

Review Article

Effects of medication on neuroimaging findings in bipolar disorder: an updated review

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Objective: Neuroimaging is an important tool for better understanding the neurobiological underpinnings of bipolar disorder (BD). However, potential study participants are often receiving psychotropic medications which can possibly confound imaging data. To better interpret the results of neuroimaging studies in BD, it is important to understand the impact of medications on structural magnetic resonance imaging (sMRI), functional MRI (fMRI), and diffusion tensor imaging (DTI).

Methods: To better understand the impact of medications on imaging data, we conducted a literature review and searched MEDLINE for papers that included the key words *bipolar disorder* and *fMRI*, *sMRI*, or *DTI*. The search was limited to papers that assessed medication effects and had not been included in a previous review by Phillips et al. (Medication effects in neuroimaging studies of bipolar disorder. *Am J Psychiatry* 2008; 165: 313–320). This search yielded 74 sMRI studies, 46 fMRI studies, and 15 DTI studies.

Results: Medication appeared to influence many sMRI studies, but had limited impact on fMRI and DTI findings. From the structural studies, the most robust finding (20/45 studies) was that lithium was associated with increased volumes in areas important for mood regulation, while antipsychotic agents and anticonvulsants were generally not. Regarding secondary analysis of the medication effects of fMRI and DTI studies, few showed significant effects of medication, although rigorous analyses were typically not possible when the majority of subjects were medicated. Medication effects were more frequently observed in longitudinal studies designed to assess the impact of particular medications on the blood oxygen level-dependent (BOLD) signal. With a few exceptions, the observed effects were normalizing, meaning that the medicated individuals with BD were more similar than their unmedicated counterparts to healthy subjects.

Conclusions: The effects of psychotropic medications, when present, are predominantly normalizing and thus do not seem to provide an alternative explanation for differences in volume, white matter tracts, or BOLD signal between BD participants and healthy subjects. However, the normalizing effects of medication could obfuscate differences between BD and healthy subjects, and thus might lead to type II errors.

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Studies utilizing neuroimaging methods [e.g., structural magnetic resonance imaging (sMRI), functional MRI (fMRI), and diffusion tensor imaging (DTI)] facilitate the investigation of bipolar

disorder (BD) at the level of neural circuitry and allow for integration between objective biomarkers and clinical factors. A better understanding of neural circuitry can inform and improve the

diagnostic boundaries of BD and ultimately lead to more appropriate and effective treatments (1). To date, studies employing neuroimaging techniques have revealed a number of abnormalities, both structural and functional, in children and adults with BD (2). However, an important consideration when interpreting these findings is the impact of medication. Medication exposure is an important potential confound, as these agents certainly have direct effects on brain function, given their ability to treat psychiatric symptoms. It is therefore possible that the neurobiological differences observed between those with BD and healthy subjects (HS) are partly or completely due to exposure to psychotropic medications.

Due to the high morbidity of BD, patients who come to academic research centers are usually receiving psychotropic medications, and thus the majority of imaging studies in BD have been conducted in medicated populations. Of course, this problem of medication confounds could be solved by including only unmedicated populations in neuroimaging studies. These populations could either be medication-naïve, or have been medicated in the past but go through a washout period prior to participation. A number of studies have successfully recruited currently unmedicated individuals with BD (following a washout period) and findings from these studies have added significant value to the literature (e.g., 3, 4). However, these approaches have limitations, which must be considered when deciding whether to exclude medicated individuals from a study.

There are several reasons why conducting studies in medication-naïve individuals with BD can be challenging, particularly for adult study populations. It is often difficult to find individuals with BD that have never been medicated, limiting the feasibility of this option. Although the prevalence of BD is relatively high, the incidence of new (first-episode) cases is low, limiting the recruitment of these patients. Also, many patients in a first-episode manic sample initially developed depression, for which they previously received treatment; consequently, many first-episode manic patients will not be treatment-naïve. In addition, it would be difficult to recruit euthymic BD patients who had never been medicated; thus, interpretation of results would be limited by mood state. Even if such a study population was collected, it is unlikely that they would be representative of the overall population with BD. For example, those who had never taken medication and achieved euthymia would likely have a milder form of the illness, and thus neuroimaging findings might be specific to that bipolar subtype. It would therefore be difficult

to generalize results from such a study to patients with BD more broadly.

Similarly, a washout period for medications has significant limitations. For medications with a longer half-life (such as fluoxetine), the duration of withdrawal required could potentially be several months (5). During that time, individuals would be at risk for relapse into mania or depression, both of which could have serious consequences. For patients with higher morbidity, such a lengthy washout period would probably not be feasible and would be ethically questionable given the likelihood of relapse. Thus, we would again be left with a study population with a milder course, who could tolerate such an unmedicated period. It is certainly possible that neural circuitry impairments would be different in this selected population, compared to the general patient population with BD. Finally, even if the medications were washed out, it is possible that they would have lingering effects on neural circuitry, including structural and connectivity effects, particularly in pediatric populations still undergoing significant neurodevelopment. It is also plausible that removing medications, particularly those that have been taken for a long period of time, would lead to compensatory changes in neural function that are independent of the disease process.

Given the challenges and limitations to the above approaches, the inclusion of individuals with BD, regardless of medication exposure, has been the prevailing approach in most past studies. Thus, understanding the impact of medications on neuroimaging findings continues to be critical for the interpretation of results from current and future studies in this population. Phillips et al. (5) published a review article in 2008 that focused on medication effects in fMRI and sMRI studies in BD populations through 2007. The authors found psychotropic medications to have either no significant effect or a normalizing effect on abnormal findings in those with BD, compared to HS. Since 2007, more than 150 additional imaging studies of patients with BD have been published, using not only standard structural and functional imaging, but also more novel techniques to examine connectivity, including DTI and analyses of functional connectivity (FC). The purpose of this review is to provide an updated evaluation of the effect of psychotropic medications on imaging results, including fMRI, sMRI, and DTI studies in pediatric and adult populations with BD.

Methods

We performed three Ovid MEDLINE literature searches on studies in BD from 2007 to 2011 using

the following key words: (i) *bipolar disorder* and *functional magnetic resonance imaging* (or *fMRI*); (ii) *bipolar disorder* and *diffusion tensor imaging* (or *DTI*); and (iii) *bipolar disorder* and *structural magnetic resonance imaging* (or *sMRI*). In addition to searching *bipolar disorder* as a key word, it was also searched as a subject heading; an additional search with *mania* as a key word did not identify any additional papers. From the results of these searches, we only included studies that conducted supplemental analyses to address the possible effects of medication on the results.

Results

Methodologies utilized in reviewed studies

Studies have used a variety of methods to assess medication effects on neuroimaging data in BD. To interpret findings, it is necessary to first describe the methods used in these studies, as well as their strengths and limitations. One standard method has been to compare those subjects who are medicated to those who are not, and assess whether there are any differences in neuroimaging findings (e.g., 6, 7). However, participants are often on a variety of medications, and if only one medication (e.g., lithium) has an effect, a simple dichotomy of medicated versus unmedicated might dilute this finding. In addition, such a comparison requires a substantial number of participants to be unmedicated, which is often not the case.

An alternative method is to do several analyses, comparing individuals who are medicated with a specific class of medication versus those who are not (e.g., 8, 9). Such analyses have the advantage of parsing out the different effects of each medication. Of course, a significant limitation is the number of people in each medication class, since small numbers will diminish the power to detect differences. A further consideration is that many patients are taking multiple psychotropic medications and it is possible that different medications might interact to produce effects that are different to those of each medication alone. This method also does not take into account the dose of medications, which might impact findings.

To address these limitations, others have looked for a correlation between medication dose [particularly antipsychotic dose, often measured in chlorpromazine equivalents (10)], number of medications (11), or medication load [a measure of total medication dose (12)], and neuroimaging results. One advantage of such an analysis is that, if there is in fact a relationship between increased

medication dose and neuroimaging changes (as we might expect), this method would more accurately model the dose–response relationship. In addition, this approach addresses the problem of power to detect medication effects in a population with few unmedicated individuals, assuming that there is variability in dosage. However, methods for assessing dose have significant limitations. For example, the assessment of overall medication load combines different types of medications, which might obfuscate the impact of specific medications. Similarly, the construct of chlorpromazine equivalents addresses the potency (i.e., anti-dopaminergic activity) of antipsychotic agents, but not effects on other neurotransmitter systems that might contribute to neuroimaging changes, and not the impact of mood stabilizers or antidepressants.

The analyses address the impact of medication on neuroimaging parameters, but do not directly answer the most pressing question, which is usually whether the observed differences between BD and HS are attributable to medication effects. Two approaches have been used to directly address this question. One strategy is to account for medication status (or related variable) as a nuisance covariate and test whether the differences observed between those with BD and HS persisted (13). This strategy should be used with caution, since the strong association between diagnosis and medication exposure will often violate the assumptions of the regression analysis. Specifically, there are generally no medicated participants in the HS group, and often only a few unmedicated individuals in the BD group; this situation leads to sparse cells and limited power to conduct a valid regression analysis. Alternatively, some studies have used a sensitivity analysis approach, excluding individuals using medication (or a particular class of medication) and testing whether observed differences still persist (14, 15). The finding of differences between unmedicated subjects with BD and HS is the strongest evidence that most observed differences are largely not due to medication effects. However, such an analysis again requires substantial numbers of unmedicated participants; in addition, it is difficult to interpret a negative finding (i.e., no difference between unmedicated BD and HS), since this observation could simply be due to a lack of power in many instances.

The analyses described thus far are secondary, and studies are generally not powered to assess the effects of medication. As a result, the finding that medication status did not impact neuroimaging results might simply reflect the small number of subjects, and does not mean that the observed

differences between BD and HS were not due to medication effects. An additional limitation is that studies rarely assess past medication use, or the length of time that a medication has been used, which could also impact neuroimaging findings. Finally, patients in a naturalistic study are usually taking medications for a clinical reason, and neuroimaging findings associated with medication might be attributable to clinical presentation (e.g., severity or types of symptoms) rather than the medication itself; this problem is known as ‘confounding by indication’.

To address these concerns, an alternative strategy is to conduct prospective, clinical trials to assess the impact of medication over time. In these studies, participants are scanned twice: at baseline (prior to the administration of a particular medication) and then again following several weeks of treatment with medication. Neuroimaging parameters are compared across scans. The majority of these studies have examined the effects of lamotrigine and one examined divalproex. Some studies used a HS group, while others did not. One limitation of this methodology is that individuals are only followed over a short time course, so the long-term impact on structural and functional neuroimaging cannot feasibly be assessed. Also, it is difficult to distinguish between neuroimaging markers of medication *per se* versus general clinical improvement, which is often observed over the course of the study.

sMRI results

Morphometric imaging studies have provided a wealth of data regarding differences between patients with BD and HS. However, prior to 2000, authors were not routinely including medication exposure in peer-reviewed reports of their research findings. In the past five years, however, the majority of studies have reported at least the current medications that subjects were taking. We report here on 74 morphometric studies since 2007 that performed some type of analysis regarding the impact of medications on the MRI results (shown in Table 1).

Twenty-three of 74 studies compared subjects taking any medication to those who were medication-free. Only 30% of these studies (7/23) found volumetric differences between medicated and unmedicated subjects (16–22). Interestingly, 5/7 (71%) of these studies (16–18, 20, 21) examined patients treated with a more homogeneous group of medications (e.g., lithium and valproate only, or lithium only). Thus, it is difficult to extrapolate from these data the effects of psychotropic

medications overall on brain structure. Of note, only seven of 74 studies considered past exposure to psychotropic medications (23–29). The rest of the studies only reported current medication exposure. This situation is clearly a potential limitation of currently published data, as previous exposure to psychotropic medications may have a lasting impact on brain morphometry.

Forty-four studies examined the effects of lithium specifically. Of these studies, 20/44 (45%) found lithium to either normalize or increase volumes, compared to HS or subjects not taking lithium. Sixteen of these studies were cross-sectional; four were prospective studies in which patients were medication-free at a baseline scan, and then rescanned after weeks or months of lithium treatment. Based on these studies, the overall effect of lithium appears to be increases in or normalization of gray matter volume, particularly in the hippocampus, amygdala, anterior cingulate, and subgenual cingulate. Interestingly, these gray matter increases have also been positively correlated with treatment response (29, 30). Twenty-four out of 44 (55%) studies did not find any significant effects of current lithium treatment on their findings. Only 3/44 (7%) studies reported that lithium exposure resulted in decreased volume: one for pituitary volume (31), one for right hemispheric gray matter volume (32), and one for thalamic volume (33).

Twenty-five studies examined the effects of antipsychotic agents – mostly atypical antipsychotic agents – on gray matter volumes. Some studies converted dosages to chlorpromazine equivalents to address differences in dosing and potency. However, only one study found an effect of antipsychotic agents on brain volume; Lisy and colleagues (34) found that longitudinal exposure to atypical antipsychotic agents and anticonvulsants was associated with increased gray matter volume in the medial prefrontal cortex and portions of the cerebellum, whereas exposure to lithium was not.

Twenty-two studies examined mood stabilizers, which were mostly anticonvulsants. The majority (17/22) did not show any effect of mood stabilizers on measured brain volumes, while 5/22 (23%) showed an increased or normalized volume. Two out of these five studies examined anticonvulsants alone (34, 35), while the other three included lithium with anticonvulsants in the mood stabilizer category (20, 26, 36). To our knowledge, there has been only one prospective MRI study of valproate in populations with major depressive disorder (MDD) and/or attention-deficit hyperactivity disorder (ADHD), and

Medication effects on neuroimaging in bipolar disorder

this study did not find changes in total brain volume or amygdala volume after 12 weeks of valproate monotherapy in youth at risk for BD

(37). Finally, seven studies examined antidepressant effects, but none of these reported any significant effect on findings.

Table 1. Medication effects in structural magnetic resonance imaging (sMRI) studies

Study	Participants	Medications	Main findings	Medication effects
Bearden et al. 2011 (101)	21 adult BD 19 non-BD co-twins 34 age-, gender-, and zygosity-matched HS twins	16 BD currently medicated with Li (n = 11) and/or neuroleptics (n = 13) All BD subjects had taken Li or neuroleptics at some point in the past	(i) BD < HS callosal thickness and callosal area (most pronounced in the genu and splenium) (ii) Altered callosal curvature in BD (iii) Genu and splenium areas were significantly correlated with verbal processing speed and response inhibition	(i) BD Li+ = BD Li- callosal measures (ii) No correlation between Li dose and/or chlorpromazine equivalents with callosal area or thickness
Périco et al. 2011 (102)	26 adult BD 20 demographically matched MDD 94 demographically matched HS	19 BD medicated with AP (n = 11), AD (n = 2), MS (n = 11), and/or BZD (n = 5) 18 MDD medicated with AP (n = 15), AD (n = 11), MS (n = 4), and/or BZD (n = 5)	(i) BD > HS volume of the R dorsal ACC (ii) MDD < HS bilateral dIPFC GM (iii) MDD < BD R dIPFC GM (iv) BD = MDD dorsal anterior cingulate gyrus GM	(i) No significant voxel-wise differences either between BD patients based on current or past Li exposure (ii) No significant correlations between duration of exposure to Li and extracted GM volumes
Delaloye et al. 2011 (103)	15 adult BD 15 demographically matched HS	BD medicated with MS (n = 10), AD (n = 3), BZD (n = 6), and/or neuroleptics (n = 4)	BD = HS mean trajectory of GM and WM changes over 2 years	No significant correlation between medication load and brain volumes
Foland-Ross et al. 2011 (23)	34 adult BD 31 demographically matched HS	24 BD medicated with anticonvulsants (n = 18), AP (n = 17), AD (n = 9), and/or BZD (n = 1) All Li-free for 1 month before scan	BD < HS thickness of PFC and ACC, especially in BD with psychosis	No significant differences in cortical thickness between BD on versus off medication, or those with versus without a history of Li exposure
Hallahan et al. 2011 (104)	321 BD (age range: 16–55) 442 age- and gender-matched HS	BD medicated with MS (n = 217) [including Li (n = 141), VPA (n = 74), and/or CBZ (n = 17)], AP (n = 90), and/or AD (n = 26)	(i) BD > HS in R lateral ventricle, L temporal lobe, R putamen (ii) Cerebral volume inversely correlated with illness duration	BD Li+ > BD Li- and HS in hippocampus/amygdala
Haller et al. 2011 (105)	19 adult BD 47 age- and education-matched HS	17 medicated with MS (n = 16), AD (n = 5), BZD (n = 7), and/or neuroleptics (n = 6)	DTI study with GM VBM analysis: BD < HS GM in insula, caudate, nucleus accumbens, ventral putamen, and OFC	Results were the same after controlling the ANOVA for medication load (quantified as number of meds weighted by high/low dose)
Hartberg et al. 2011 (27)	121 adult BD 117 SCZ 192 HS	<u>SCZ/BD (n):</u> AP (99/52), Li (1/16), antiepileptic (12/43), AD (31/39), sedatives (15/12)	(i) BD and SCZ > HS in ventricle (ii) BD and SCZ < HS in bilateral hippocampi and L thalamus (iii) SCZ > BD and HS in R putamen (iv) BD < HS cerebellar cortex	No differences in basal ganglia volumes between patients using RISP, OLAN, aripiprazole, or QUET

Table 1. (Continued)

Study	Participants	Medications	Main findings	Medication effects
James et al. 2011 (106)	15 BD with psychosis (age range: 11–17) 20 age- and gender-matched HS	OLAN (n = 7), QUET (n = 3), RISP (n = 1), fluoxetine (n = 1), VPA (n = 2), Li (n = 3)	BD < HS in L OFC, L pars triangularis, R premotor, occipital, fusiform, and cerebellar GM volumes	No significant correlation between GM density and chlorpromazine equivalents
Kempton et al. 2011 (107)	Meta-analysis of 225 studies: 9533 BD [mean age = 52.2 (9.1)] 8846 age- and gender-matched HS	8127 BD medicated with AD (n = 930), [SSRI (n = 369), tricyclics (n = 215), MAOI (n = 6), other (n = 289)], MS (n = 69), and/or AP (n = 86)	(i) MDD > HS lateral ventricle, CSF volume (ii) MDD < HS basal ganglia, thalamus, hippocampus, frontal lobe, OFC, gyrus rectus (iii) MDD in episode < MDD in remission hippocampal volume (iv) MDD < BD rates of deep WM hyperintensities, hippocampus, basal ganglia (v) MDD > BD corpus callosum cross-sectional area (vi) BD and MDD > HS lateral ventricle volume, rates of subcortical GM hyperintensities	Meta-regression showed no significant effect of percentage of patients using AD on the difference in hippocampal volume between patients and HS
Lisy et al. 2011 (34)	58 adult BD 48 age-, gender-, and handedness-matched HS	All BD unmedicated at baseline At follow-up, 57 BD medicated on atypical AP (n = 27), anticonvulsants (n = 11), and/or Li (n = 7)	(i) At baseline, HS > BD GM volume in frontal cortex, temporal regions, and bilateral caudate (ii) BD showed increasing GM volume over time in portions of the temporal and PFC but HS showed decreasing subcortical GM bilaterally	Exploratory model analysis: scan order was considered the parameter of interest to analyze changes in GM volume for the three medication groups Findings: patients receiving anticonvulsants and AP showed increases in GM in the medial frontal cortex and cerebellum; patients receiving Li did not demonstrate GM volume changes
Liu et al. 2011 (28)	17 BD + ADHD (mean age = 14.4, SD = 2.6) 12 BD (mean age = 15.8, SD = 2.5) 11 ADHD (mean age = 13.4, SD = 3.3) 24 HS (mean age = 14.2, SD = 2.7)	16 AD, 5 MS, 5 AP, 12 STIM 2 AD, 3 MS, 2 AP, 2 STIM 2 AD, 1 AP, 8 STIM No medications	(i) ADHD associated with smaller caudate and putamen volumes (ii) BD associated with larger caudate, putamen, and globus pallidus volumes	Each type of medication added to the regression model individually No significant effect on caudate, putamen, or globus pallidus from STIM, AP, MS, or AD
Matsuo et al. 2011 (22)	35 adult BD 20 UAR 40 HS All groups demographically matched	13 BD currently medicated	(i) BD and UAR < HS in L anterior insula GM (ii) BD < HS in R inferior frontal gyrus GM (iii) UAR < HS in R medial frontal WM volumes	(i) Unmedicated BD < HS in L anterior insula GM and L middle frontal gyrus GM (ii) Voxel-wise <i>F</i> -test revealed medication was not significantly correlated with L anterior insular GM, R inferior frontal gyrus GM, or R medial frontal gyrus WM

Medication effects on neuroimaging in bipolar disorder

Table 1. (Continued)

Study	Participants	Medications	Main findings	Medication effects
Mitsunaga et al. 2011 (26)	20 BD [mean age = 14.6 (2.8), 80% male] 20 age-, gender-, and IQ-matched HS	Includes past exposure for at least 2 weeks: SSRI (n = 16), other AD (n = 10), Li (n = 7), VPA (n = 9), AP (n = 10)	BD = HS subgenual cingulate volumes	Compared volumes in BD with past MS exposure (Li and/or VPA) versus BD without prior MS exposure versus HS Findings: BD with past MS exposure > BD without MS exposure and HS in subgenual cingulate volumes
Perrier et al. 2011 (108)	41 adult BD 50 HS	Unknown how many BD were medicated	Compared brain volumes in AA/AG (high risk for BD) genotype versus GG (low risk): (i) BD w/GG type < HS w/GG type in putamen volume (ii) All GG type < AA/AG type in R amygdala and hypothalamus for all diagnoses	Results remained significant after controlling for medication status
Savitz et al. 2011 (21)	22 adult unmedicated BD 15 medicated BD 28 MDD 32 MDD-remitted 74 HS	Unmedicated BD were not medicated for 2 months before scan Medicated BD: Li (n = 8), VPA (n = 6), chlorpromazine (n = 1) MDD and MDD-remitted were non-medicated for ≥ 4 weeks before scan	(i) BD without meds < HS habenula volume (ii) Depressed MDD women < HS women in habenula volume	Smaller habenula was found in unmedicated subjects only
van Erp et al. 2012 (109)	10 adult BD Li+ 8 BD Li- 14 non-BD co-twins 32 HS twins	Total BD Li+ (n = 10) Total BD Li- (n = 8) Total BD with any psychotropic medication (n = 12)	(i) BD Li+ > HS twins and non-BD co-twins in hippocampal volume (ii) BD Li- = non-BD co-twins = HS twins in hippocampal volume (iii) Trend for BD Li+ > BD Li- in hippocampal volume; BD Li+ and co-twins > HS twins in hippocampal thickness	Li use was incorporated into main study (see main study findings)
Wang et al. 2011 (35)	41 BD (age range: 10–21) 77 HS	31 medicated with Li (n = 7), anticonvulsants (n = 16), atypical AP (n = 18), AD (n = 12), STIM (n = 8), and/or BZD (n = 3)	BD < HS in orbitofrontal, insular, and temporopolar cortices, inferior prefrontal and superior temporal gyri, and cerebellum	(i) No significant effects of medication on volumes in the regions that differed between BD and HS, but trend for BD meds > BD no meds in frontotemporal volumes (ii) BD Li+ > BD Li- in OFC volume (iii) BD with anticonvulsants > BD no anticonvulsants in OFC volume (iv) BD with anticonvulsants or STIM > BD no anticonvulsants or STIM volume of temporal association cortex

Table 1. (Continued)

Study	Participants	Medications	Main findings	Medication effects
Baloch et al. 2010 (36)	51 BD (age range: 7–17) 41 age- and gender-matched HS	36 BD currently medicated with MS (n = 8), AP (n = 6), AD (n = 11), and/or STIM (n = 6) 41 exposed to medication at some point in lifetime	Familial mood disorder subgroup of BD (but not non-familial BD) < HS in subgenual volume	(i) Current use of MS was associated with larger R subgenual volumes (ii) Trend for larger R subgenual volume in patients taking AP (iii) No difference in subgenual PFC in those on versus off meds
Cousins et al. 2010 (110)	49 adult BD 47 age-, gender-, and IQ-matched HS	44 BD currently medicated on MS: Li (n = 33), CBZ (n = 13), VPA (n = 6), LTG (n = 6), AD (n = 12), atypical AP (n = 4), and/or typical AP (n = 7) BZD (n = 2), gabapentin (n = 1), drug free (n = 2)	(i) BD > HS width of 3rd ventricle; correlation between age and width of 3rd ventricle (ii) Female BD < female HS in pituitary volume (iii) BD = HS in pituitary volume	No differences between BD on versus off AP; no other meds tested
Ekman et al. 2010 (111)	55 adult BD	54 BD medicated with Li (n = 41), AD (n = 20), AP (n = 20), anticonvulsant (n = 11), and/or BZD (n = 10)	Inverse correlation between inferior frontal volume and lifetime number of manic episodes	No differences in inferior frontal volume for Li+ (n = 41) versus Li- (n = 14) using VBM
Germaná et al. 2010 (112)	74 adult BD (remitted)	All medicated with Li (n = 28), VPA (n = 8), CBZ (n = 10), other/combined anticonvulsants (n = 10), AP (n = 18) [of the 18, OLAN (n = 11), RISP (n = 4), QUET (n = 3)]	(i) Global GM equal in all medicated groups (ii) Li group had increased GM in subgenual cingulate, postcentral gyrus, hippocampus, amygdala, and insula compared to the anticonvulsant or AP groups	See main study findings
Hajek et al. 2010 (113)	15 AO (age range: 15–30) 20 unaffected offspring 18 HS 19 BD/no FH	11 AO currently medicated with AP (n = 6), anticonvulsants (n = 3), AD (n = 5), and/or Li (n = 1) 18 BD/no FH currently medicated with AP (n = 11), anticonvulsants (n = 8), AD (n = 2), Li (n = 8) Ever medicated with Li: AO (n = 3), BD/no FH (n = 2)	AO = unaffected offspring = non-familial BD + HS in subgenual cingulate volumes	No differences in sgACC volume between groups with and without Li exposure; did not compare patients without Li exposure to HS
Javadapour et al. 2010 (114)	24 adult BD 24 demographically matched HS	20 BD medicated with Li (n = 12) and/or anticonvulsant [VPA and/or CBZ (n = 12)]	(i) BD > HS L hippocampus (ii) Duration of illness inversely correlated with L hippocampal volume	(i) Only Li+ BD > HS in hippocampal volume (Li- = HS) (ii) Li+ patients = Li- patients in hippocampal volume
Lopez-Larson et al. 2010 (115)	44 BD (age range: 6–16) 22 age- and gender-matched HS	Atypical AP (n = 33), STIM (n = 10), Li (n = 8), MS other than Li (n = 18), AD (n = 13), beta-adrenergics (n = 8)	(i) BD < HS middle and posterior corpus callosum (ii) BD < HS age-related increase in corpus callosum	No correlation between chlorpromazine equivalents and volume of any subregion of corpus callosum

Medication effects on neuroimaging in bipolar disorder

Table 1. (Continued)

Study	Participants	Medications	Main findings	Medication effects
Lyoo et al. 2010 (29)	22 adult BD 14 age- and gender-matched HS	Patients were randomly assigned to Li (n = 13) or VPA (n = 9) Medication history: no AP or MS in past, past AD (n = 9), but all were medication-free for 2 months	Li group had GM volume increases (2.56%) peaking at 10–12 weeks of treatment, VPA and HS did not; GM increases correlated with improvement in depression scores in Li group only	See main study results
Mackay et al. 2010 (116)	49 adult BD (46.9% male) 47 demographically matched HS	Li (n = 33), any MS (n = 44)	BD > HS in total CSF; significant diagnosis × sex interaction in the L frontal/temporal, and R parietal/occipital cortex: BD males > HS males while BD females < HS females	More male (n = 5) than female patients (n = 1) were taking VPA, so analyses repeated after removing those 6 patients; all results remained significant except for the L temporal lobe
Radenbach et al. 2010 (33)	41 adult BD: Li+ (n = 15), Li- (n = 24) 41 demographically matched HS	<u>Total BD/Li+/Li- (n):</u> Other MS (11/9/2), typical AP (4/2/2), atypical AP (14/5/9), AD (14/5/9)	(i) BD = HS in R and L thalamus (ii) BD Li- < HS in R thalamus	Only BD subjects not taking Li had smaller R thalamus than HS; no effect of other MS or AP on thalamic volumes
Rimol et al. 2010 (117)	139 adult BD 173 SCZ spectrum 207 HS	121 BD medicated with typical AP (n = 4), atypical AP (n = 55), Li (n = 19), antiepileptic (n = 51), AD (n = 48), and/or sedatives (n = 13) 157 SCZ medicated with typical AP (n = 9), atypical AP (n = 126), Li (n = 3), antiepileptic (n = 17), AD (n = 45), and/or sedatives (n = 17)	(i) BD and SCZ < HS in hippocampus, L thalamus, R nucleus accumbens, L cerebellar cortex, brainstem (ii) BD and SCZ > HS ventricle volume (iii) BD-I subjects had cortical thinning in frontal, superior temporal, and temporoparietal cortices	Tested effects of typical AP, atypical AP, AD, and Li using MANOVA; no effect of any medication on any brain measure
Rosa et al. 2010 (118)	88 adult FE psychosis (62 SCZ, 26 BD) 94 HS	<u>SCZ/BD (n):</u> Typical AP (26/8), atypical AP (14/3), MS (4/12), AD (8/2), BZD (7/5), anticholinergics (17/6) Medication history: all BD and 26 SCZ exposed to psychotropic medication at some point	(i) SCZ > BD and HS in L lateral ventricle and R temporal horn volumes (ii) BD = HS in ventricle volumes	(i) No correlation between duration of exposure to AP and ventricle volume measurements within any patient group; no correlation for typical and atypical tested separately (ii) No difference in ventricle size between BD patients on versus off MS at time of scan
Savitz et al. 2010 (20)	18 adult unmedicated BD 18 age- and gender-matched HS 17 adult BD taking Li + VPA 17 age- and gender-matched HS	17 BD Li + VPA (with 17 separately age- and gender-matched HS)	(i) BD without meds < HS in amygdala volume (ii) Trend for BD with meds > HS in amygdala volume (iii) BD with meds > BD without meds in amygdala volume	See main study results

Table 1. (Continued)

Study	Participants	Medications	Main findings	Medication effects
Takahashi et al. 2010 (119) (insular cortex)	26 adult BD 24 age- and gender-matched HS	21 BD currently medicated with Li (n = 12), VPA (n = 12), and/or CBZ (n = 2) Medication history: all 26 BD previously exposed to AP, but not within 12 months of scan	BD = HS insula volume; negative correlation between age and insula volume in BD group; those with more depressive episodes had smaller insula.	No effects of Li or VPA on insula volume in the BD group
Takahashi et al. 2010 (120) (midline brain)	26 adult BD 24 age- and gender-matched HS	21 BD currently medicated with Li (n = 12), VPA (n = 12), and/or CBZ (n = 2) Medication history: all 26 BD previously exposed to AP, but not within 12 months of scan	(i) BD = HS in cavum septum pellucidum length and prevalence (ii) BD < HS length of adhesion interthalami (iii) BD > HS size of third ventricle (iv) Adhesion interthalami length correlated with illness duration	No correlation between brain measures and dose of Li or VPA
Takahashi et al. 2010 (121) (superior temporal gyrus)	26 adult BD 24 age- and gender-matched HS	21 BD currently medicated with Li (n = 12), VPA (n = 12), and/or CBZ (n = 2) Medication history: all 26 BD previously exposed to AP, but not within 12 months of scan	BD < HS in L planum temporale and L caudal superior temporal gyrus volumes	(i) Dose of Li correlated with R planum polare and R rostral superior temporal gyrus volume (ii) No analysis of effects of medications on primary findings
Van der Schot et al. 2010 (18)	49 adult BD twin pairs: 23 MZ (9 concordant for BD) 26 DZ (4 concordant for BD) 67 healthy twin pairs	Li/no Li (n): MZ: 26/6 DZ: 20/10	(i) Risk for BD associated with reduced GM in medial PFC, precentral gyrus, and insula, and WM in superior longitudinal fasciculus (ii) Liability for BD associated with decreased GM in prefrontal and limbic regions and superior longitudinal fasciculus	Analyses were controlled for the presence of Li; results not significant without controlling for Li
Chepenik et al. 2009 (122)	20 adult BD 18 HS	14 BD medicated with Li (n = 5), anticonvulsant (n = 8), atypical AP (n = 6), and/or AD (n = 6)	BD < HS hippocampus volume; presence of BDNF <i>met</i> allele associated with smaller hippocampus volume in both BD and HS	No significant effects of any medication class on hippocampal volume
Fornito et al. 2009 (123)	26 BD-I with FE psychosis [mean age = 21.64 (3.23)], less than 1-year duration of illness 26 age- and gender-matched HS	12 BD medicated with Li (n = 7), typical AP (n = 2), and/or atypical AP (n = 4)	Male BD > male HS thickness of R subcallosal cingulate volume	(i) Excluding 7 patients taking Li did not change findings (ii) Patients taking typical AP (n = 2) not different than patients taking atypical AP (n = 4) on cortical thickness
Ha et al. 2009 (124)	23 adult BD-I 23 age- and gender-matched BD-II 23 age- and gender-matched HS	17 BD-I medicated with Li (n = 8), VPA (n = 6), and/or AP (n = 10) 12 BD-II medicated with Li (n = 7), VPA (n = 3), AP (n = 8), and/or AD (n = 3)	VBM: (i) All BD < HS in ventromedial PFC (ii) BD-I < HS in widespread areas of bilateral frontal, parietal, temporal, and parahippocampal regions (BD-II did not)	No differences in GM volumes in all patients taking meds versus all patients not taking meds

Medication effects on neuroimaging in bipolar disorder

Table 1. (Continued)

Study	Participants	Medications	Main findings	Medication effects
Kalmar et al. 2009 (7)	21 BD (age range: 10–18) 30 HS	17 BD medicated with Li (n = 4), anticonvulsants (n = 9), atypical AP (n = 11), AD (n = 6), and/or STIM (n = 5)	BD < HS amygdala volume; significant inverse correlation between amygdala volume and activation during emotional face processing	Medicated subjects (n = 17) not different than unmedicated subjects (n = 4) on amygdala volume
Kalmar et al. 2009 (125)	10 BD (age range: 10–21) 8 age- and gender-matched HS	Baseline medication: 5 BD medicated with MS (n = 2), anticonvulsants (n = 3), AD (n = 2), atypical AP (n = 2), STIM (n = 1), levothyroxine (n = 1), and/or clonidine (n = 1) All BD exposed to psychotropic medication at some point	BD > HS in volume loss in prefrontal regions including ventral and rostral PFC and rostral ACC	No significant differences between those taking meds (n = 5) versus those not taking meds (n = 5) at baseline
Kempton et al. 2009 (126)	30 adult BD 50 relatives (27 offspring, 23 siblings) 52 demographically matched HS	29 BD medicated with AP (n = 12), AD (n = 13), and/or MS (n = 19) [Li (n = 12), CBZ (n = 3), VPA (n = 3), LTG (n = 4)]	(i) Relatives and BD > HS in L insula (ii) BD > HS and relatives in L substantia nigra (iii) Healthy relatives > HS and BD in cerebellar (vermal) volume (iv) No differences in amygdala, sgACC, hippocampus, ACC, and pACC	(i) Examined Li+ versus Li- and AP versus no-AP (ii) No effect on VBM findings (iii) Authors did not examine possible effect on negative ROI findings
Lopez-Larson et al. 2009 (19)	31 BD (age range: 6–19) 23 BD + ADHD 24 ADHD 28 HS All groups age- and gender-matched	<u>BD/BD + ADHD/ADHD (n):</u> Atypical AP (22/17/0), STIM (5/6/12), MS (11/11/0), AD (6/9/3), clonazepam (2/0/2)	(i) ADHD < BD with and without ADHD in caudate/putamen (ii) ADHD < all in amygdala (iii) BD with ADHD > HS in nucleus accumbens (iv) Female BD < ADHD and HS in hippocampus	For the BD with ADHD group only, nucleus accumbens volume negatively correlated with the no. of meds (no individual meds analyzed)
Matsuo et al. 2009 (127)	63 adult BD	41 currently medicated with MS (n = 16) [Li (n = 3)], AP (n = 8), AD (n = 14)	(i) VBM, whole-brain correlation with BIS scores (ii) L rostral ACC GM volume inversely correlated with impulsivity	Compared medicated and unmedicated subjects L rostral ACC volume: no difference; however, it is unclear whether unmedicated subjects had past med exposure
Mirakhor et al. 2009 (128)	18 adult BD 18 age-, gender-, and IQ-matched HS	Li (n = 8), AP (n = 6), AD (n = 6), anticonvulsant (n = 6)	(i) Ventral and dorsal GI decreased significantly over time in both the BD and HS groups, BD = HS rate of decrease (ii) Within BD, individuals with BDNF <i>met</i> alleles showed greater rate of decrease in GI	Exposure to 4 meds (Li, typical AP, anticonvulsants, and AD) examined by repeated-measures ANOVA: found no effect of medication on rate of change of GI

Table 1. (Continued)

Study	Participants	Medications	Main findings	Medication effects
Moore et al. 2009 (30)	28 adult BD	Treated with Li for 4 weeks	(i) Total GM volume increased significantly in all subjects after 4 weeks of Li treatment. (ii) Responders (but not non-responders) showed a significant increase in GM volume in the PFC (trend in subgenual)	See main study results
Nery et al. 2009 (17)	28 adult BD 28 age- and gender-matched HS	18 BD medicated with Li	(i) BD = HS in orbitofrontal GM volumes (ii) Depressed BD (n = 10) < euthymic BD (n = 18) in total orbitofrontal GM volume (iii) Total orbitofrontal GM volume inversely correlated with depressive symptom intensity	(i) Li+ = Li- in OFC volume (ii) Li exposure not significantly different between depressed (6/10) and non-depressed (4/18) groups
Penttilä et al. 2009 (32)	22 adult early-onset BD 14 age- and gender-matched intermediate-onset BD 50 age- and gender-matched HS	15 early-onset BD medicated with MS (n = 10): [Li (n = 5), VPA (n = 3), CBZ (n = 3)], AD (n = 8), and/or AP (n = 7) 12 intermediate-onset BD medicated with MS (n = 12): [Li (n = 6), VPA (n = 6)], AD (n = 5), and/or AP (n = 4)	(i) Intermediate-onset BD < early-onset BD and HS in local sulcal index in R dlPFC (ii) Intermediate-onset BD < HS in g-SI in both hemispheres	Medication type (MS, AP, AD) were added one at a time as a factor in the linear model; no effects found in the dlPFC or g-SI
Penttilä et al. 2009 (129)	16 adult BD (depressed) 25 BD (euthymic) 35 unipolar depression 70 HS All groups age- and education-matched	<u>Depressed BD/euthymic BD/unipolar depressed (n):</u> MS (4/19/4): [Li (2/11/0)], AP (2/7/3), AD (5/8/13), BZD (8/6/21)	g-SI studied – higher is more folding: (i) BD < HS in g-SI in R hemisphere by 4% (ii) Euthymic BD = HS in g-SI	(i) Li+ < Li- in R g-SI and R GM volume (ii) Li dose positively correlated with g-SI (findings are somewhat contradictory)
Stanfield et al. 2009 (130)	66 adult BD 66 age-, gender-, and IQ-matched HS	MS (n = 28), AP (n = 31), AD (n = 24)	VBM: (i) BD < HS GM density in L and R lateral orbital gyri and R inferior frontal gyrus (ii) BD < HS WM density in corona radiata and L temporal stem	MANOVA found no effects of AP, Li, or AD medications on peak density in these regions
Takahashi et al. 2009 (31)	26 adult BD 24 age- and gender-matched HS	21 BD medicated with Li (n = 12), VPA (n = 12), and/or CBZ (n = 2) Medication history: all 26 BD previously exposed to AP, but not within 12 months of scan	BD > HS in pituitary volume; females > males in pituitary volume for both groups	(i) Trend for BD subjects taking Li to have smaller pituitary volume than those not taking Li (p = 0.06) (ii) Other medications tested and had no effect
van der Schot et al. 2009 (131)	50 adult twin pairs with BD: 24 MZ, 26 DZ, and 67 zygosity-, birth order-, age-, gender-, and parental education-level-matched HS twin pairs	Li+ (n = 46), Li- (n = 17): MZ Li+ (n = 26), MZ Li- (n = 7) DZ Li+ (n = 20), DZ Li- (n = 10)	BD < HS total cortical and WM volumes	When effects of lithium were statistically controlled, findings were even more pronounced, suggesting that Li treatment tended to normalize findings

Medication effects on neuroimaging in bipolar disorder

Table 1. (Continued)

Study	Participants	Medications	Main findings	Medication effects
Vita et al. 2009 (132)	Meta-analysis of 11 MRI studies of FE BD versus HS: 221 BD (mean age = 23.4) 312 HS	Two studies included a proportion of patients under Li treatment	BD < HS for total intracranial and WM volumes, but not GM or whole-brain	Meta-analysis re-run while excluding studies that have Li-treated subjects: confirmed absence of significant differences in GM volume between BD and HS (did not discuss other results)
Walterfang et al. 2009 (133)	70 BD (age range: 17–65) 45 first-degree relatives 75 HS	Li (n = 23), VPA (n = 8), CBZ (n = 12), LTG (n = 13), AP (n = 19)	(i) BD < HS corpus callosal thickness and thickness of the anterior body (ii) First-degree relatives did not differ from HS in callosal size or shape (iii) BD duration of illness and age associated with thinning in anterior body	BD patients on Li showed a thicker anterior mid-body than those on other psychotropics
Walterfang et al. 2009 (134)	24 adult BD 24 age-, gender-, and education-matched HS	20 BD medicated with Li (n = 12), VPA (n = 11), and/or CBZ (n = 2)	BD < HS, thickness of corpus; psychotic = non-psychotic	Dosage of Li or VPA did not significantly correlate with any main callosal measure
Arnone et al. 2008 (135)	Meta-analysis of 5 studies of adults with BD versus HS that measured corpus callosum: Included 91 BD (range of mean ages: 15.5–40.4) 114 HS	One study was medication-free, the other 4 had medications reported to be mostly MS	BD < HS in callosal area (includes 5 studies)	Of the 5 studies included in the meta-analysis, the one that used unmedicated subjects was removed, and the results of the meta-analysis remained the same
Bearden et al. 2008 (136)	16 BD (age range: 10–21) 20 demographically matched HS	14 BD medicated with Li (n = 10), VPA (n = 8), and/or thyroid hormone (n = 3)	(i) BD < HS total hippocampal volume (ii) Within the BD group, positive correlation of hippocampal volume with age, within HS group, negative correlation of hippocampal volume and age	(i) Tested whether duration of medication was related to age (ii) No correlation between age and duration of meds (iii) Did not test for volume differences between medicated and unmedicated subgroups
Bearden et al. 2008 (137)	33 adult BD 62 demographically matched HS	21 BD Li-treated for at least 2 weeks 12 not medicated for at least 2 weeks	BD taking Li > HS and unmedicated BD in total hippocampal volume	See main study findings
Chiu et al. 2008 (138)	16 BD (age range: 7–13) 24 age- and gender-matched ASD 15 age- and gender-matched HS	ASD/BD (n): SSRI (9/9), non-SSRI (4/3), MS (4/9), atypical AP (5/8), typical AP (1/0), adrenergic agents (3/3)	BD < HS and ASD in L anterior cingulate gyrus volume	(i) Using ANCOVA with medication exposure as factor, no effects of medication on L or R ACC (ii) BD group exposed to atypical AP had ACC volume = HS, while BD with MS exposure and BD without MS and BD without atypical neuroleptic exposure < HS ACC volume

Table 1. (Continued)

Study	Participants	Medications	Main findings	Medication effects
Doty et al. 2008 (25)	54 adult BD 41 demographically matched HS	Medication history: Li (n = 38), VPA (n = 35), neuroleptics (n = 31) 49 currently medicated with Li (n = 16), VPA (n = 17), and/or neuroleptics (n = 17)	BD showed decreasing amygdala volume with age, but HS did not	Age remained a significant factor in determining amygdala volume after controlling for (any) medication use
Foland et al. 2008 (139)	49 adult BD: 37 Li- and 12 age-matched Li+	Li- group: AP (n = 4), SSRI (n = 12), BZD (n = 4), anticonvulsants (n = 25) Li+ group: BZD (n = 1), anticonvulsants (n = 4)	(i) Li exposure associated with larger amygdala and hippocampus (ii) Li+ > Li- in total (driven by L) amygdala and total hippocampal volume (L and R also)	See main study findings
Frazier et al. 2008 (140)	35 BD without psychosis (age range: 6–17) 19 BD with psychosis 20 SCZ spectrum 29 HS All groups gender-matched	<u>BD without psychosis/BD with psychosis/SCZ (n):</u> Li (3/8/3), STIM (7/4/2), MS (14/9/4), AD (9/7/6), atypical AP (26/16/19), sedatives (0/2/1), others (6/4/1)	BD > HS amygdala volume; inverse correlation between amygdala volume and mania severity in BD group	Chlorpromazine equivalents used for quantifying AP exposure (current)—no correlation between this and amygdala volume; other meds not examined
Hajek et al. 2008 (141)	24 unaffected with first-degree relative with BD (age range: 15–30) 19 age- and gender-matched affected with first-degree relative with BD 31 age- and gender-matched HS	5 affected medicated Li+ (n = 2), AD (n = 1), AP (n = 1), and/or LTG (n = 1)	Unaffected = affected = HS subgenual cingulate volume	Exclusion of the five medicated subjects did not change the results
Hajek et al. 2008 (142)	24 unaffected with first-degree relative with BD (age range: 15–30) 19 age- and gender-matched affected with first-degree relative with BD 31 age- and gender-matched HS	5 affected medicated Li+ (n = 2), AD (n = 1), AP (n = 1), and/or LTG (n = 1)	Unaffected = affected = HS pituitary volume	Exclusion of the five medicated subjects did not change the results
Kempton et al. 2008 (89)	141 studies: 3509 BD [mean age = 32.6 (12.4)] 4687 HS [mean age = 31.7 (11.9)]	No. of studies reporting variable/pooled no. of subjects in meta-analysis (n): Non-medicated (54/350), MS (32/512), Li (55/700), anticonvulsant (32/170), VPA (38/169), CBZ (33/44), AP (48/287), AD (48/182), BZD (32/22)	(i) BD > HS lateral ventricle size and WM hyperintensities (ii) GM volume increased among patients when the proportion of patients using Li increased	(i) Meta-regression analysis found that GM volume increased among BD compared with HS when the proportion of patients using Li increased (ii) The proportion of patients using Li in a given study had no observable effect on deep WM hyperintensities

Medication effects on neuroimaging in bipolar disorder

Table 1. (Continued)

Study	Participants	Medications	Main findings	Medication effects
Koo et al. 2008 (143)	80 adult FE psychosis: 39 SCZ (FESZ) 41 FEAFF 40 HS All groups demographically matched	<u>FESZ/FEAFF at baseline (n):</u> Typical neuroleptics (8/7), atypical neuroleptics (12/11), Li (1/6), VPA (2/7)	(i) At first hospitalization, FESZ < HS L subgenual, L and R posterior cingulate (ii) At 1.5-year follow-up, FESZ shows greater decreases in volume of subgenual and posterior cingulate compared to HS (iii) FEAFF < HS initial and progressive subgenual region abnormalities (iv) FESZ less asymmetric paracingulate pattern than HS	No significant differences in cingulate volumes between medicated and unmedicated (typical or atypical AP, or presence or absence of MS) patients within FESZ or FEAFF groups
Monkul et al. 2008 (144)	16 BD (age range: 10–21) 21 demographically matched HS	14 BD currently medicated with Li (n = 10) and/or VPA (n = 8) 3 BD were on AP in the past	(i) BD = HS in cerebellum and vermis (ii) Trend (p = 0.06) for V2 smaller volume in BD (iii) Inverse correlation with no. of affective episodes and V2 volume in males	No differences between 3 groups on cerebellar volumes: Li, VPA, and Li + VPA, although very small group size in medication analyses
Papiol et al. 2008 (145)	20 adult BD 45 HS	Li (n = 14), VPA (n = 4), CBZ (n = 2), LTG (n = 2), AP (n = 2)	A -511C/T polymorphism of <i>IL-1B</i> gene was associated with whole-brain GM deficits and L dIPFC GM deficits in BD patients	Nonparametric analysis showed no effect of Li treatment on whole-brain GM or L dIPFC GM in the entire BD sample
Scherk et al. 2008 (146)	35 adult BD 32 demographically matched HS	Lifetime medication: Li (n = 12), other MS (n = 27), typical AP (n = 2), atypical AP (n = 15)	VBM: BD = HS in GM and WM volume	No correlation between GM/WM volume and exposure to Li or AP
Yucel et al. 2008 (16)	26 adult BD 30 HS	All subjects medication-naïve before study [mean age = 24.2 (8.4), 33% male] 12 Li for 1–8 weeks, 7 VPA or LTG for 1–8 weeks, 9 no meds	Trend for larger total cerebral volume in controls (p = 0.06)	(i) Li group (n = 12) > unmedicated (n = 9) and HS groups in bilateral hippocampi (ii) VPA/LTG group with no differences from HS or unmedicated BD subjects
Ahn et al. 2007 (93)	46 BD (age range: 6–16) 22 age- and gender-matched HS	Atypical AP (n = 35), Li (n = 11), anticonvulsants (n = 18), AD (n = 15), STIM (n = 11), alpha agonists (n = 7), BZD (n = 2)	(i) Total group: BD = HS caudate, putamen, and globus pallidus volumes (ii) Prepubertal BD > HS nucleus accumbens volume, but pubertal BD = HS nucleus accumbens volume	(i) AP doses (chlorpromazine equivalents) not correlated with brain volumes (ii) No. of medications was inversely correlated with R nucleus accumbens volume (iii) Type of medication was not a significant factor in determining nucleus accumbens volume
Javadapour et al. 2007 (147)	24 adult BD 24 demographically matched HS	20 BD medicated with Li (n = 12) and/or anticonvulsant (VPA and/or CBZ) (n = 12)	BD > HS R ACC	(i) Li+ > Li- and HS for measures of R ACC volume (ii) After correcting for age and sex, Li+ = Li- for measures of ACC volume

Table 1. (Continued)

Study	Participants	Medications	Main findings	Medication effects
Kim et al. 2007 (24)	41 adult BD 41 age- and gender-matched HS	27 BD currently medicated with Li (n = 12), VPA (n = 8), and/or other medications (n = 7) 31 BD exposed to psychotropic medications at some point in the past	(i) BD > HS prevalence of abnormal CSP enlargement (ii) BD with abnormal CSP enlargement had a significantly earlier onset of BD than those without	Within BD group, no significant difference in prevalence of enlarged CSP in drug-naïve versus drug-exposed patients
Moorhead et al. 2007 (148)	20 adult BD 21 demographically matched HS	All BD currently medicated with Li (n = 10), AD (n = 6), AP (n = 5), and/or anticonvulsant (n = 7)	BD > HS decline in hippocampus, fusiform, and cerebellum GM over 4 years	No association found between any medication class and GM tissue loss
Najt et al. 2007 (149)	14 BD (age range: 10–21) 20 HS	10 BD currently medicated with Li (n = 9) and/or VPA (n = 4)	(i) Female BD > female HS L lateral regions OFC volume (ii) Male BD < male HS R medial lateral OFC volume	No correlation between OFC measurements and treatment status
Yucel et al. 2007 (150)	12 adult BD 40 age- and gender-matched HS	All subjects started Li within 1 month of the baseline scan	(i) BD = HS hippocampal volume at baseline scan (ii) Within BD group, significant increase in hippocampal volume after 4-year continuous treatment with Li	See main study findings

BD = bipolar disorder; BD-I = bipolar I disorder; BD-II = bipolar II disorder; HS = healthy subjects; Li = lithium; Li+ = on Li; Li- = not on Li; MDD = major depressive disorder; SCZ = schizophrenia; ADHD = attention-deficit hyperactivity disorder; UAR = unaffected first-degree relatives; AO = affected offspring; FH = family history; MZ = monozygotic; DZ = dizygotic; FE = first episode; ASD = autism spectrum disorder; FESZ = first-episode schizophrenia; FEAFF = first-episode affective psychosis; AP = antipsychotic; AD = antidepressant; MS = mood stabilizer; BZD = benzodiazepine; VPA = valproic acid; CBZ = carbamazepine; LTG = lamotrigine; OLAN = olanzapine; QUET = quetiapine; RISP = risperidone; SSRI = selective serotonin reuptake inhibitor; MAOI = monoamine oxidase inhibitor; STIM = stimulant; R = right; L = left; WM = white matter; GM = gray matter; ACC = anterior cingulate cortex; dlPFC = dorsolateral prefrontal cortex; PFC = prefrontal cortex; OFC = orbitofrontal cortex; sgACC = subgenual anterior cingulate cortex; pACC = perigenual anterior cingulate cortex; g-SI = global sulcal index; CSP = cavum septi pellucidi; DTI = diffusion tensor imaging; VBM = voxel-based morphometry; CSF = cerebrospinal fluid; BDNF = brain derived neurotrophic factor; ROI = region of interest; GI = gyrification index; IQ = intelligence quotient; BIS = Barrett Impulsivity Scale; ANOVA = analysis of variance; ANCOVA = analysis of covariance; MANOVA = multivariate analysis of variance; V2 = vermol region lobules VI-VII.

fMRI results: secondary analyses

fMRI studies can be grouped according to the experimental paradigm: resting state, processing of emotional stimuli, cognitive tasks, and cognitive tasks in the presence of emotional stimuli. These fMRI studies were designed to look at differences in the blood oxygen level-dependent (BOLD) signal between BD and HS groups (and sometimes other diagnostic categories); secondary analyses were conducted to determine the effect of medications, and whether psychotropic medications could explain the main findings. Reviewed fMRI studies (n = 41) are shown in Table 2. Many of these studies found structural and functional abnormalities in areas implicated in emotion processing and regulation (38, 39). Specifically, comparing individuals with BD to HS, the literature indicates limbic hyperactivation and frontal hypoactivation, especially in resting state paradigms and emotion processing tasks; this

finding has been most pronounced in manic populations, but also has been shown in other mood states (39).

Resting state paradigms. BD has been associated with altered resting state FC between the prefrontal cortex (PFC) and more posterior structures (superior temporal gyrus, amygdala) (40, 41), circuits that have been implicated in emotion processing and regulation (38). One study showed decreased medial PFC activation and increased recruitment of the parietal cortex (42), consistent with increased negative FC. There were no effects of medication status, class, or dose of antipsychotic agent on these findings (40–42).

Processing of emotional stimuli. Tasks include explicit processing of emotional faces, implicit processing of emotional faces, and emotional processing of neutral faces. BD has been associated with increased amygdala activation in response to emotional stimuli (7, 43, 44), although this finding is not universal (45–47). An increased amygdala

Medication effects on neuroimaging in bipolar disorder

Table 2. Medication effects in functional magnetic resonance imaging (fMRI) studies (secondary analyses)

Study	Experimental paradigm	Participants	Medications	Main findings	Medication effects
Costafreda et al. 2011 (10)	Verbal Fluency Task (generating words that begin with a given letter)	32 BD (adult, euthymic) 32 SCZ 40 HS	26 BD medicated with Li (n = 14), anticonvulsant (n = 10), AP (n = 8), and/or AD (n = 8)	(i) SCZ > BD > HS activation in anterior cingulate, L dlPFC, R putamen, precuneus, and posterior cingulate (ii) Pattern of neural responses correctly classified BD 79% of the time	No effects of antipsychotic dose on results; other medications not assessed
Lelli-Chiesa et al. 2011 (6)	Processing of sad affect	40 BD (adult, type I) 47 first-degree relatives 50 HS	No. of medicated individuals is not given	(i) BD = relatives = HS activation in amygdala and vmPFC (ii) COMT Val158 allele associated with greater amygdala activation (iii) <i>Met</i> allele associated with greater vmPFC and vIPFC activation	No differences between medicated and unmedicated BD in the ROIs examined (amygdala, vmPFC, vIPFC)
Strakowski et al. 2011 (65)	Continuous Performance Task with emotional and neutral distractors	40 BD (type I, manic) (age range: 16–50) 36 demographically matched HS	31 BD medicated with atypical AP (n = 23), anticonvulsant (n = 11), and/or Li (n = 7)	BD < HS activation in many regions of ventrolateral emotional pathway (vIPFC, R ACC, L fusiform, amygdala), especially with emotional/neutral distractors versus targets	(i) No difference between medicated and unmedicated (ii) Li versus not showed change in inferior frontal gyrus activation; anticonvulsant versus not showed change in inferior frontal gyrus, fusiform gyrus, putamen, and cerebellar vermis activation; atypical AP versus not showed no differences (iii) Repeating analysis removing those on Li and anticonvulsants did not impact results
Allin et al. 2010 (13)	Paced Verbal Fluency Task (generating words that begin with a given letter)	18 BD (adult, euthymic) 19 unaffected first-degree relatives 19 HS	13 BD medicated with Li (n = 8), other MS (n = 7), AD (n = 3), and/or atypical AP (n = 3)	(i) BD/relatives > HS activation in retrosplenial/posterior cingulate cortex (ii) BD < relatives activation in retrosplenial/posterior cingulate cortex in the hard condition	(i) No effect of medication use on activation in posterior cingulate (ii) Covarying for use of psychotropic medication did not alter results

Table 2. (Continued)

Study	Experimental paradigm	Participants	Medications	Main findings	Medication effects
Almeida et al. 2010 (44)	Explicit processing of emotional faces	15 BD (adult, depressed) 15 BD (euthymic) 15 MDD (depressed) 15 HS	13 BD (depressed) medicated with mean medication load of 3.9 (2.3) 14 BD (euthymic) medicated with medication load of 3.2 (1.9)	BD (depressed) > BD (euthymic)/MDD/HS activation in L amygdala during the sad condition (mild and neutral faces)	(i) Negative correlation between medication load and amygdala activation in sad condition (intense faces) (ii) Within the BD (euthymic), AD treated versus non-AD-treated showed increased amygdala activation to mild sad and neutral faces (not different from HS)
Bermpohl et al. 2010 (61)	Monetary Incentive Delay Task	15 BD (adult, type I, manic) 16 age-matched HS 7/15 BD re-scanned once they were euthymic	All BD medicated with atypical AP (n = 10), Li (n = 8), and/or anticonvulsant (n = 6)	(i) BD (manic) > HS L OFC activation when expecting increased reward (ii) BD (manic) < HS L OFC activation when expecting increasing loss (iii) Differences corrected with remission	No effect of AP medication (presence versus absence, or dose) on activation in the ventral striatum or OFC
Brotman et al. 2010 (45)	Emotional processing of neutral faces	43 BD (combined mood state) (age range: 8–17) 29 SMD 18 ADHD 37 HS (age range: 8–17)	32 BD medicated with anticonvulsant (n = 22), atypical AP (n = 19), Li (n = 15), AD (n = 13), and/or STIM (n = 10)	(i) BD = HS activation in amygdala (ii) ADHD > BD, SMD, and HS activation in amygdala (ii) SMD < BD, SMD, and HS activation in amygdala	No relationship between no. or classes of medication and amygdala activation
Chepenik et al. 2010 (41)	Resting state	15 BD (adult, combined mood state) 10 HS	12 BD medicated with anticonvulsant (n = 7), Li (n = 5), AP (n = 5), AD (n = 4), and/or BZD (n = 2)	(i) BD < HS inverse vPFC–amygdala functional connectivity (ii) BD > HS L and R vPFC connectivity	No effect of medication status on either vPFC–amygdala FC or whole-brain analysis (though power of analysis is limited)
Dickstein et al. 2010 (8)	Reversal task	16 BD (euthymic) (age range: 7–17) 15 age-, sex-, IQ-matched HS	13 BD medicated with atypical AP (n = 8), anticonvulsant (n = 8), Li (n = 6), STIM (n = 5), and/or AD (n = 3)	(i) BD > HS activation in fronto-parietal regions during the reversal phase, particularly in response to errors (ii) BD = HS activation in OFC	No differences between those taking atypical AP or antiepileptic, versus those not
Dickstein et al. 2010 (40)	Spontaneous resting state functional connectivity (RSFC)	15 BD (euthymic) (age range: 7–17) 15 HS	All BD medicated with atypical AP (n = 35), Li (n = 9), and/or STIM (n = 6)	BD > HS negative RSFC between L dIPFC and R superior temporal gyrus	No effect of medication class

Medication effects on neuroimaging in bipolar disorder

Table 2. (Continued)

Study	Experimental paradigm	Participants	Medications	Main findings	Medication effects
Glahn et al. 2010 (9)	Face-name Paired Association Task (declarative memory paradigm)	15 BD (adult, type I, euthymic) 24 demographically matched HS	14 BD medicated with MS (n = 11), atypical AP (n = 7), and/or AD (n = 5)	(i) BD > HS activation in bilateral dlPFC during encoding (ii) BD < HS activation in R dlPFC and hippocampal regions during recognition	No effect of presence versus absence of MS, AD, or atypical AP on activation in hippocampus or dlPFC
Gruber et al. 2010 (59)	Verbal Delayed Matching to Sample Task (articulatory versus non-articulatory strategies)	18 BD (adult, euthymic) 18 age- and gender-matched HS	15 BD medicated with MS (n = 14), AP (n = 4), AD (n = 8), and/or BZD (n = 4)	(i) Only BD (not HS) showed increase in R amygdala activation during articulatory rehearsal (ii) BD > HS activation in R frontal eye field, intraparietal cortex, precentral gyrus, and cerebellum during articulatory rehearsal	Single subject analyses showed increased amygdala activation in medication-free patients (n = 3), as well as those who had never received Li or LTG
Hall et al. 2010 (64)	Face-name Paired Association Task (declarative memory paradigm)	14 BD (adult, type I) 15 SCZ 14 HS	BD medicated with AP (n = 8), AD (n = 4), Li (n = 5), and/or valproate (n = 3)	(i) BD < SCZ/HS activation in dlPFC during encoding (ii) BD/HS > SCZ activation in anterior hippocampus during encoding (iii) BD/HS < SCZ activation in dmPFC during retrieval	(i) Positive correlation between AP dose and dlPFC in BD group (normalizing effect) (ii) MS (presence versus absence) had no effect on activation in dlPFC, dmPFC, or hippocampus
Liu et al. 2010 (11)	Emotional processing of neutral faces	39 BD (unspecified mood state) (age range: 9–19) 29 HS (age range: 9–18)	29 BD medicated with anticonvulsants (n = 22), atypical AP (n = 17), AD (n = 13), Li (n = 12), and STIM (n = 8)	(i) BD = HS amygdala activation under hostility contrast (ii) Under hostility contrast, R amygdala activation associated with SNP in gene DOK5 (involved in neurotrophin signaling) (iii) No significant diagnosis × gene interactions	No relationship between no. of medications and amygdala activation
Ongur et al. 2010 (42)	Resting state	17 BD (adult, type I, manic/mixed) 14 SCZ 15 HS	All BD medicated with MD (Li or anticonvulsant) and AP	(i) BD < HS activation in medial PFC (ii) BD > HS activation in parietal cortex (associated with severity of mania)	No correlation between AP dose (in chlorpromazine equivalents) and activation of default mode network
Singh et al. 2010 (54)	Response inhibition	26 BD (unspecified mood state) (age range: 9–18) 22 age-, gender-, and IQ-matched controls	All medicated with AD (n = 16), STIM (n = 14), valproic acid (n = 14), Li (n = 8), and/or atypical AP (n = 6)	BD > HS activation in R dlPFC in the Go/NoGo contrast	(i) Greater activation in L anterior cerebellum and decreased activation in L ACC in Li-exposed versus unexposed BD (ii) Greater activation in R ACC and precuneus in atypical AP-exposed versus unexposed BD (iii) No effect of valproic acid, STIM, or AD

Table 2. (Continued)

Study	Experimental paradigm	Participants	Medications	Main findings	Medication effects
Surguladze et al. 2010 (43)	Implicit processing of emotional faces (happy and fearful)	20 BD (adult, type I, unspecified mood state) 20 unaffected first-degree relatives 20 HS	16 BD medicated with Li (n = 9), anticonvulsant (n = 7), AP (n = 4), and/or AD (n = 2)	(i) BD/relatives > HS activation in medial PFC (fearful/happy faces), L putamen (fearful faces), and amygdala (intense happy faces) (ii) BD > relatives/HS activation in L putamen (intense happy faces)	No effect of medication load on activation in putamen, amygdala, or medial PFC
Thermenos et al. 2010 (15)	N-back Working Memory Task	19 BD (adult, unspecified mood state) 18 first-degree relatives 19 demographically matched HS	9 BD medicated with AP (n = 8), MS (n = 6), and/or MS (n = 2)	(i) BD/relatives > HS activation in L anterior insula (ii) BD < HS/relatives activation in L frontopolar cortex (iii) Relatives > HS activation in OFC and superior parietal region	Results were replicated on an unmedicated subset of BD (n = 10)
Versace et al. 2010 (50)	Explicit processing of emotional faces	31 BD (adult, type I, 17 euthymic and 14 depressed) 24 age- and gender-matched HS	<u>Depressed/euthymic BD medicated with (n):</u> MS (12/10), AP (9/9), AD (7/8), BZD (7/3), and/or Li (4/6)	(i) BD (depressed/euthymic) > HS R amygdala–OFC FC to sad faces (ii) BD (depressed/euthymic) < HS bilateral amygdala–OFC FC to happy faces (iii) BD (depressed) > HS L amygdala–OFC FC to sad faces	AD versus non-AD-treated BD showed decreased L amygdala–OFC FC to mild sad faces (normalizing effect)
Almeida et al. 2009 (48)	Emotional labeling of happy faces	21 BD (adult, euthymic) 25 age- and gender-matched HS	19 BD medicated with MS (n = 15), atypical AP (n = 13), AD (n = 9), and/or BZD (n = 5) Average medication load 2.5 (1.8)	(i) BD < HS activation in PHG (ii) BD > HS R PHG–sgCG connectivity (iii) BD = HS dlPFC–sgCG connectivity	No effect of medication load on connectivity, particularly between PHG and sgCG
Almeida et al. 2009 (52)	Explicit processing of happy and sad faces	15 BD (adult, depressed) 16 MDD 16 age- and gender-matched HS	13 BD (depressed) medicated with mean medication load of 3.9 (2.3)	(i) BD/MDD < HS L-sided top-down omPFC–amygdala connectivity in reaction to both happy and sad faces (ii) BD < MDD/HS R-sided bottom-up amygdala–omPFC connectivity only in reaction to happy faces	(i) Within the BD group, no significant effect of medication load or individual medication classes on omPFC–amygdala connectivity (ii) Trend (p = 0.07) toward those on antipsychotics having increased L-sided top-down connectivity in response to happy faces (normalizing)

Medication effects on neuroimaging in bipolar disorder

Table 2. (Continued)

Study	Experimental paradigm	Participants	Medications	Main findings	Medication effects
Hassel et al. 2009 (12)	Implicit processing of happy and fearful faces	14 BD (adult, type I, euthymic) 16 HS	12 BD medicated with atypical AP (n = 8), MS (n = 6) [including Li (n = 3)], AD (n = 4), and/or BZD (n = 4)	(i) BD < HS activation in dorsal PFC during all faces (ii) BD > HS activation in striatum during happy and neutral faces (iii) Comorbidities (eating disorders, substance abuse) associated with abnormalities in PFC and striatum	(i) Increased medication load associated with decreased R dorsal PFC activation with fearful and neutral faces (more abnormal) (ii) Increased medication load associated with increased L caudate activation with happy and neutral faces (more abnormal)
Kaladjian et al. 2009 (14)	Go/NoGo Task (response inhibition)	20 BD (adult, type I, euthymic) 20 demographically matched HS	19 BD medicated with Li (n = 5), anticonvulsant (n = 4), AP (n = 6), or combination treatment (n = 4)	BD < HS activation in bilateral amygdala and L frontopolar cortex	(i) Relative to HS, each medication-defined subgroup (Li, anticonvulsant, AP) showed decreased activation in amygdala and L PFC (ii) No significant differences observed between subgroups
Kalmar et al. 2009 (7)	Implicit processing of emotional faces (Male-female Labeling Task)	21 BD (combined mood state) (age range = 10–18) 30 HS (age range: 10–18)	17 BD medicated with atypical AP (n = 11), anticonvulsant (n = 9), AD (n = 6), STIM (n = 5), and/or Li (n = 4)	(i) BD > HS activation in amygdala (ii) BD < HS amygdala volume (iii) Inverse correlation between amygdala volume and activation	No effects of presence versus absence of medications on amygdala activation
Kim et al. 2009 (68)	Virtual Reality Social Cognition Task (interpreting verbal and non-verbal cues given by an avatar)	14 BD (adult, type I, euthymic) 14 HS	All BD medicated with divalproex (n = 11), Li (n = 7), and/or AP (n = 6)	BD < HS activation in R inferior frontal cortex, premotor cortex, and insula (<i>mirror neuron system</i>)	Neural activation not associated with the dose or no. of medications
Mazzola-Pomietto et al. 2009 (56)	Response Inhibition Task (Go/NoGo Task)	16 BD (adult, type I, manic) 16 age- and sex-matched HS	All BD medicated with MS (n = 11) and/or atypical AP (n = 10)	BD < HS activation in bilateral vIPFC	(i) No significant differences in vIPFC activation between those treated with MS and atypical AP (ii) Both subgroups showed decreased vIPFC activation relative to HS
Robinson et al. 2009 (60)	Delayed Nonmatch-to-Sample Task using abstract shapes (novel versus familiar conditions)	15 BD (adult, type I, euthymic) 15 demographically matched HS	14 BD medicated with anticonvulsant (n = 12), AP (n = 8), and/or AD (n = 7)	(i) BD > HS activation in R prefrontal gyrus (both conditions) and ACC (novel condition only) (ii) BD < HS activation in visual processing regions (both conditions) and medial temporal regions (novel condition only)	No effect of medication class (included as regressors in model) on results

Table 2. (Continued)

Study	Experimental paradigm	Participants	Medications	Main findings	Medication effects
Shah et al. 2009 (49)	Implicit processing of emotional faces (Male–female Labeling Task)	30 BD (adult, remitted) 48 HS	26 BD medicated on anticonvulsant (n = 18), AD (n = 15), atypical AP (n = 13), Li (n = 10), and/or BZD (n = 3)	(i) BD < HS activation in ventral ACC during fear and happy conditions (regardless of genotype) (ii) Short allele of 5-HT transporter promoter polymorphism (versus long allele) showed decreased activation in ventral ACC (regardless of diagnostic category) (iii) No effect of diagnostic category or genetic polymorphism on amygdala activation	No significant effect of medication (presence versus absence or class) on activation in ventral ACC or amygdala; however, there was a trend toward the unmedicated patients (n = 4) having increased amygdala activation
Wang et al. 2009 (51)	Implicit processing of emotional faces (happy, fearful, neutral)	33 BD (adult, type I, unspecified mood state) 31 HS	27 BD medicated with anticonvulsants (n = 16), atypical AP (n = 14), AD (n = 12), Li (n = 9), and/or BZD (n = 7)	BD < HS pACC–amygdala functional connectivity during fearful and happy faces; correlated with DTI results	No effect of medication status (medications overall or class) on pACC–amygdala functional activation
Welander-Vatn et al. 2009 (62)	Response Inhibition Task (Go/NoGo Task)	27 BD (adult, type II, unspecified mood state) 28 HS	16 BD medicated with anticonvulsant (n = 10), atypical AP (n = 3), and/or AD (n = 2)	BD = HS activation in dACC	No differences between medicated and unmedicated in activation of the dACC
Whalley et al. 2009 (66)	Emotional Memory Task (recognition of previously seen positive versus neutral scenes)	14 BD (adult, type I, unspecified mood state) 15 SCZ 14 HS	BD medicated with AP (n = 8), Li (n = 4), and/or AD (n = 3)	(i) BD > HS/SCZ activation in L hippocampus in response to emotional versus neutral scenes (ii) Correlation between mania scores and activation in ACC (iii) Correlation between depression scores and activation in dIPFC	(i) No effect of AP, Li, or, valproate dose on activation in L hippocampus (ii) No effect of AP dose, Li (yes versus no), or valproate (yes versus no) on whole-brain analysis
Calhoun et al. 2008 (151)	Identify target stimuli (1.5 kHz tones) versus non-target stimuli (1 kHz tones)	14 BD (adult) 21 SCZ 26 HS	BD medicated with AD (n = 10), atypical AP (n = 8), and/or anticonvulsant (n = 3)	Using a combination of data from temporal lobe and default mode network, diagnostic category could be predicted with high validity	No effect of AP or AD medication on neuroimaging results
Deckersbach et al. 2008 (67)	Working Memory Task (2-back) under no mood induction versus neutral state versus acute sadness	9 BD (adult, depressed, female) 17 age-, gender-, education-, and IQ-matched HS	All BD medicated with Li (n = 5) or anticonvulsants (n = 4)	BD > HS activation in L dIPFC and dACC during acute sadness condition	No effect of the presence versus absence of Li or anticonvulsants on activation in a priori ROI (dACC and dIPFC)

Medication effects on neuroimaging in bipolar disorder

Table 2. (Continued)

Study	Experimental paradigm	Participants	Medications	Main findings	Medication effects
Hassel et al. 2008 (47)	Implicit processing of happy and fearful faces	19 BD (adult, type I, euthymic) 24 HS	18 BD medicated with atypical AP (n = 11), MS (n = 10) [including Li (n = 6)], AD (n = 8), and/or BZD (n = 4)	(i) BD < HS activation in R dlPFC during happy and neutral faces (ii) BD < HS activation in L dlPFC during fearful and neutral faces (iii) BD > HS activation in L striatum during happy faces (iv) BD = HS activation in amygdala	No association between medication load and abnormal activation in dlPFC or striatum
McIntosh et al. 2008 (58)	Sentence Completion Task	42 BD (adult, type I) 27 SCZ 37 age- and gender-matched HS	BD medicated with Li (n = 21), AP (n = 18), and/or AD (n = 19)	BD > HS activation in OFC and ventral striatum with increasing difficulty	No association between class of medication and any significant cluster
Rich et al. 2008 (53)	Emotional processing of neutral faces	33 BD (type I and II, unspecified mood state) (age range: 7–18) 24 demographically matched HS	27 BD medicated with AP (n = 17), Li (n = 10), AD (n = 10), anticonvulsant (n = 9), STIM (n = 9), and/or sedative (n = 4)	(i) BD < HS FC between L amygdala and R posterior cingulate/precuneus (ii) BD < HS FC between L amygdala and R fusiform/ parahippocampal gyri	(1) No significant relationship between number of medications and connectivity (ii) Results were replicated in youth not receiving a particular medication class versus HS, indicating that results were not driven by medication
Robinson et al. 2008 (46)	Affective Face-matching Task	15 BD (adult, type I, euthymic) 16 demographically matched HS	All BD medicated with anticonvulsant (n = 11), AD (n = 6), and/or atypical AP (n = 7)	(i) BD > HS activation in inferior PFC (ii) BD = HS activation in amygdala	(i) Anticonvulsants versus not showed decreased activation in the inferior PFC (normalizing). Prior to adjustment, BD > HS activation in L inferior PFC. Including anticonvulsants in analysis led to a bilateral increase. (ii) AD versus not showed decreased activation in the amygdala. Including this variable in analysis did not change results.
Strakowski et al. 2008 (63)	Response Inhibition Task (Stop-signal design)	16 BD (adult, type I, manic or mixed) 16 demographically matched HS	8 BD medicated briefly (since the start of hospitalization) with atypical AP (n = 7) and/or AD (n = 2)	(i) BD < HS activation in cingulate gyrus, middle temporal gyrus, precuneus, and medial dorsal thalamus (ii) BD > HS activation in PFC	(i) Medicated < unmedicated activation in amygdala, insula, and parietal lobule (ii) Medicated > unmedicated activation in middle temporal gyrus and precuneus (iii) No medication effects in regions that differed in primary analysis

Table 2. (Continued)

Study	Experimental paradigm	Participants	Medications	Main findings	Medication effects
Curtis et al. 2007 (57)	Phonetic and Semantic tasks (verbal fluency)	12 BD (adult, euthymic) 12 age-, education-, and IQ-matched HS	All BD medicated with only Li	(i) BD > HS activation in L PFC and bilateral cerebellum/fusiform/lingual gyrus during both semantic and phonetic verbal fluency tasks (ii) BD > HS during more difficult tasks	No correlation between Li level and BOLD signal
Marchand et al. 2007 (152)	(i) Paced Motor Activation Task (ii) Stroop Color-naming Task	10 BD (adult, type I) scanned initially during a depressive episode and later when euthymic	All medicated with MS (n = 9), AD (n = 8), and/or atypical AP (n = 5)	(i) BD (depressed) < BD (euthymic) activation in R anterior cingulate and medial frontal gyrus during Non-dominant-hand Paced Motor Activation Task (ii) BD (depressed) = BD (euthymic) during Dominant-hand Paced Motor Task and Stroop task	(i) In those taking atypical AP versus not, increased activation in two clusters (R temporal/parietal and R parietal/occipital/limbic lobes) during Non-dominant-hand Paced Motor Task in the depressed scan (ii) No differences in Dominant-hand Paced Task or Stroop
Nelson et al. 2007 (55)	Response flexibility	25 BD (combined mood state) (age range: 8–17) 17 age-, gender-, and IQ-matched HS	13 BD medicated with atypical AP (n = 11), anticonvulsant (n = 11), Li (n = 6), AD (n = 4), and/or STIM (n = 4)	BD > HS activation in dlPFC and primary motor cortex	Both medicated and unmedicated showed increased activation in dlPFC; only unmedicated showed increased activation in primary motor cortex

BD = bipolar disorder; HS = healthy subjects; SCZ = schizophrenia; MDD = major depressive disorder; ADHD = attention-deficit hyperactivity disorder; SMD = severe mood dysregulation; Li = lithium; AP = antipsychotic; MS = mood stabilizer; AD = antidepressant; STIM = stimulant; BZD = benzodiazepine; R = right; L = left; dlPFC = dorsolateral prefrontal cortex; PFC = prefrontal cortex; vlPFC = ventrolateral prefrontal cortex; vmPFC = ventromedial prefrontal cortex; ACC = anterior cingulate cortex; OFC = orbitofrontal cortex; vPFC = ventral prefrontal cortex; dlPFC = dorsolateral prefrontal cortex; dmPFC = dorsomedial prefrontal cortex; PHG = parahippocampal gyrus; sgCG = subgenual cingulate gyrus; omPFC = orbitomedial prefrontal cortex; pACC = perigenual anterior cingulate cortex; dACC = dorsal anterior cingulate cortex; COMT = catechol-O-methyltransferase; SNP = single nucleotide polymorphism; FC = functional connectivity; 5-HT = serotonin; DTI = diffusion tensor imaging; ROI = region of interest; BOLD = blood oxygen level-dependent; IQ = intelligence quotient.

response to happy/fearful faces has been observed in remitted BD populations (7, 43), whereas increased activation to sad faces has been shown in a depressed BD population (44). Several studies have also shown altered PFC activation with emotional stimuli. While several studies have shown decreased prefrontal activation in participants with BD (12, 47–49), others have shown increased activation (43, 46). Finally, several studies found changes in FC between the orbitofrontal cortex (OFC) and amygdala during the presentation of emotional stimuli. BD populations have shown decreased OFC–amygdala activation in response to happy/fearful (50–52) and neutral (53) stimuli. In response to sad stimuli, some studies have demonstrated an increase in OFC–amygdala connectivity (48, 50), while others have shown a decrease (52).

Most studies have not found any effects of medication presence versus absence (6, 7, 49, 51), class (49, 51–53), or load (43, 47, 48, 52) on the BOLD signal in response to emotional stimuli. Others have found differences, but they have been normalizing; notably, these have all been studies looking at the explicit processing of emotional faces. One such study found that increased medication load was associated with decreased amygdala activation in response to intensely sad faces, which was a normalizing effect (44). In a study that found increased amygdala–OFC connectivity to sad faces, this effect was decreased in those treated with an antidepressant (50). Similarly, in a study that showed increased PFC activation in BD versus HS, anticonvulsants were found to decrease this effect (46). Finally, in a study that showed

decreased OFC–amygdala connectivity to happy faces, there was a trend association ($p = 0.07$) between increased connectivity in those on anti-psychotic agents (52).

It is possible that these normalizing effects might have mitigated differences between individuals with BD and HS, thus leading to a type II error; that is, erroneously accepting the null hypothesis that there is no difference between BD and HS on a particular neuroimaging measure. For example, comparing individuals with BD to HS, Almeida et al. (44) found increased activation in the amygdala in response to mild and neutral faces (under the sad condition), but not intense faces. It is possible that the absence of a finding in the intense faces condition was due to the normalizing effects of medication in this condition, as medication load was negatively correlated with amygdala activation in this condition (but not others).

While none of the main findings (of diagnosis on amygdala or PFC activation) were explained by medication, there were two abnormal findings associated with medication. In a remitted BD population, being treated with an antidepressant (versus not) was associated with elevated amygdala activation to sad faces (although there was no overall difference between the remitted BD population and HS) (44). The authors note that treatment with an antidepressant might be a marker of a depressive tendency (e.g., a history of multiple depressive episodes) that would in turn be associated with increased amygdala activation. In a study that showed decreased PFC activation in BD versus HS, increased medication load was associated with further decreased PFC activation (12). The authors' interpretation of this finding was that increased medication load was associated with a more severe illness course, which was in turn associated with more abnormal findings on fMRI.

Cognitive tasks. During response inhibition/reversal tasks, studies of youth with BD have shown increased activation in the PFC (8, 54, 55). By contrast, studies of adults using reversal tasks have shown decreased PFC activation in BD versus HS (14, 56), although these results are not universal (39). During a verbal fluency task, BD populations have shown increased activation in the posterior cingulate (10, 13) and PFC (57); increased activation in the ventrolateral PFC (vlPFC), striatum, and middle temporal gyrus was found in BD versus HS on a sentence completion task (58). During working memory tasks (delayed non-match to sample, n-back tasks), increased activation has been observed in parts of the PFC (anterior insula, prefrontal gyrus), anterior cingulate cortex, and amygdala, while decreases have been observed in

other parts of the PFC (frontopolar cortex) (15, 59, 60).

No associations between psychotropic medication and the BOLD signal were found on language tasks (10, 13, 57, 58), the delayed reward task (61), or working memory tasks (15, 59, 60). For response inhibition/reversal paradigms, most studies showed no effect of medication class (8, 14, 56, 62). The observed effects of medication were either normalizing in nature or in areas outside the region of interest. For example, in a study that found increased activation in the dorsolateral PFC (dlPFC) on a Go/NoGo task, lithium use was associated with increased cerebellar activation, and antipsychotic agent use was associated with increased activation in the precuneus and right anterior cingulate cortex; no medications were associated with dlPFC activation (54). In another study, medication use was associated with increased activation in the middle temporal gyrus and precuneus, and decreased activation in the amygdala, insula, and parietal lobule (63). These effects appear normalizing, although the authors point out that medication effects were not observed in the specific areas found to differ between those with BD and HS. The authors also emphasize that the analysis does not account for multiple comparisons, and is exploratory; thus, the interpretation of effects is limited (63). Regarding declarative memory tasks, one study showed no effect of medication class on the region of interest (dlPFC) (9); a second study found no effect of mood stabilizer on the region of interest (dlPFC), but did find a correlation between dose of antipsychotic agent and dlPFC activation (normalizing) (64).

Cognitive tasks in the presence of emotional stimuli. During cognitive tasks with emotional components, manic and remitted BD adults had decreased prefrontal activation (vlPFC, inferior frontal, premotor) (65, 66), while one study found depressed BD adults to have increased prefrontal activation (dlPFC) (67). Most studies found no effect of medication class or dose on the results (66–68). One study found differences in lithium-treated versus non-lithium-treated, and anticonvulsant-treated versus non-anticonvulsant-treated patients, but these were not in the regions of interest, and removing these participants from the study did not affect the results (65).

fMRI results: prospective clinical trials

Several fMRI studies have assessed the effect of psychotropic medications prospectively, to compare brain activation before and after medication (Table 3). A number of such studies have shown

changes, which have been primarily normalizing. Multiple studies have shown differences between BD and HS in PFC and temporal regions at baseline that either diminished or disappeared with several weeks of lamotrigine therapy (69–71). For example, on a response inhibition task, Pavuluri et al. (69) found decreased prefrontal activation in youth with BD relative to HS at baseline; these differences were normalized after 14 weeks of therapy with lamotrigine. Of note, clinical improvement of manic symptoms was correlated with an increase in vPFC activation at follow-up versus baseline (69). Another study by Haldane et al. (72) found a number of changes with lamotrigine treatment during both cognitive and emotional tasks (in the PFC, cingulate gyrus, middle frontal gyrus, and thalamus). While it is unclear whether these changes were normalizing (due to the absence of a HS group), the direction of the finding in the PFC (increased after medication versus at baseline) is consistent with normalizing effects seen in other studies. Other longitudinal studies have found a correlation between clinical improvement and changes in the amygdala (with lamotrigine) or PFC (with divalproex) (37, 73). It is not clear whether these changes are effects of the particular medications used or an indication of general clinical improvement.

DTI results

DTI studies measure fractional anisotropy (FA) to understand structural connectivity in white matter (WM) tracts (74). Specifically, decreased FA means that the ratio of longitudinal to radial diffusivity is decreased, suggesting that the WM tract is compromised. Reviewed DTI studies are shown in Table 4.

In studies that compared individuals with BD in a depressed mood state, FA was decreased compared to HS in several regions, including the corpus callosum, corona radiata, superior longitudinal fasciculus, uncinate fasciculus, anterior thalamic radiation, and anterior cingulum (51, 75–84); only one study that included symptomatic individuals in the BD group showed increased FA in the uncinate fasciculus, optic radiation, and anterior thalamic radiation (85). In remitted BD versus HS groups, results have been less consistent; two studies showed increased FA (86, 87), one showed no effect (77), and one showed decreased FA in the corpus callosum (88). These results indicate that BD groups (especially those that are depressed) have decreased coherence and directionality of WM tracts connecting the right and left hemisphere (corpus callosum), as well as those connect-

ing the frontal lobe to other parts of the brain (uncinate fasciculus, superior longitudinal fasciculus, anterior thalamic radiation, and anterior cingulum) (74).

Most studies show no significant effect of medication status (class, dose, number, and/or load) on FA (51, 76–84, 86, 87). A few studies have shown normalizing effects. Specifically, in a study by Macritchie et al. (88) that showed decreased FA values in BD versus HS, lithium-treated subjects demonstrated increased FA relative to those who did not receive lithium. In a study that showed increased FA in anterior thalamic and optic radiations in BD versus HS, those treated with a mood stabilizer (versus not) showed decreased FA in these WM tracts (85). Finally, in a study that showed decreased FA in the anterior limb of the internal capsule in BD versus HS, lithium versus non-lithium-treated subjects showed a trend toward increased FA values in this WM tract (80).

Only one study has found abnormalities in the medicated, but not unmedicated, subjects. This study showed decreased FA values in BD versus HS, and these differences were observed in the subset treated with lithium, but not in those who were unmedicated (75). The authors point out that the lithium-free group still showed abnormalities in radial and mean diffusivity relative to HS; however, the FA finding was not significant in the non-medicated group. In addition, the lithium and non-lithium groups did not differ from each other statistically on measures of FA or diffusivity. While the authors could not rule out the possibility that such a difference was due to a toxic effect of lithium, alternative explanations include type II error (due to lack of power in the lithium-free group to detect a difference), or the possibility that lithium treatment is a marker of a more severe disease course.

Discussion

Most neuroimaging studies in patients with BD using secondary analyses have not found an effect of psychotropic medication exposure status on neuroimaging results. As discussed above, these post-hoc analyses have usually been underpowered to fully assess the impact of medications on imaging data. In many cases, the subgroups that were being compared (e.g., medicated versus non-medicated, or lithium-treated versus non-lithium-treated) had very small numbers (as small as $n = 2$), so it would be incorrect to conclude that medications do not have effects based on the fact that no significant differences were observed. In other cases, several types of medication were grouped together (either

Medication effects on neuroimaging in bipolar disorder

Table 3. Medication effects in functional magnetic resonance imaging (fMRI) studies (longitudinal studies)

Study	Experimental paradigm	Participants	Medications	Medication effects
Pavuluri et al. 2010 (70)	Affective Color Matching Task	17 BD (type I or II, manic/hypomanic/mixed) (age range: 10–18) 14 demographically matched HS	BD initially unmedicated; all given atypical AP × 4 weeks and LTG × 14 weeks	(i) At baseline, BD > HS activation in cognitive regions (e.g., dlPFC) and emotion-regulation regions (e.g., vlPFC, vmPFC) (ii) With medication, all hyper-activation reduced to some degree (BD = HS in vlPFC; BD < HS in dlPFC; BD > HS in vmPFC) (iii) Improvement in manic symptoms correlated with decrease in vmPFC activation
Pavuluri et al. 2010 (69)	Response Inhibition Task	13 BD (type I or II, manic/hypomanic/mixed) (age range: 10–18) 13 demographically matched HS	BD initially unmedicated; all given atypical AP × 4 weeks and LTG × 14 weeks	(i) At baseline, BD < HS activation in PFC, which normalized (BD = HS) at 14 weeks (ii) BD > HS activation in motor cortex at baseline and 14 weeks (iii) BD < HS activation in thalamus and putamen at 14 weeks, but not at baseline (driven by increased activation in HS) (iv) Improvement in manic symptoms correlated with increase in bilateral vlPFC and inferior frontal gyri
Chang et al. 2009 (37)	Emotional rating of negative, positive, and neutral objects	6 BD (subsyndromal, with first-degree BD relative, manic or depressed) (age range: 9–18) 5 group-matched HS	2 BD initially medicated with AD (n = 1) or stimulant (n = 1); all given divalproex × 12 weeks	(i) BD (subsyndromal) = HS activation in dlPFC and amygdala, both at baseline and at 12 weeks (ii) Decrease in prefrontal brain activation over 14 weeks correlated with decrease in depressive symptoms
Chang et al. 2008 (73)	Emotional rating of negative, positive, and neutral objects	8 BD (type I/II/NOS, depressed) (age range: 13–17)	All given LTG × 8 weeks	(i) Clinical improvement over 8 weeks correlated with decreased R amygdalar activation (ii) Depression severity score correlated with bilateral amygdalar activation at 8 weeks, but not at baseline
Jogia et al. 2008 (71)	Sad Affect Recognition Task	12 BD (adult, type I, unspecified mood state) 12 demographically matched HS	All BD titrated off medications prior to study and given LTG × 12 weeks	(i) At baseline, BD > HS activation in temporal regions and BD < HS activation in PFC (dorsal medial and ventrolateral) and dorsal cingulate gyrus (ii) Compared to baseline, BD after 12 weeks of LTG had decreased activation in temporal regions and increased activation in PFC (normalizing) (iii) No correlation between depression severity score and observed changes in frontal or temporal regions
Haldane et al. 2008 (72)	(i) N-back Task (ii) Angry Affect Recognition Task	12 BD (adult, type I, unspecified mood state)	All BD titrated off medications prior to study and given LTG × 12 weeks	Compared to baseline, BD after 12 weeks of LTG had increased activation in medial PFC and cingulate gyrus during the N-back Task, and increased activation in R middle frontal gyrus and thalamus during Angry Affect Recognition Task

BD = bipolar disorder; HS = healthy subjects; NOS = not otherwise specified; AP = antipsychotic; LTG = lamotrigine; AD = antidepressant; dlPFC = dorsolateral prefrontal cortex; vlPFC = ventrolateral prefrontal cortex; vmPFC = ventromedial prefrontal cortex; PFC = prefrontal cortex.

Table 4. Medication effects in diffusion tensor imaging (DTI) studies

Study	Participants	Medications	Main findings	Medication effects
Benedetti et al. 2011 (75)	40 BD (adult, type I, depressed) 21 HS	14 with Li only	(i) BD < HS FA values in corpus callosum and corona radiate (ii) BD > HS diffusivity in corpus callosum, corona radiate, superior longitudinal fasciculus, and thalamic radiation	(i) No differences between medicated versus unmedicated on FA or diffusivity (ii) Increased diffusivity seen in both medicated and unmedicated groups, relative to HS (iii) Decreased FA seen in medicated group, but not unmedicated group, relative to HS
Macritchie et al. 2010 (88)	28 BD (adult, type I or II, euthymic) 28 demographically matched HS	26 medicated with Li (n = 16), anticonvulsants (n = 9), and/or AP (n = 6)	BD < HS FA values in 13 of 15 ROIs (in corpus callosum and deep/periventricular WM), and increased diffusivity in all 15 ROIs	(i) Non-Li versus Li-treated showed decreased FA values and increased diffusivity (ii) Decreased FA seen in both Li and non-Li treated groups, relative to HS (iii) Increased diffusivity seen in non-Li treated group, but not Li treated group, relative to HS
Versace et al. 2010 (76)	15 BD (adult, type I, depressed) 16 MDD (depressed) 24 HS	BD medicated with MS (n = 10), AP (n = 10), AD (n = 8), and/or BZD (n = 6)	(i) BD < HS FA values in L superior longitudinal fasciculus (primary sensory cortex) (ii) BD < MDD FA values in L superior longitudinal fasciculus (inferior temporal cortex)	No relationship between medication load or class and FA values
Barnea-Goraly et al. 2009 (78)	21 BD (unspecified mood state, with at least one BD parent) (age range: 9–18) 18 age- and IQ-matched HS	BD medicated with MS (n = 22), SSRI (n = 15), stimulant (n = 15), and/or AP (n = 7)	(i) BD < HS FA values in fornix, posterior cingulate gyrus, corpus callosum, fornix to thalamus, and corona radiate (ii) BD = HS diffusivity	No correlation between medication exposure and FA values
Chaddock et al. 2009 (79)	19 BD (adult, type I, predominantly euthymic, from multiple-affected families) 21 first-degree relatives 18 HS	15 BD medicated with Li (n = 9), anticonvulsants (n = 8), AD (n = 5), and/or AP (n = 3)	(i) BD < HS FA values in the corpus callosum, inferior and superior longitudinal fasciculus (ii) First-degree relatives showed FA values intermediary between BD and HS	No difference between unmedicated and medicated on FA values; did not look at effect of class or dose
Sussmann et al. 2009 (80)	42 BD (adult, type I, unspecified mood state, from multiple-affected families) 28 SCZ 38 HS	BD medicated with Li (n = 24), AD (n = 21), and/or AP (n = 19)	BD/SCZ < HS FA values in the anterior limb of the internal capsule, uncinate fasciculus, and anterior thalamic radiation	(i) No significant associations between class of medication and FA values. (ii) Nonsignificant association between Li and increased FA values in the anterior limb of the internal capsule (p = 0.082)
Wang et al. 2009 (51)	33 BD (adult, type I, unspecified mood state) 31 HS	27 BD medicated with anticonvulsant (n = 16), atypical AP (n = 14), AD (n = 12), Li (n = 9), and/or BZD (n = 7)	(i) BD < HS FA values in ventrofrontal WM (including uncinate fasciculus) (ii) Correlated with decreased amygdala–pACC functional connectivity	No effect of medication status (medications overall or class) on FA values

Medication effects on neuroimaging in bipolar disorder

Table 4. (Continued)

Study	Participants	Medications	Main findings	Medication effects
Wessa et al. 2009 (86)	22 BD (adult, type I or II, euthymic) 21 age- and sex-matched HS	18 BD medicated with anticonvulsant (n = 11), Li (n = 10), AD (n = 6), and/or atypical AP (n = 5)	(i) BD > HS FA values in medial frontal, precentral, inferior parietal, and occipital areas (ii) BD = HS diffusivity	No association between medication class, Li dose, or duration of medication and FA values
Zanetti et al. 2009 (77)	37 BD (adult, type I, 16 depressed/21 euthymic) 26 HS	<u>Depressed/euthymic BD medicated with (n):</u> AP (8/11), AD (7/9), Li (6/6), anticonvulsant (6/5), BZD (6/4), and/or LTG (5/0)	BD (depressed) < BD (euthymic)/HS FA values in prefronto-limbic-striatal areas, superior and inferior longitudinal fasciculi	No correlation between medication load and FA values or diffusivity
McIntosh et al. 2008 (82)	40 BD (adult, unspecified mood state, from multiple-affected families) 25 SCZ 49 HS	BD medicated with Li (n = 22), AP (n = 18), and/or AD (n = 21)	BD/SCZ < HS FA values in uncinate fasciculus and anterior thalamic radiations	No association between Li, AP, or AD use and FA values
Versace et al. 2008 (85)	31 BD (adult, type I, 17 depressed/14 euthymic) 25 HS	BD medicated with MS (n = 22) [including Li (n = 11)], AP (n = 17), AD (n = 15), and/or BZD (n = 12)	(i) BD > HS FA values in L uncinate fasciculus, L optic radiation, and R anterior thalamic radiation (ii) BD < HS FA values in R uncinate fasciculus	(i) Negative correlation between medication load and FA values in the L optic radiation (ii) MS versus non-MS treated BD showed decreased FA values in the L optic radiation and R anterior thalamic radiation (iii) No effect of other classes of medication
Wang et al. 2008 (83)	42 BD (adult, unspecified mood state) 42 HS	35 BD medicated with anticonvulsant (n = 20), atypical AP (n = 19), AD (n = 17), Li (n = 11), BZD (n = 8), and/or levothyroxine (n = 5)	BD < HS FA values in anterior, but not posterior, cingulum	No association between medication status and FA values
Wang et al. 2008 (81)	33 BD (adult, unspecified mood state) 40 HS	27 BD medicated with anticonvulsant (n = 17), atypical AP (n = 16), Li (n = 8), and/or BZD (n = 8)	BD < HS FA values in anterior and middle corpus callosum	No association between medication and FA values
Frazier et al. 2007 (84)	10 BD (type I, unspecified mood state) (age range: 4–12) 7 AR (unaffected children with first-degree BD relative) 8 HS	BD all medicated on AP (n = 8), anticonvulsant (n = 5), AD (n = 3), atomoxetine (n = 3), and/or alpha agonist (n = 2)	(i) BD < HS FA values in corpus callosum, cingulum, orbitofrontal WM (ii) BD/AR < HS FA values in superior longitudinal fasciculus	No correlation between no. of medications and FA values
Yurgelun-Todd et al. 2007 (87)	11 BD (adult, type I, euthymic) 10 age- and sex-matched HS	9 BD medicated with anticonvulsant (n = 6), AP (n = 4), AD (n = 3), and/or Li (n = 3)	BD > HS FA values in corpus callosum (genu, not splenium)	No association between AP medication (presence versus absence) and FA values

BD = bipolar disorder; HS = healthy subjects; MDD = major depressive disorder; SCZ = schizophrenia; AR = at risk; Li = lithium; AP = antipsychotic; MS = mood stabilizer; AD = antidepressant; BZD = benzodiazepine; SSRI = selective serotonin reuptake inhibitor; FA = fractional anisotropy; ROI = region of interest; WM = white matter; pACC = perigenual anterior cingulate cortex; IQ = intelligence quotient.

as a dichotomous variable or a score of medication load), which could obscure class-specific differences. Analyses focus on current medications and do not take into account duration or past use, which might also impact study findings. Despite these limitations, several studies using post-hoc analyses have found differences based on medication status, and these have largely indicated that medication exposure tends to mitigate the observed differences between BD and HS groups. This suggestion is consistent with a growing literature of prospective clinical trials, which have shown effects of medication on volumetric measures and the BOLD signal that are generally normalizing.

The most consistent finding in the literature so far is the impact of lithium on morphometric MRI findings. Multiple studies have indicated that lithium normalizes or increases gray matter volume, particularly in areas important for subserving emotion processing and mood regulation (the amygdala, hippocampus, and anterior and subgenual cingulate cortex). These results are consistent with a previous meta-regression of 55 studies and 700 subjects (before 2008), that found a positive correlation between the proportion of subjects taking lithium and gray matter volume (89). This concept is further supported by a growing literature showing the *in vitro* neurotrophic effects of lithium (90, 91). However, it should be noted that the majority (55%) of sMRI studies reviewed here did not find any significant effects of current lithium treatment. There are many possible reasons for these negative findings, as discussed previously. It is also possible that lithium had no effect on the particular structures studied, as little is known about the regional specificity of lithium. Despite these limitations in the data, lithium remains the best examined medication in this regard and appears to promote increases in regional gray matter volume or prevent decreases in volume.

Of note, atypical antipsychotic agents, anticonvulsants, and antidepressants were generally not associated with volumetric differences in the studies included in this review. These results are somewhat surprising, given previous findings in related literature. For example, antipsychotic agents have been previously reported to affect striatal volumes, predominantly in patients with psychotic disorders and mostly associated with increases in volume (92). In the current review, only two studies specifically measured striatal volume, but neither found an effect of antipsychotic agent exposure on volume (28, 93). Regarding anticonvulsants, preclinical evidence has pointed to neurotrophic and neuroprotective attributes of valproate (91); these effects were not

corroborated in this review. Finally, antidepressants have been previously shown to normalize hippocampal volumes in depressed populations (94), which we did not find in populations with BD. The absence of such findings in populations with BD may reflect illness \times treatment interactions; that is, medications may have different effects on different populations. These negative results could also be due to the limitations of the studies reviewed, as discussed above.

Medication confounds in neuroimaging research present similar challenges in other psychiatric disorders (e.g., schizophrenia), which have been addressed using similar strategies: recruiting unmedicated populations, adjusting for medications in analysis, and conducting longitudinal studies to assess medication effects (95, 96). fMRI studies in other psychiatric disorders have also found the effects of medication to be predominantly normalizing. For example, antidepressants have been shown to reverse deficits observed in MDD, leading to increased cortical activation, decreased limbic activation, and increased corticolimbic connectivity (97–99). Similarly, a growing body of literature indicates that atypical antipsychotic agents tend to increase the BOLD signal in the PFC, reversing the deficit observed in schizophrenia (95, 96, 100). In fact, one study found that atypical antipsychotic agents not only reversed deficits in frontal activation observed in unmedicated schizophrenia, but also led to increased activation relative to HS (100). Thus, medications have been primarily found to be normalizing in other disorders, but could overcorrect for deficits and potentially lead to effects in the opposite direction.

The prevailing concern with medication exposure in these studies has been that such exposure may be causing type I errors; that is, erroneously accepting the alternative hypothesis that a difference between BD and HS exists (due to medication effects). Based on the results of the studies reviewed, this does not seem to be the case. In studies using secondary analyses, the vast majority of differences seen between medicated and unmedicated subjects indicated either (i) changes in areas that were not the primary areas of differences seen between BD and HS or (ii) changes that make medicated BD individuals more similar to HS on BOLD or FA in regions of interest. Sensitivity analyses performed by a number of investigators (e.g., progressively excluding each class of medications) indicated that differences persist, regardless of whether a particular class of medication was removed. Prospective clinical trials also indicated that medications do not seem to cause differences between BD and HS in regions of interest, but

rather tend to be normalizing. Findings from other psychiatric disorders corroborate that antidepressants and antipsychotic agents tend to have normalizing effects, although the possibility that atypical antipsychotic agents might overcorrect observed deficits (as in schizophrenia) should be considered.

A more compelling, but often overlooked, concern is whether including medicated patients in neuroimaging studies leads to type II error. Medication exposure may affect the brain so as to obscure an underlying difference between patients with BD and HS. As we found that medication effects tend to be normalizing in patients with BD, it is likely that previously published or unpublished studies reporting *negative* findings were affected in this way. Given that a number of studies have shown that medicated BD individuals are more similar to HS than their unmedicated counterparts, this concern is indeed valid. It is possible that including medicated participants would lead to fewer observed differences between BD and HS groups. This should be a consideration when interpreting the negative findings of neuroimaging studies. To better understand the particular effects of psychotropic medications, there is a need for further prospective studies of medication effects on neuroimaging results.

Every study design has limitations, and there is no perfect method for assessing the impact of medication on neuroimaging findings. However, based on a review of this literature, we recommend the following:

- At a minimum, it is important to provide adequate documentation of medication status and methodology. An investigator should report the types of medications that participants are taking, and the specific variable (medication status versus medication type, etc.) that was used in the analysis. Optimally, past exposure to psychotropic medications should also be recorded and taken into account, since prolonged exposure to medication can lead to measurable effects on morphometry, and potentially WM development and brain activation.
- As discussed above, the most convincing secondary analysis is to replicate the finding in the subset of unmedicated individuals (versus HS). If this is not possible (due to too few unmedicated participants), we recommend a sensitivity analysis approach of removing individuals on a particular class of medication, and repeating the primary analysis. Even if the results of all analyses are not statistically significant, it

would be reassuring if they are qualitatively similar. Secondary analyses to assess the impact of medication status, type, or dose on neuroimaging parameters are less helpful, since it is likely that negative results are due to low statistical power.

- Ideally, studies should take medication status into account when recruiting subjects, so that meaningful secondary analyses can be conducted. For example, if approximately one-third of the study population is taking lithium, one-third antipsychotic agents, and one-third valproic acid, convincing sensitivity analyses can be done by progressively excluding each medication type, and assessing differences between BD and HS.
- Prospective clinical trials designed to assess the impact of medications should compare the impact of more than one medication to distinguish specific medication effects from general clinical improvement. Such trials should also have HS to assess whether observed changes are normalizing and, for fMRI, to assess the effects of repeated scanning on brain activation.
- Naturalistic studies designed to assess the impact of medication on neuroimaging parameters over time would be helpful for assessing the long-term effects of medications. Such studies would ideally include multiple imaging modalities (fMRI, DTI, and sMRI) to better understand the relationship between structural and functional changes caused by medication.
- Given the demonstrated effects of lithium on brain volume, a recommended direction of inquiry would be to more fully characterize these effects in terms of their regional specificity, mechanism, dependence on duration of treatment, etc. In addition to neurotrophic effects, lithium-induced volumetric increases might also be due to water shifts, a hypothesis that could be more fully explored by combining sMRI and DTI methodologies.

A previously published review of studies from 1996–2007 indicated that the effects of medication on neuroimaging findings were generally either absent or normalizing in nature. The current review adds to the literature by reviewing the tremendous number of studies that have been published since 2007 that conducted a secondary analysis on medication effects. Similar to previous findings, the results from the current review indicate that most studies have not found significant effects of medication, and the effects that have been found have been normalizing in nature. Additionally, the current review includes studies utilizing

DTI, a technique for which medication effects have not previously been compiled. Finally, the current review includes new prospective clinical trials which are able to provide additional evidence that medication effects appear to be normalizing.

Only including unmedicated BD populations presents significant problems of feasibility, generalizability, and ethical considerations. While studies with unmedicated participants provide valuable information, studies of medicated individuals are essential to assess neuroimaging findings in a population with a more clinically severe, and arguably more representative, course of illness. The preponderance of evidence indicates that medication effects are unlikely to explain the observed differences between BD and HS on neuroimaging parameters. However, medication use should always be considered to be a potential confound, as it might have different effects on new tasks or new modes of analysis. Additionally, further studies designed to assess the impact of medication over time are essential to better understand the effects of medication in this population.

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