging studies because of an inability to tolerate medication withdrawal and washout has not been previously reported, probably because individuals with the disorder at higher risk of experiencing problems with withdrawal are usually not referred for study.

The Study of Medicated Individuals With Bipolar Disorder: Findings From Neuroimaging Studies

We performed an Ovid MEDLINE literature search on studies in bipolar disorder from 1996 to 2007 using the key words "bipolar disorder" and "neuroimaging." The majority of these studies examined adults with bipolar disorder type 1. Many were studies that employed functional and structural neuroimaging to measure abnormalities in neural regions associated with important domains of pathology in bipolar disorder: impaired cognitive control, abnormal emotion processing, and mood instability. These neural regions include the prefrontal cortical and subcortical limbic regions (12). Inclusion of all existing neuroimaging studies of bipolar disorder was clearly beyond the scope of this review. Furthermore, not all existing neuroimaging studies in bipolar disorder examined the potential effects of psychotropic medication. Since our main focus was to examine potential medication effects on *direct* measures of activity in neural regions implicated in the pathophysiology of bipolar disorder, we included in this review all existing functional neuroimaging studies of adult and pediatric bipolar disorder that employed cognitive control and emotion-processing paradigms and examined potential effects of psychotropic medication on neuroimaging measures (see Table 1 for specific details of these studies). To complement these studies, we also include a brief overview of volumetric structural neuroimaging studies that examined the potential effects of psychotropic medication on regional cerebral volumes in adult and pediatric bipolar disorder. We additionally note the importance of spectography and ligand studies in bipolar disorder to the examination of potential confounding effects of psychotropic medication on neurochemical and neuroreceptor systems of interest in bipolar disorder, although a full description of all existing spectrography and ligand studies was beyond the scope of this review.

Functional Neuroimaging Studies

Functional neuroimaging studies in bipolar adults and adolescents demonstrate abnormally decreased activity in prefrontal cortical regions during cognitive control and abnormally increased activity in subcortical limbic regions during emotion processing that may persist during remission, depression, and mania (14,15,27). More recent studies have examined neural activity in remitted bipolar populations, many of whom were medicated (13,21–23). Reports of the effects of medication include 1) no significant association between psychotropic medication and magnitude of activity in anterior cingulate gyral and prefrontal cortical regions during cognitive control tasks, e.g., selective attention (16,24), 2) increased activity in the dorsolateral prefrontal cortex during selective attention (17), and 3) increases and decreases in anterior cingulate gyral and dorsolateral prefrontal cortical activity, respectively, during executive control (23) in medicated relative to unmedicated remitted individuals with bipolar disorder. A significant positive correlation has also been reported between antipsychotic medication dose (in chlorpromazine equivalents) and activity in the rostral anterior cingulate gyrus and the dorsolateral prefrontal cortex during a cognitive control task in remitted

individuals (22). Medicated more than unmedicated bipolar individuals demonstrate levels of prefrontal cortical activity during cognitive control that are similar to those observed in healthy individuals. Similarly, other studies of remitted individuals with bipolar disorder report ameliorative effects of different types of psychotropic medication upon the magnitude of subcortical limbic activity to emotional stimuli such that abnormally elevated subcortical limbic activity is decreased in bipolar individuals (19,21). A specific effect of antipsychotics in reducing amygdala activity has been demonstrated in bipolar men (26). As was found for cognitive tasks, medicated more than unmedicated individuals with bipolar disorder demonstrate levels of subcortical limbic activity to emotional stimuli that are similar to those observed in healthy individuals. Inconsistent with the above findings is a report of decreased prefrontal cortical activity in bipolar individuals during executive control (word generation) after taking lithium (18).

The few studies that have examined the effects of psychotropic medication on neural activity in bipolar individuals during depression or mania report a positive correlation between levels of chlorpromazine equivalents and decision-making task-related activity in the rostral prefrontal cortex during mania (25) but no effect of such medication on the magnitude of ventral prefrontal cortical activity in mania during attentional control (20). In pediatric bipolar populations, studies indicate no significant effect of the number of psychotropic medications taken upon the magnitude of neural activity to emotional stimuli (15). One study demonstrated an ameliorative effect of psychotropic medication in reducing abnormally elevated striatal and ventral prefrontal cortical activity on a motor inhibition task (14). To our knowledge, no studies have examined the potential effects of psychotropic medication on neural regions implicated in cognitive control in pediatric bipolar disorder.

Volumetric Structural Neuroimaging Studies

Volumetric structural neuroimaging studies in adults and adolescents with bipolar disorder have shown gray matter volume abnormalities in different neural regions subserving cognitive control and emotional processing. The main findings include decreased ventral/orbital medial prefrontal cortical gray matter volume and amygdala and striatal gray matter volume increases in adults with bipolar disorder (see reference 28 for a review of this literature), although amygdala gray matter volume decreases in bipolar youth, adolescents, and young adults (29, 30). Studies of individuals in first-episode psychosis, including both schizophreniform and nonschizophreniform psychoses, have not revealed any significant effect of antipsychotic medication upon regional gray matter volume (31). In non-first-episode individuals with schizophrenia, however, there are associations between antipsychotic medication and enlargement of basal ganglia volumes (32), and in non-first-episode individuals with bipolar disorder, there are associations between concurrent use of psychotropic medication and both decreased (33) and increased (34) ventral prefrontal cortical gray matter volume. Lithium has been associated with significantly increased total and anterior cingulate gyral (35) and hippocampal (36) gray matter volume, although see reference 37. Valproate and valproate-plus-quetiapine combination have been associated with significantly increased anterior and posterior cingulate gyral volumes (38). In pediatric and adolescent bipolar disorder, findings suggest no effect of psychotropic medication exposure upon regional cerebral volumes (29, 39,40). Other findings indicate an association between past lithium or valproate exposure and greater amygdalar gray matter volume in children and adolescents with bipolar disorder type 1 (41), although lifetime antidepressant exposure has been associated with reduced amygdala gray matter volume in these populations (42). The most consistent finding from volumetric structural neuroimaging studies is an association between lithium and increased gray matter volume in key neural regions, such as the anterior cingulate gyrus, amygdala, and hippocampus, implicated in cognitive control and emotion processing, indicating a neurotrophic—and potentially neuroprotective—effect of lithium (43).

Magnetic Resonance Spectography (MRS) and Ligand Studies

Some MRS studies have examined the extent to which psychotropic medication is associated with changes in abnormal concentrations of metabolites that are measures of neuronal integrity, including *N*-acetyl-aspartate and myoinositol, in previously unmedicated individuals with bipolar disorder after treatment with different psychotropic medications (44). Findings from these studies include either no changes in such measures after treatment with lithium (45) or increases in *N*-acetyl-aspartate concentration over several neural regions after 4 weeks of lithium treatment (46). The few receptor ligand studies in bipolar disorder that have examined the effects of psychotropic medication upon neuroreceptor availability have focused on the serotonin transporter, the 5-HT$_{1A}$, and dopamine D$_2$ receptors. Findings indicate no change in cortical 5-HT$_{2A}$ receptor availability observed in seven manic individuals successfully treated with sodium valproate, one of whom had also received lithium (47). Similarly, sodium valproate monotherapy over 2–6 weeks for nonpsychotic mania had no significant effect on the availability of striatal D$_2$ receptors (48). These preliminary findings need to be expanded with further research but suggest either ameliorative or no significant effects of mood-stabilizing medications upon neurochemical systems and neuroreceptor availability so far studied in bipolar disorder.

Effects of Psychotropic Medication on Functional Neuroimaging Measures in Individuals With Bipolar Disorder

There is a convergence of findings from the functional neuroimaging studies described above, predominantly in adult bipolar populations, that indicates that abnormal frontal cortical and subcortical limbic activity during cognitive control and emotion-processing paradigms may reflect pathophysiologic processes of bipolar disorder (13,16–26). While the strength of these studies is the consistency of these main findings, there are inconsistencies regarding the potential effects of psychotropic medication and associated methodological limitations that make it difficult to draw firm conclusions. Some studies find no significant effects of psychotropic medication on functional neuroimaging measures (14–16,20,24). In many of these studies, however, the small sample sizes inherent in examining individuals taking versus those not taking each individual class of psychotropic medication make it possible that findings of no significant effect of psychotropic medication resulted from type II error, as authors of these studies have emphasized in discussions of their findings (e.g., reference 24). Other studies found significant ameliorative effects of psychotropic medications upon functional neuroimaging measures (19,21,22,26).

Specifically, both antipsychotics and lithium increased prefrontal cortical activity during cognitive control and reduced abnormally elevated subcortical limbic activity during emotion processing in bipolar adults so that activity in these regions resembled that observed in healthy individuals participating in the studies. These findings suggest that abnormalities reflect pathophysiologic processes that may be partly ameliorated by, rather than abnormalities that are secondary to, psychotropic medication. The majority of studies to date, however, either did not include examination of unmedicated individuals or included only small numbers of unmedicated individuals (13,16,20–23,25,26), making definitive conclusions about the effects of psychotropic medication upon neuroimaging variables in bipolar disorder difficult. There is supporting evidence of either no significant effects or ameliorative effects of psychotropic medication upon regional cerebral volumes from the larger number of volumetric structural neuroimaging studies in adult and pediatric bipolar disorder, but these studies do not allow measurement of the functional integrity of neural regions that may be implicated in the pathophysiology of bipolar disorder. There are also similar findings of no significant effects or ameliorative effects of psychotropic medication upon measures of neural integrity and

neuroreceptor availability from the more preliminary MRS and ligand studies described above, but these latter studies require replication.

Strategies for Examining Psychotropic Medication Effects in Individuals With Bipolar Disorder in Functional Neuroimaging Studies

Although there are no definitive methods for examining the potential effects of medication in studies of psychiatric populations, such as individuals with bipolar disorder who often receive polypharmacy, there are several potential options. The first option is to limit study to individuals taking certain numbers and categories of medications only, but this may not always be feasible in real world contexts, where individuals with bipolar disorder are typically treated with a number of different psychotropic medications and medication combinations. The second option, therefore, is to employ specific strategies for resolving the issue of potential effects of psychotropic medications in individuals taking a variety of different medications. One strategy is to compare individuals taking versus those not taking each class of psychotropic medication, including mood stabilizers, antipsychotics, antidepressants, and anxiolytics (13,21), but this strategy may have the limitation of examination of multiple small subgroups. Other studies have converted doses of each medication within a specific class into dose equivalents of prototypical medications for each class, e.g., converting all antipsychotics into chlorpromazine dose equivalents, followed by correlational analyses to examine associations between medication dose and relevant dependent variables in larger subgroups of individuals taking each class of psychotropic medication (22,25,26).

Since different classes of psychotropic medications may exert effects by different mechanisms, testing the effects of each medication class separately is important. A problem with this strategy is that it does not account for interactions between different psychotropic medications. Composite measures of total psychotropic medication load, reflecting the dose, variety, and duration of different medications taken, may therefore be preferable to the separate examination of individual classes of psychotropic medication. The computation of a single index of psychotropic medication load for each medicated individual will also allow the inclusion of larger numbers of medicated individuals taking different types of psychotropic medication and may be the most feasible option for the examination of psychotropic medication effects in large neuroimaging studies of individuals with the disorder, particularly for studies of individuals with bipolar disorder type 1. Ideally, comparisons of medicated with unmedicated individuals should be included in cross-sectional functional neuroimaging studies of bipolar disorder.

Future studies can also include longitudinal designs in which the potential effects of individual psychotropic medications upon neuroimaging variables are examined over time. These studies clearly have the advantage of powerful, within-subject designs and can recruit individuals with bipolar disorder (either in remission or in an acute illness episode) into carefully controlled clinical treatment platforms. This type of design is especially important for MRS and ligand studies measuring the potential confounding effects of psychotropic medication on neurochemical and neuroreceptor systems of interest in bipolar disorder. Longitudinal treatment designs examining the within-group effects of specific psychotropic medications over time have, for example, been previously employed in major depressive disorder (49) but rarely in bipolar disorder (18).

The interpretation of findings regarding potential effects of psychotropic medication in individuals with bipolar disorder will necessarily be informed by the extensive preclinical literature that has examined the effects of psychotropic medication upon neural regions and behaviors relevant to domains of pathology in bipolar disorder. The emerging field of pharmacological fMRI that allows examination of the effects of different psychotropic medications upon task-related neural activity in healthy individuals will also inform

interpretation of likely effects of psychotropic medication in bipolar groups studied in neuroimaging studies. Here it has been demonstrated, for example, that different categories of psychotropic medication can reduce amygdala activity to emotional stimuli (50). The development and employment of strategies to examine potential confounding effects of psychotropic medication in functional neuroimaging studies of bipolar disorder should continue be a major focus of research in this disorder.

References

1. Kupfer, DJ.; First, MB.; Regier, DA. Washington, DC: American Psychiatric Association; 2002. A Research Agenda for DSM-V.

2. Phillips ML, Frank E. Redefining bipolar disorder: toward DSM-V. Am J Psychiatry 2006;163:1135–1136. [PubMed: 16816214]

3. DePaulo JR Jr. Bipolar disorder treatment: an evidence-based reality check. Am J Psychiatry 2006;163:175–176. [PubMed: 16449464]

4. Ghaemi SN, Ko JY, Goodwin FK. "Cade's disease" and beyond: misdiagnosis, antidepressant use, and a proposed definition for bipolar spectrum disorder. Can J Psychiatry 2002;47:125–134. [PubMed: 11926074]

5. Preskorn SH, Lacey RL. Polypharmacy: when is it rational? J Psychiatr Pract 2007;13:97–105. [PubMed: 17414685]

6. Andrade C. Antidepressant-withdrawal mania: a critical review and synthesis of the literature. J Clin Psychiatry 2004;65:987–993. [PubMed: 15291689]

7. American Medical Association. Drug Evaluations Annual 1993. Milwaukee: AMA; 1993.

8. Mah L, Zarate J, Singh J. Regional cerebral glucose metabolic abnormalities in bipolar II depression. Biol Psychiatry 2007;61:765–775. [PubMed: 17027930]

9. Brooks JO III, Wang PW, Strong C, Sachs N, Hoblyn JC, Fenn R, Ketter TA. Preliminary evidence of differential relations between prefrontal cortex metabolism and sustained attention in depressed adults with bipolar disorder and healthy controls. Bipolar Disord 2006;8:248–254. [PubMed: 16696826]

10. Adler CM, DelBello MP, Jarvis K, Levine A, Adams J, Strakowski SM. Voxel-based study of structural changes in first-episode patients with bipolar disorder. Biol Psychiatry 2007;61:776–781. [PubMed: 17027928]

11. Pavuluri MN, O'Connor MM, Harral E, Sweeney JA. Affective neural circuitry during facial emotion processing in pediatric bipolar disorder. Biol Psychiatry 2007;62:158–167. [PubMed: 17097071]

12. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception I: the neural basis of normal emotion perception. Biol Psychiatry 2003;54:504–514. [PubMed: 12946879]

13. Wessa M, Houenou J, Paillère-Martinot ML, Berthoz S, Artiges E, Leboyer M, Martinot JL. Fronto-striatal overactivation in euthymic bipolar patients during an emotional go/no-go task. Am J Psychiatry 2007;164:638–646. [PubMed: 17403978]

14. Leibenluft E, Rich BA, Vinton DT, Nelson EE, Fromm SJ, Berghorst LH, Joshi P, Robb A, Schachar RJ, Dickstein DP, McClure EB, Pine DS. Neural circuitry engaged during unsuccessful motor inhibition in pediatric bipolar disorder. Am J Psychiatry 2007;164:52–60. [PubMed: 17202544]

15. Rich BA, Vinton DT, Roberson-Nay R, Hommer RE, Berghorst LH, McClure EB, Fromm SJ, Pine DS, Leibenluft E. Limbic hyper-activation during processing of neutral facial expressions in children with bipolar disorder. Proc Natl Acad Sci U S A 2006;103:8900–8905. [PubMed: 16735472]

16. Kronhaus DM, Lawrence NS, Williams AM, Frangou S, Brammer MJ, Williams SCR, Andrew CM, Phillips ML. Stroop performance in bipolar disorder: further evidence for abnormalities in the ventral prefrontal cortex. Bipolar Disord 2006;8:28–39. [PubMed: 16411978]

17. Strakowski SM, Adler CM, Holland SK, Mills NP, DelBello MP, Eliassen JC. Abnormal fMRI brain activation in euthymic bipolar disorder patients during a counting Stroop interference task. Am J Psychiatry 2005;162:1697–1705. [PubMed: 16135630]

18. Silverstone PH, Bell EC, Willson MC, Dave S, Wilman AH. Lithium alters brain activation in bipolar disorder in a task- and state-dependent manner: an fMRI study. Ann Gen Psychiatry 2005;4:14. [PubMed: 16029502]

19. Blumberg HP, Donegan NH, Sanislow CA, Collins S, Lacadie C, Skudlarski P, Gueorguieva R, Fulbright RK, McGlashan TH, Gore JC, Krystal JH. Preliminary evidence for medication effects on functional abnormalities in the amygdala and anterior cingulate in bipolar disorder. Psychopharmacology 2005;183:308–313. [PubMed: 16249909]

20. Altshuler LL, Bookheimer SY, Townsend J, Proenza MA, Eisenberger N, Sabb F, Mintz J, Cohen MS. Blunted activation in orbitofrontal cortex during mania: a functional magnetic resonance imaging study. Biol Psychiatry 2005;58:763–769. [PubMed: 16310510]

21. Lawrence NS, Williams AM, Surguladze S, Giampietro V, Brammer MJ, Andrew C, Frangou S, Ecker C, Phillips ML. Subcortical and ventral prefrontal cortical neural responses to facial expressions distinguish patients with bipolar disorder and major depression. Biol Psychiatry 2004;55:578–587. [PubMed: 15013826]

22. Gruber SA, Rogowska J, Yurgelun-Todd DA. Decreased activation of the anterior cingulate in bipolar patients: an fMRI study. J Affect Disord 2004;82:191–201. [PubMed: 15488247]

23. Adler CM, Holland SK, Schmithorst V, Tuchfarber MJ, Strakowski SM. Changes in neuronal activation in patients with bipolar disorder during performance of a working memory task. Bipolar Disord 2004;6:540–549. [PubMed: 15541070]

24. Blumberg HP, Leung HC, Skudlarski P, Lacadie CM, Fredericks CA, Harris BC, Charney DS, Gore JC, Krystal JH, Peterson BS. A functional magnetic resonance imaging study of bipolar disorder: state- and trait-related dysfunction in ventral prefrontal cortices. Arch Gen Psychiatry 2003;60:601–609. [PubMed: 12796223]

25. Rubinsztein JS, Fletcher PC, Rogers RD, Ho LW, Aigbirhio FI, Paykel ES, Robbins TW, Sahakian BJ. Decision-making in mania: a PET study. Brain 2001;124:12–63.

26. Yurgelun-Todd DA, Gruber SA, Kanayama G, Killgore WD, Baird AA, Young AD. fMRI during affect discrimination in bipolar affective disorder. Bipolar Disord 2000;2:237–248. [PubMed: 11249801]

27. Yurgelun-Todd DA, Ross AJ. Functional magnetic resonance imaging studies in bipolar disorder. CNS Spectr 2006;11:287–297. [PubMed: 16641834]

28. Brambilla P, Glahn DC, Balestrieri M, Soares JC. Magnetic resonance findings in bipolar disorder. Psychiatr Clin North Am 2005;28:443–467. [PubMed: 15826742]

29. Blumberg HP, Kaufman J, Martin A, Whiteman R, Zhang JH, Gore JC, Charney DS, Krystal JH, Peterson BS. Amygdala and hippocampal volumes in adolescents and adults with bipolar disorder. Arch Gen Psychiatry 2003;60:1201–1208. [PubMed: 14662552]

30. Blumberg HP, Fredericks C, Wang F, Kalmar JH, Spencer L, Papademetris X, Pittman B, Martin A, Peterson BS, Fullbright RK, Krystal JH. Preliminary evidence for persistent abnormalities in amygdala volumes in adolescents and young adults with bipolar disorder. Bipolar Disord 2005;7:570–576. [PubMed: 16403182]

31. Velakoulis D, Wood SJ, Wong MT, McGorry PD, Yung A, Phillips L, Smith D, Brewer W, Proffitt T, Desmond P, Pantelis C. Hippocampal and amygdala volumes according to psychosis stage and diagnosis: a magnetic resonance imaging study of chronic schizophrenia, first-episode psychosis, and ultra-high-risk individuals. Arch Gen Psychiatry 2006;63:139–149. [PubMed: 16461856]

32. Scherk H, Falkai P. Effects of antipsychotics on brain structure. Curr Opin Psychiatry 2006;19:145–150. [PubMed: 16612194]

33. Nugent AC, Milham MP, Bain EE, Mah L, Cannon DM, Marrett S, Zarate CA, Pine DS, Price JL, Drevets WC. Cortical abnormalities in bipolar disorder investigated with MRI and voxel-based morphometry. Neuroimage 2006;30:485–497. [PubMed: 16256376]

34. Blumberg HP, Krystal JH, Bansal R, Martin A, Dziura J, Durkin K, Martin L, Gerard E, Charney DS, Peterson BS. Age, rapid-cycling, and pharmacotherapy effects on ventral prefrontal cortex in bipolar disorder: a cross-sectional study. Biol Psychiatry 2006;59:611–618. [PubMed: 16414030]

35. Bearden CE, Thompson PM, Dalwani M, Hayashi KM, Lee AD, Nicoletti M, Trakhtenbroit M, Glahn DC, Brambilla P, Sassi RB, Mallinger AG, Frank E, Kupfer DJ, Soares JC. Greater cortical gray matter density in lithium-treated patients with bipolar disorder. Biol Psychiatry 2007;62:7–16. [PubMed: 17240360]

36. Yucel K, Taylor VH, McKinnon MC, MacDonald K, Alda M, Young LT, Macqueen GM. Bilateral hippocampal volume increase in patients with bipolar disorder and short-term lithium treatment. Neuropsychopharmacology. 2007(E pub ahead of print)

37. Chen X, Wen W, Malhi GS, Ivanovski B, Sachdev PS. Regional gray matter changes in bipolar disorder: a voxel-based morphometric study. Aust N Z J Psychiatry 2007;41:327–336. [PubMed: 17464719]

38. Atmaca M, Ozdemir H, Cetinkaya S, Parmaksiz S, Belli H, Poyraz AK, Tezcan E, Ogur E. Cingulate gyrus volumetry in drug free bipolar patients and patients treated with valproate or valproate and quetiapine. J Psychiatr Res 2007;41:821–827. [PubMed: 16950400]

39. Chang K, Barnea-Goraly N, Karchemskiy A, Simeonova DI, Barnes P, Ketter T, Reiss AL. Cortical magnetic resonance imaging findings in familial pediatric bipolar disorder. Biol Psychiatry 2005;58:197–203. [PubMed: 16084840]

40. Sanches M, Roberts RL, Sassi RB, Axelson D, Nicoletti M, Brambilla P, Hatch JP, Keshavan MS, Ryan ND, Birmaher B, Soares JC. Developmental abnormalities in striatum in young bipolar patients: a preliminary study. Bipolar Disord 2005;7:153–158. [PubMed: 15762856]

41. Chang K, Karchemskiy A, Barnea-Goraly N, Garrett A, Simeonova DI, Reiss A. Reduced amygdalar gray matter volume in familial pediatric bipolar disorder. J Am Acad Child Adolesc Psychiatry 2005;44:565–573. [PubMed: 15908839]

42. DelBello MP, Zimmerman ME, Mills NP, Getz GE, Strakowski SM. Magnetic resonance imaging analysis of amygdala and other subcortical brain regions in adolescents with bipolar disorder. Bipolar Disord 2004;6:43–52. [PubMed: 14996140]

43. Moore GJ, Bebchuk JM, Wilds IB, Chen G, Manji HK. Lithium-induced increase in human brain grey matter. Lancet 2000;356:1241–1242. [PubMed: 11072948]

44. Atmaca M, Yildirim H, Ozdemir H, Poyraz AK, Tezcan E, Ogur E. Hippocampal 1H MRS in first-episode bipolar I patients. Prog Neuropsychopharmacol Biol Psychiatry 2006;30:1235–1239. [PubMed: 16725248]

45. Delbello MP, Strakowski SM. Neurochemical predictors of response to pharmacologic treatments for bipolar disorder. Curr Psychiatry Rep 2004;6:466–472. [PubMed: 15538996]

46. Moore GJ, Bebchuk JM, Hasanat K, Chen G, Seraji-Bozorgzad N, Wilds IB, Faulk MW, Koch S, Glitz DA, Jolkovsky L, Manji HK. Lithium increases N-acetyl-aspartate in the human brain: in vivo evidence in support of bcl-2's neurotrophic effects? Biol Psychiatry 2000;48:1–8. [PubMed: 10913502]

47. Yatham LN, Liddle PF, Lam RW, Shiah IS, Lane C, Stoessl AJ, Sossi V, Ruth TJ. PET study of the effects of valproate on dopamine D(2) receptors in neuroleptic- and mood-stabilizernaive patients with nonpsychotic mania. Am J Psychiatry 2002;159:1718–1723. [PubMed: 12359678]

48. Yatham LN, Liddle PF, Lam RW, Adam MJ, Solomons K, Chinnapalli M, Ruth TJ. A positron emission tomography study of the effects of treatment with valproate on brain 5-HT2A receptors in acute mania. Bipolar Disord 2005;7:53–57. [PubMed: 16225561]

49. Kennedy SH, Konarski JZ, Segal ZV, Lau MA, Bieling PJ, McIntyre RS, Mayberg HS. Differences in brain glucose metabolism between responders to CBT and venlafaxine in a 16-week randomized controlled trial. Am J Psychiatry 2007;164:778–788. [PubMed: 17475737]

50. Takahashi H, Yahata N, Koeda M, Takano A, Asai K, Suhara T, Okubo Y. Effects of dopaminergic and serotonergic manipulation on emotional processing: a pharmacological fMRI study. Neuroimage 2005;27:991–1001. [PubMed: 15978846]

TABLE 1

Functional Neuroimaging Studies of Bipolar Disorder Examining Potential Medication Effects Upon Neural Regions Implicated in Cognitive Control and Emotion Processing[a]

Study	Neuroimaging Technique and Experimental Paradigm	Participants
Wessa et al., 2007 (13)	fMRI; emotional and nonemotional go/no-go task	17 euthymic bipolar adults (10 type I, seven type II; 15 medicated) 17 healthy volunteers
Leibenluft et al., 2007 (14)	fMRI; motor inhibition task	26 children with bipolar disorder (13 unmedicated; 15 with comorbid ADHD) 17 age-, gender- and IQ-matched healthy volunteers
Rich et al., 2006 (15)	fMRI; neutral facial expression labeling for threat level; subjective fearful response; and nonemotional facial feature size	22 youth with bipolar disorder (12 euthymic, four depressed, six hypomanic; 18 medicated: with 2.5±1.8 medications per subject) 21 age-, gender- and IQ-matched healthy volunteers
Kronhaus et al., 2006 (16)	fMRI; Stroop task	10 bipolar (type 1) adults (eight subthreshold depressed; two euthymic; all medicated) 11 age-matched healthy volunteers
Strakowski et al., 2005 (17)	fMRI; counting Stroop task	16 euthymic bipolar (type 1) adults (eight unmedicated) 16 healthy volunteers
Silverstone et al., 2005 (18)	fMRI: word generation task and verbal memory task	10 bipolar adults (five depressed—three of whom were type II; five were euthymic—four of whom were type II); before and 14 days after starting lithium (in six as monotherapy); two of the euthymic patients were concurrently taking antidepressants; two of the depressed patients were taking other psychiatric medication
Blumberg et al., 2005 (19)	fMRI; happy, sad, fearful, or neutral facial expression emotion labeling	17 bipolar (type 1) adults (five unmedicated: one mixed state, two depressed, two euthymic; two rapid cycling; 12 medicated: manic/hypomanic/mixed states, one depressed, seven euthymic; five rapid cycling) 17 healthy volunteers
Altshuler et al., 2005 (20)	fMRI; go/no-go task	11 bipolar adults (type 1; all manic; four unmedicated) 13 healthy volunteers
Lawrence et al., 2004 (21)	fMRI; mild and intense fear, happy and sad versus neutral facial expression; gender labeling	12 bipolar (type 1) adults (nine subthreshold depression; three euthymic; all medicated); nine depressed adults with MDD (all medicated) 11 healthy volunteers
Gruber et al., 2004 (22)	fMRI; Stroop task	11 bipolar (type 1) adults; (nine euthymic; two subthreshold depression; three unmedicated) 10 healthy volunteers
Adler et al., 2004 (23)	fMRI; a two-back working memory task alternating with a zero-back control/attention task	12 euthymic bipolar (type not stated) adults (four unmedicated) 15 age- and gender-matched healthy volunteers
Blumberg et al., 2003 (24)	fMRI; Stroop task	36 bipolar (type 1) adults (11 manic/hypomanic/mixed—seven unmedicated; 10 depressed—three unmedicated; 15 euthymic—three unmedicated) 20 healthy volunteers
Rubinsztein et al., 2001 (25)	H_2O^{15} PET; a probability-based decision-making task	six bipolar adults (type 1; all manic); six depressed MDD; all patients except one manic adult (taking no medication for 1 week) were medicated 10 healthy volunteers
Yurgelun-Todd et al., 2000 (26)	fMRI; fearful and happy facial expression labeling	14 stable bipolar adults (type and mood state not described; all medicated) 10 healthy volunteers

Main Findings	Medication Effects
Bipolar adults showed increased activity in the temporal cortex during the emotional go/no-go task and in the orbitofrontal cortex, the insula, the caudate nuclei, and the dorsal anterior and posterior cingulate cortices when inhibiting emotional versus neutral stimuli.	No difference in activation in regions showing between-subgroup differences in bipolar adults who were medication-free and those taking lithium, anticonvulsive, antipsychotic, and antidepressant medication.
On failed inhibitory trials, healthy volunteers showed greater bilateral striatal and right ventral prefrontal cortex activation than did both bipolar groups.	Similar decreases in activity in the bilateral striatum and right ventral prefrontal cortex were reported in unmedicated and medicated bipolar groups on failed inhibitory versus go trials. Decreases inactivity in bipolar striatum and right anterior cingulate gyrus were reported in medicated versus unmedicated bipolar children on failed versus correct inhibitory trials.
Compared with healthy volunteers, bipolar youth perceived in neutral faces greater hostility and more subjective fear and showed greater activation in the left amygdala, accumbens, putamen, and ventral	There were no significant correlations between activation and number or classes of medications in bipolar youth. There were similar patterns of activation in medication-free and medicated bipolar youth.

Main Findings	Medication Effects
prefrontal cortex when rating face hostility and greater activation in the left amygdala and bilateral accumbens when rating subjective fear.	
During Stroop interference, healthy volunteers showed greater activation in visual and dorsolateral and ventrolateral prefrontal cortical areas; bipolar adults showed deactivation in orbital and medial prefrontal cortices.	The magnitude of activation in neural regions showing significant between-group differences in activation was not significantly different between medicated and unmedicated bipolar adults for each type of medication: antidepressants, antipsychotics, and lithium.
During the task, healthy volunteers showed increased activation relative to bipolar adults in the temporal cortical regions, middle frontal gyrus, putamen, and midline cerebellum. Bipolar adults showed greater activation relative to healthy volunteers in the medial occipital cortex.	There were no differences in activation in regions showing between-diagnostic-group differences in activation between medicated and unmedicated bipolar adults; medicated bipolar adults showed greater activation in anterior cingulate gyrus and the DLPFC.
At baseline, there were similar patterns of activation in prefrontal, parietal, and occipital cortical regions of interest in euthymic and depressed bipolar adults during both tasks.	After lithium, activation decreased significantly in euthymic bipolar adults in the word generation task in the left DLPFC, the left pre-central gyrus, and the supplemental motor area.
The group-by-emotion stimulus condition interaction was significant for amygdala activation, with the greatest effects in the happy face condition.	Amygdala activation was significantly greater in unmedicated bipolar adults but lower in medicated bipolar adults versus healthy volunteers; rostral anterior cingulate gyral activation was significantly decreased in unmedicated bipolar adults and similar in medicated bipolar adults relative to healthy volunteers.
Manic adults showed significantly less activation than healthy volunteers in the right lateral orbitofrontal cortex, right hippocampus, and left anterior cingulate gyrus.	Unmedicated and medicated manic adults showed a similar pattern of reduced activation in the lateral orbitofrontal cortex.
Compared with other groups, bipolar adults showed increased subcortical (ventral striatal, thalamic, hippocampal) and ventral prefrontal cortical activation to mild and intense fearful, mild happy, and mild sad expressions. Healthy volunteers showed increased subcortical activation to intense happy and mild fearful expressions and increased dorsal prefrontal cortical activation to intense sad expressions.	The main effects of different medications were ameliorative in bipolar adults. Lithium reduced activation in the right globus pallidus/thalamus to mild fearful expressions and increased activation in the right dorsal prefrontal cortex to mild sad expressions. Antidepressants increased activation in the bilateral thalamus/midbrain to intense happy expressions and decreased activation in the right dorsal cingulate gyrus to intense sad expressions. Antipsychotics reduced activation in the right DLPFC to intense happy expressions.
Compared with healthy volunteers, bipolar adults showed significantly reduced activity in the right anterior cingulate gyrus and increased activity in the right DLPFC during Stroop interference.	In bipolar adults, activation was significantly correlated with medication dose, as measured by CPZ dose equivalents, in the right rostral/pregenual anterior cingulate gyrus and the left DLPFC.
After covarying for task performance and reaction time, bipolar adults showed significantly greater activation than healthy volunteers in the frontopolar prefrontal cortex, temporal cortex, basal ganglia, thalamus, and posterior parietal cortex.	Comparison of medicated and unmedicated bipolar adults showed little overlap with areas found to differ between diagnostic groups. Unmedicated bipolar adults showed increased activation in the DLPFC, whereas medicated patients showed increased activation in the anterior insula, anterior cingulate, temporal cortex, and right precuneus.
All bipolar adults relative to healthy volunteers showed decreased activation in left rostral ventral prefrontal cortex. There was reduced activation in the right ventral prefrontal cortex in manic/hypomanic/mixed and increased activation in the left ventral prefrontal cortex in depressed relative to euthymic bipolar adults.	Between-mood state subgroup analyses for bipolar adults in the ventral prefrontal cortex remained significant in a comparison between the unmedicated subgroups.
Manic adults showed significantly greater task-related activation than healthy volunteers in the left dorsal anterior cingulate gyrus and decreased activation in the right frontal polar cortex. Healthy volunteers showed greater task-related activation than manic adults in the inferior frontal gyrus.	Manic adults had a significant positive correlation between CPZ equivalents and task-related activation in the rostral prefrontal cortex.
Female bipolar adults showed significantly increased left amygdala activation to fear facial expressions.	Male bipolar adults showed a significant negative correlation between CPZ equivalents and amygdala activation to fearful facial expressions.

[a] References are in chronological order by year and in alphabetical order within each year. DLPFC=dorsolateral prefrontal cortex; MDD=major depressive disorder; H_2O^{15} PET=positron emission tomography using oxygen-15 water (H_2O^{15}) and the positron emitting O^{15} isotope; fMRI=functional magnetic resonance imaging; CPZ=chlorpromazine.