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Mood stabilizer treatment increases serotonin type 1A receptor binding in bipolar depression

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Abstract

Abnormal serotonin type 1A (5-HT_{1A}) receptor function and binding have been implicated in the pathophysiology of mood disorders. Preclinical studies have consistently shown that stress decreases the gene expression of 5-HT_{1A} receptors in experimental animals, and that the associated increase in hormone secretion plays a crucial role in mediating this effect. Chronic administration of the mood stabilizers lithium and divalproex (valproate semisodium) reduces glucocorticoid signaling and function in the hippocampus. Lithium has further been shown to enhance 5-HT_{1A} receptor function. To assess whether these effects translate to human subject with bipolar disorder (BD), positron emission tomography (PET) and [18F]trans-4-fluoro-N-(2-[4-(2-methoxyphenyl) piperazino]-ethyl)-N-(2-pyridyl) cyclohexanecarboxamide ([^{18}F]FCWAY) were used to acquire PET images of 5-HT_{1A} receptor binding in 10 subjects with BD, before and after treatment with lithium or divalproex. Mean 5-HT_{1A} binding potential (BP_P) significantly increased following mood stabilizer treatment, most prominently in the mesiotemporal cortex (hippocampus plus amygdala). When mood state was also controlled for, treatment was associated with increases in BP_P in widespread cortical areas. These preliminary findings are consistent with the hypothesis that these mood stabilizers enhance 5-HT_{1A} receptor expression in BD, which may underscore an important component of these agents' mechanism of action.

Keywords

Positron-emission tomography; lithium; valproic acid; serotonin type 1A receptor; bipolar disorder

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Introduction

Serotonin type 1A (5-HT_{1A}) receptor function has been implicated in the pathophysiology of both bipolar disorder (BD) and major depressive disorder (MDD). Furthermore, the effects of chronic lithium and divalproex (valproate semisodium) treatment on neuroendocrine function in patients with BD suggest that mood stabilizing medications enhance post-synaptic 5-HT_{1A} receptor function (reviewed in Drevets et al., 2007; Savitz et al., 2009). In humans, genetic variation in the 5-HT_{1A} receptor gene (HTR1A; rs6295) that putatively reduces post-synaptic 5-HT_{1A} receptor expression (Drevets et al., 2007; Le Francois et al., 2008; Szewczyk et al., 2009) has been associated with increased risk for developing BD, MDD (Lemonde et al., 2003), and major depressive episodes following interferon treatment (Kraus et al., 2007) or hip fracture (Lenze et al., 2008). In addition, the single nucleotide polymorphism (SNP) rs6295 on the 5-HT_{1A} gene has been associated with BD in a meta-analysis of Japanese samples (Kishi et al., 2011). Moreover, epigenetic studies have demonstrated increased peripheral DNA methylation in the promotor region of HTR1A in BD (Carrard et al., 2011).

In unmedicated individuals with BD, post-synaptic 5-HT_{1A} receptor binding (measured as binding potential, BP) reportedly differs with respect to healthy controls. For instance, 5-HT_{1A} receptor density was significantly decreased in the prefrontal cortex in a postmortem study of BD subjects versus controls (Gray et al., 2006). Another post-mortem study found that 5-HT_{1A} mRNA expression was decreased in the dorsolateral prefrontal cortex and hippocampus of MDD subjects, and that BD subjects showed non-significant trends in the same direction versus controls (Lopez-Figueroa et al., 2004). Using positron emission tomography (PET) and [^{11}C]carbonyl-WAY100635, an initial series demonstrated that 5-HT_{1A} binding potential (BP_{ND}, the ratio of specifically bound to nondisplaceable radioligand) was reduced in the mesiotemporal cortex (MTC) and other regions in unmedicated depressed subjects with BD or bipolar spectrum disorder who also showed significantly elevated stressed plasma cortisol levels relative to controls (Drevets et al., 1999, 2007; Moses-Kolko et al., 2007). More recently, we assessed 5-HT_{1A} receptor binding in unmedicated BD subjects (n=26) and healthy controls (n=37) using PET and the highly selective 5-HT_{1A} radioligand [18F] trans-4-fluoro-N-(2-[4-(2-methoxyphenyl) piperazino]-ethyl)-N-(2-pyridyl) cyclohexanecarboxamide ([^{18}F]FCWAY); in the MTC the mean BP_P (ratio of specifically bound radioligand to plasma radioligand) value was significantly lower in BD subjects versus controls, and individual BP_P values were inversely correlated with trough plasma cortisol levels (Nugent et al., in press). In contrast, another study that assessed 5-HT_{1A} receptor binding using PET and [^{11}C] carbonyl-WAY100635 reported that the BP_F (ratio of specifically bound radioligand to free radioligand in tissue) was increased in BD subjects versus controls, although this study did not include measures of cortisol secretion (Sullivan et al., 2009). Notably, Sargent and colleagues found no abnormalities in 5-HT_{1A} receptor binding in euthymic BD subjects who were currently medicated with psychotropic medications; most were receiving either lithium or divalproex, suggesting that effective mood stabilizing treatment normalizes 5-HT_{1A} expression (Sargent et al., 2010).

The effects of lithium and divalproex on neuroendocrine function or 5-HT metabolites suggest that they enhance serotonergic neurotransmission (Price et al., 1990). In patients with mood disorders, lithium treatment enhanced plasma prolactin response to L-tryptophan (Cowen et al., 1991) as well as plasma cortisol response to fenfluramine, suggesting increased 5-HT neurotransmission (Mannel et al., 1997; Muhlbauer and Muller-Oerlinghausen, 1985). The addition of lithium to antidepressant drug treatment increased plasma 5-HIAAA (5-hydroxyindoleacetic acid, the main metabolite of serotonin) concentrations in depressed subjects with MDD, suggesting enhanced 5-HT turnover, although platelet and plasma 5-HT did not change (Birkenhager et al., 2007). Subchronic

divalproex administration attenuated the hypothermia induced by ipsapirone without affecting the associated increase in ACTH/cortisol release in healthy volunteers (Shiah et al., 1997), but increased the serotonin precurser L-5-hydroxy-tryptophan (L-5-HTP) induced cortisol response in manic subjects, suggesting that divalproex enhances central 5-HT neurotransmission in BD (Maes et al., 1997). These effects may be mediated at the receptor level rather than the post-receptor level, as divalproex did not affect 5-HT-induced calcium mobilization in the platelets of healthy volunteers (Kusumi et al., 1994). Notably, post-synaptic 5-HT_{1A} receptor stimulation plays a role in ACTH and cortisol release (reviewed in Lesch et al., 1990; Li et al., 2004; Savitz et al., 2009); therefore, these data collectively support the hypothesis that post-synaptic 5-HT_{1A} receptor function increases in BD subjects following treatment with lithium or divalproex.

The current preliminary study investigated whether treatment of a small group of BD subjects with lithium and/or divalproex would be associated with increases in post-synaptic 5-HT_{1A} receptor BP_{ND}, as measured via PET. This is the first study to use a longitudinal design to measure treatment effects on 5-HT_{1A} receptor binding in BD subjects, and the results may further elucidate the mechanism of action of mood stabilizing drugs.

Methods and materials

Patients and controls

This research was funded and carried out under the National Institute of Mental Health (NIMH) Intramural Research Program (IRP). Subjects were informed regarding the purpose of the study and the risks involved, and gave written consent as approved by the National Institutes of Health (NIH) Combined Neuroscience Institutional Review Board and the NIH Radiation Safety Committee. The participants (n=10; 9 female; mean age 34±11.4 years, range 23–54 years) met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR; APA, 2000) criteria for either BD-I, most recent episode depressed, or BD-II, most recent episode depressed. In addition, all BD patients met criteria for a current major depressive episode, and no subject met DSM-IV-TR criteria for a “mixed bipolar” episode based on DSM-IV-TR criteria. Diagnosis was established by both an unstructured diagnostic interview conducted by a psychiatrist (authors PJC, EEB, or WCD) and the Structured Clinical Interview for DSM-IV-TR (First et al., 2002). Volunteers were excluded from participation if they had: exposure to psychotropic medications within the three weeks prior to the first PET scan; a history of substance dependence (excluding nicotine); a history of substance abuse within six months; laboratory evidence of hepatic, thyroid, or renal impairment; a positive urine pregnancy test; or were currently pregnant or nursing. Female subjects were not scanned during a specific menstrual phase so that treatment of acute depressive symptoms was not delayed. Previous studies have not shown significant differences in 5-HT_{1A} binding between menstrual phases (Jovanovic et al., 2006, 2009).

Following the baseline scan, participants were treated with lithium and/or divalproex for at least three months prior to the post-treatment scan; choice of drug was guided by patient history and clinical issues (divalproex, or valproate semisodium, is a compound of sodium valproate and valproic acid). Drug dosage was guided using conventional clinical guidelines and therapeutic blood monitoring (American Psychiatric Association, 2002). One subject also received bupropion to manage depressive symptoms, which was not expected to significantly alter 5-HT_{1A} binding. Clinical depression and mania symptoms were assessed using the Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979) and the Young Mania Rating Scale (YMRS: Young et al., 1978) on both days of PET scanning. Baseline PET data from all subjects were previously published as part of a

larger sample of BD patients whose 5-HT_{1A} receptor binding potentials were compared to those of healthy controls (Nugent et al., in press).

PET image acquisition

PET scans were acquired with a GE Advance tomograph (35 contiguous slices, 4.25 mm plane separation; reconstructed resolution=7 mm full-width at half-maximum (FWHM) in all planes) (DeGrado et al., 1994). A transmission scan was performed to enable attenuation correction; a 120-minute dynamic emission scan then was initiated following intravenous bolus administration of approximately 8 mCi of [^{18}F]FCWAY. All scans were performed between 10:00–13:30, and the largest difference in time of day between a patient's pre-treatment and post-treatment scans was 1 h 17 min.

Arterial input function

Whole blood and plasma radioactivity were measured during PET scanning by radial artery sampling. The method of parent compound and metabolite concentrations was performed as previously described (Nugent et al., in press). The fraction of parent radioligand in plasma that was unbound by plasma proteins (f_p) was determined from a blood sample drawn from each subject prior to tracer infusion, to which parent radioligand was added.

Magnetic resonance (MR) anatomical imaging

To provide an anatomical framework for the PET data analysis, whole brain anatomical images were obtained with a GE Sigma Scanner (3.0 Tesla) and a 3D MPRAGE sequence (Echo time, TE=2.982 ms, repetition time, TR=7.5 ms, inversion time=725 ms, voxel size=0.9×0.9×1.2 mm). Non-brain tissues were removed from the brain images using either a combination of the brain extraction tool (BET) (Smith, 2002) and manual editing, or the Analysis of Functional NeuroImages (AFNI) tool 3dSkullStrip (NIMH, NIH, Besthesda, Maryland, USA). The resulting whole brain images were segmented into gray matter, white matter, and cerebrospinal fluid (CSF) components using the FMRIB automated segmentation tool (FAST) (Zhang et al., 2001), and separate binary mask images were created for each component.

PET image processing and analysis

Individual dynamic PET images were corrected for motion and attenuation and then coregistered with the anatomical MR image. Partial volume correction (PVC) was applied with the Muller-Gartner et al. (1992) method. PVC was applied frame by frame with the mean white matter value estimated as per Giovacchini and colleagues (2005). Images were corrected for intravascular activity (5%), for the partial volume effects of skull activity from [^{18}F]fluoride, and for the [^{18}F]FC metabolite as described by Carson and colleagues (2003). Tissue time-radioactivity curves were then generated on a voxel-wise basis and fitted to a four-parameter, two-tissue compartment model with one parameter fixed for rapid parametric image calculation (Carson et al., 2002). The distribution volume (V_T) was calculated as $V_T = K_1/k_2 \cdot (1 + k_3/k_4)$, where K_1 is the rate constant for transfer from arterial plasma to tissue, and the remaining k rate constants represent transfer rates between tissue compartments.

Image analysis

Regions of interest (ROI) were defined in structures with abundant post-synaptic 5-HT_{1A} receptor concentrations on a template image, then transferred to a co-registered magnetic resonance image (MRI) and adjusted to accommodate individual anatomy. Regions were defined in the left and right (L and R) mesial temporal cortex (MTC, hippocampus plus amygdala), anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), anterior

insula (AI), and parieto-occipital cortex (POC), as described by Neumeister and colleagues (2004). The ROI were then transformed from the stereotaxic space of the template back to the original space of the subject's MRI and applied to the V_T image. The V_T value for each ROI was defined as the mean V_T value for all gray matter voxels within that ROI, using the binary gray matter mask derived from the MRI. Regions normally of interest lying close to the skull (e.g. orbital cortex, temporal polar cortex) could not be examined because the [^{18}F]fluoride secondary metabolite of [^{18}F]FCWAY is largely taken up by bone in [^{18}F] FCWAY images.

The anatomical boundaries of the raphe nucleus are not clearly evident in MR images, so the ROI for measuring radioactivity in this structure was defined directly on PET images (Drevets et al., 1999; Toczek et al., 2003). A cylindrical ROI (9 mm diameter, 4.8 mm height) was positioned over the raphe in the V_T image with the inferior-most aspect situated at the midbrain/pontine junction. The raphe V_T values were measured by applying the ROI to V_T images calculated without PVC, because the raphe binding estimates that use gray matter-based PVC would be highly sensitive to small errors in delineation of the raphe border. Where low binding made localization difficult on the PET images, the raphe ROI was placed on the MRI image based upon the spatial relationship between the raphe and the cerebral aqueduct.

A reference tissue ROI was defined in the cerebellar white matter (Parsey et al., 2005). directly on the MRI image using 12 mm diameter circular regions in the left and right cerebellar peduncles, in a slice roughly centered superiorly/inferiorly in the peduncles. The mean of the left and right distribution volumes was used as the reference V_T.

Several choices of dependent variable are available to describe radiotracer binding in PET studies. Binding potential (BP) estimates specific binding to target receptors with reference to some reference concentration. Following consensus definitions and nomenclature (Innis et al., 2007), we chose as our primary outcome measure the most reliable measure, BP_P, a measure of BP relative to total plasma concentration ($V_{T\ ROI}–V_{ND} = K_1k_3/k_2k_4 = f_p\ B_{avail}/K_D$). As a secondary measure, we also calculated BP_F, calculated as $(V_{T\ ROI}–V_{ND})/f_p = (1/f_p)\cdot K_1k_3/k_2k_4$; this measure gives specific binding relative to free plasma concentration of tracer. We treated this parameter as a secondary measure because of its relatively greater sensitivity to measurement error in f_p.

Statistical analysis

Pre- and post-treatment clinical ratings were compared using paired-sample *t*-tests. To investigate possible sources of bias in the BP measures, paired *t*-tests also were performed to detect differences before and after treatment in f_p and V_T in the cerebellar reference region.

Because we expected that all regional values would be correlated, in addition to correlations between measures over time, we carried out a linear mixed model with both time (pre-/post-treatment) and region as repeated measures and a compound symmetry covariance matrix. Diagnosis, time, gender, age, and MADRS score were fixed effects. Only main effects were included in the model, with the exception of the region by time interaction, to assess regional specificity of any significant treatment effects. Eleven regions were examined: left and right MTC, ACC, PCC, AI, POC, and raphe nucleus. False discovery rate (FDR) correction for multiple comparisons was applied, and we also reported whether *p*-values remained significant after applying the more conservative Bonferroni correction. Post-hoc tests of estimated un-weighted means were carried out to assess the difference between diagnostic groups in each region. We examined BP (BP_P, BP_F) in this manner. To determine if changes in binding correlated with clinical improvement, we repeated our mixed models adding the main effect of MADRS score.

Results

Demographic and clinical characteristic of the subject sample appear in Table 1. Three subjects had BD-I. Seven subjects (two with BD-I) were treated with lithium monotherapy, and one (BD-I) was treated with a combination of lithium and divalproex; the remainder were taking divalproex monotherapy. At the time of baseline scanning, the mean depression severity was in the moderate range, with three individuals exhibiting mild depression, and seven subjects exhibiting moderate depressive symptoms. At the post-treatment scan, the mean change in MADRS scores showed a non-significant trend towards improvement (t=2.164, p=0.062). Following treatment, three subjects had MADRS scores in the moderate range (20–33), four subjects had mild residual depressive symptoms (pre-treatment mean=22, post-treatment mean=9), two subjects had scores in the remitted range (1–4), and the post-treatment MADRS score was missing for one patient. YMRS scores significantly decreased (t=3.010, p=0.020) following treatment (pre-scan YMRS unavailable for one subject, and post-scan YMRS unavailable for another subject).

The free fraction of [^{18}F]FCWAY in plasma and in the reference tissue V_T did not change significantly between pre- and post-treatment scans (Table 1, p=0.85 and p=0.97, respectively).

Test of the a priori hypothesis that regional BP_P increases following treatment

In the linear mixed model, BP_P showed a significant main effect of time ($F_{1,196.9}$=26. 9, p<0.001), with mean BP_P increasing following treatment. A significant main effect of region was also observed ($F_{10,189.0}$=48.5, p<0.001). Age had no significant effect ($F_{1,9.505}$=0.001, p=0.978). Although the time×region interaction was not significant ($F_{10,189.0}$=0.775, p=0.653), post-hoc tests were used to evaluate regional specificity in the main effect of time finding (Table 2 and Figure 1). After applying either the FDR or the Bonferroni correction for multiple comparisons, a significant increase in binding was noted in the LMTC. The main effect of time remained significant after removing the subject exposed to bupropion (F=32.35, p<0.001). The significant increase in BP_P in the LMTC was also retained when this subject was removed from the analysis (p<0.001).

Results for secondary outcome measure: BP_F

When the mixed model was repeated for BP_F, the main effects of time ($F_{10,190.3}$=26.7, p<0.001), region ($F_{10,189.0}$=43.9, p<0.001), and age ($F_{10,8.1}$=5.7, p=0.044) were significant. No significant interactions were observed for time by region ($F_{10,189.0}$=0.62, p=0.793). The increase in binding in the bilateral left MTC remained significant after applying either the FDR or the more conservative Bonferroni correction (Table 3).

Effect of MADRS scores on BP_P and BP_F

When the linear mixed model was repeated with MADRS as a covariate, change in BP_P showed significant effects of time ($F_{1,183.4}$=66.4, p<0.001), MADRS score ($F_{1,180.3}$=29.1, p<0.001), and region ($F_{10,175.3}$=53.1, p<0.001). Age had no significant effect. After controlling for MADRS scores and applying the FDR or the Bonferroni correction for multiple comparisons, a significant effect of time was seen in all regions examined, with the exception of the raphe (see Table 2, Figure 2).

When the mixed model was repeated for BP_F, the main effects of time ($F_{10,181.8}$=7.5, p=0.007), region ($F_{10,176.468}$=49.7, p<0.001), MADRS ($F_{1,182.7}$=14.4, p<0.001), and age ($F_{10,8.4}$=5.4, p=0.047) were significant. The time by region interaction was not significant ($F_{10,176.5}$=0.88, p=0.554). When examining individual regions, the increase in binding in the

left MTC following treatment remained significant after applying the FDR or Bonferroni corrections (Table 3).

Discussion

These preliminary results demonstrate that post-synaptic 5-HT_{1A} receptor BP_P increases significantly in the bilateral MTC in BD subjects following treatment with lithium and/or divalproex. Moreover, when depression ratings were included in the statistical model as a covariate, the increase in the BP_P following treatment became significant in every cortical region examined, suggesting that the effects of mood stabilizer treatment on post-synaptic 5-HT_{1A} binding are widespread. The observation that the MTC emerged as an area of primary importance irrespective of clinical response (i.e. whether or not mood effects were not controlled for) suggests it is a site where alterations in 5-HT_{1A} receptor function may prove particularly relevant for the serotonergic mechanisms of mood stabilizer treatment. Nevertheless, the hippocampus also has the highest post-synaptic 5-HT_{1A} receptor concentration, so our comparisons may simply have been more sensitive to detecting BP_P changes in this region.

Notably BP_P did not change significantly in the raphe, where [^{18}F]FCWAY uptake is predominantly attributable to pre-synaptic 5-HT_{1A} receptor binding. This negative finding is noteworthy in light of the results of our previous study comparing 5-HT_{1A} receptor binding between unmedicated BD patients (of which the subjects in the current study are a subset) versus healthy controls (Nugent et al., in press); that study found significantly decreased BP_P in BD subjects in the MTC and some other cortical regions where [^{18}F]FCWAY uptake is predominantly attributable to post-synaptic 5-HT_{1A} receptor binding, but no group difference in the raphe. When the current group of BD subjects was compared to a gender- and age-matched subset of healthy controls from that study, they also showed reduced binding, although the result did not reach statistical significance (adjusted mean BP_P in healthy subjects was 8.239 and 7.995 for left and right MTC, respectively, while mean BP_P in BD subjects was 7.367 and 7.197, for left and right MTC, respectively). In addition, these subjects showed very little difference in mean raphe BP_P (adjusted means of 3.391 and 3.225 in healthy and BD subjects, respectively). Taken together, these data suggest that the effects of the pathophysiology of BD and of mood stabilizer treatment on 5-HT_{1A} receptor expression may selectively involve the post-synaptic 5-HT_{1A} receptor system.

The reduced 5-HT_{1A} receptor binding seen in BD could conceivably be due to the diathesis toward cortisol hypersecretion in some individuals with mood disorders (Drevets, 2001; Lopez et al., 1998), and to the fact that mood stabilizing treatments affect glucocorticoid signaling that also may influence 5-HT_{1A} receptor expression. In rodents, post-synaptic 5-HT_{1A} receptor gene expression is down-regulated by glucocorticoid receptor (GR) stimulation; for example, in rats, hippocampal 5-HT_{1A} mRNA expression was found to be increased by adrenalectomy and decreased by corticosterone administration, chronic stress, or elevated trough corticosterone levels (Drevets et al., 2007; Hesen and Joels, 1996; Lopez et al., 1998; Meijer and de Kloet, 1994, 1995; Meijer et al., 1997; Mendelson and McEwen, 1991; Watanabe et al., 1993; Zhong and Ciaranello, 1995). Glucocorticoid hormone effects are of particular interest in the pathophysiology of BD, given that glucocorticoids are among only a few agents capable of triggering both depressive and manic episodes in BD patients (Wei et al., 2004). Notably, chronic administration of the mood stabilizers lithium and divalproex robustly up-regulated the GR chaperone protein Bcl-2-associated athanogene (BAG1), which interacts with GRs and attenuates their nuclear trafficking and function (Liman et al., 2005; Schneikert et al., 1999). In experimental animals, neuronal BAG1 overexpression plays a role in regulating recovery from or conferring resilience against the development of putative rodent behavioral analogues of anxiety, depression, and mania,

particularly under conditions of elevated glucocorticoid concentrations (Maeng et al., 2008; Zhou et al., 2005). Thus, by counteracting the effects of cortisol hypersecretion, lithium and divalproex may conceivably increase post-synaptic 5-HT_{1A} receptor expression in BD.

Notably, the effects of stress and GR stimulation on 5-HT_{1A} receptor expression show a similar pattern to our results; both selectively involve post-synaptic 5-HT_{1A} receptor expression. For example, Flugge and colleagues showed that in tree shrews, chronic psychosocial stress reduced 5-HT_{1A} receptor density in the PCC, parietal cortex, prefrontal cortex, and hippocampus, but did not significantly alter receptor density in the raphe (Flugge, 1995). Moreover, Fairchild and colleagues showed that in rats, 5-HT_{1A} autoreceptor function in the raphe was attenuated following chronic exposure to elevated corticosterone levels, but this effect was not associated with reduced 5-HT_{1A} receptor mRNA expression (and instead appeared to involve changes in receptor-effector coupling) (Fairchild et al., 2003). The differential effects of lithium and divalproex observed herein on pre-synaptic versus post-synaptic 5-HT_{1A} receptor binding thus appear compatible with the hypotheses that 5-HT_{1A} receptor expression is reduced in BD subjects who hypersecrete cortisol, and that lithium and divalproex treatment increase post-synaptic 5-HT_{1A} receptor expression by attenuating glucocorticoid signaling by upregulating BAG1 activity. Moreover, because BAG1 up-regulation, lithium, and valproate all attenuate GR nuclear translocation and inhibit GR activity specifically under elevated (pathophysiologic) glucocorticoid concentrations—but not under lower glucocorticoid levels (Zhou et al 2005)—this model may accommodate evidence that lithium does not increase 5-HT_{1A} receptor expression in healthy, non-stressed rats (McQuade et al., 2004), and that divaproex enhances the cortisol response to serotonergic challenge in BD subjects (Maes et al., 1997) but not in healthy volunteers (Shiah et al., 1997). Alternative mechanisms through which lithium and divalproex may enhance 5-HT_{1A} receptor expression include their neurotrophic/neuroprotective effects, which could increase the neuronal processes expressing 5-HT_{1A} receptor protein (Manji et al., 2001). In addition, the elevation in 5-HT_{1A} receptor binding could reflect enhanced 5-HT_{1A} receptor gene promoter activity, given that high affinity activator protein 1 (AP-1) sites exist in this promoter and that both lithium and divalproex robustly increase AP-1 DNA binding activity (Chen et al., 1999; Yuan et al., 1998). Nevertheless, it is unclear whether the latter mechanisms would account for effects limited to 5-HT_{1A} receptor expression in the post-synaptic versus the pre-synaptic system or in the depressed/stressed state versus the healthy/resting state.

This study is the first to measure 5-HT_{1A} receptor binding potential in BD subjects before and after mood stabilizer treatment. Nevertheless, the observation that mood stabilizer treatment may normalize 5-HT_{1A} receptor binding is potentially compatible with the results of the above-mentioned study of euthymic BD subjects medicated with lithium and/or divalproex, which showed no difference in BP_{ND} relative to healthy controls (Sargent et al., 2010).

Although the PET methodology does not directly address the functional significance of changes in 5-HT_{1A} receptor BP_P, within the context of the clinical and preclinical data reviewed in the Introduction, our data suggest that the mood stabilizer-induced increase in post-synaptic 5-HT_{1A} receptor BP_P contributes to the increases in serotonergic neurotransmission associated with chronic lithium and divalproex administration. The reported increases in plasma cortisol response to fenfluramine following lithium treatment (Mannel et al., 1997; Muhlbauer and Muller-Oerlinghausen, 1985) and in the L-5-HTTP-induced cortisol response following divalproex treatment (Maes et al., 1997) in BD patients appear particularly compatible with enhanced post-synaptic 5-HT_{1A} receptor function. In the case of lithium, the increase in post-synaptic 5-HT_{1A} receptor BP_P fits within the context of increased serotonin release more generally, implying that these changes would interact to

enhance post-synaptic 5-HT_{1A} receptor neurotransmission. For example, an in vitro study of primary serotonergic neurons from the rat raphe nuclei found that lithium increased 5-HT release following both acute and chronic lithium exposure, and that while expression of tryptophan hydroxylase 2 (TPH2; rate-limiting enzyme in cerebral 5-HT synthesis) decreased under acute exposure, this enzyme's expression returned to normal under chronic exposure, suggesting the maintenance of enhanced 5-HT release (Scheuch et al., 2010). Nevertheless, lithium's effects on serotonergic function are complex, and also involve altered activation of protein kinase C (PKC) and the coupling of serotonin receptors to G proteins (e.g. Hahn et al., 2005). Furthermore, genetic factors associated with the risk of developing BD, such as the HTR1A variants described above and variations in the TPH2 gene (Campos et al., 2011), may conceivably influence the effects of mood stabilizers on serotonergic neurotransmission. The effect of mood stabilizers on serotonergic function may also be regionally-dependent; for example, one study found that chronic lithium administration increased serotonin release and decreased 5-HT type 2 receptor binding in the hippocampus but not in the cortex (Treiser et al., 1981), potentially compatible with our identification of the MTC as an area of particular importance to the serotonergic mechanisms of mood stabilizers.

Finally, our results conceivably relate to the neurobiological mechanisms underlying lithium's usefulness in the treatment of depression, given that antidepressant drugs from multiple classes have been shown to increase post-synaptic 5-HT_{1A} receptor neurotransmission, and that this effect appears to play a role in antidepressant mechanisms (Chaput et al., 1991; Haddjeri et al., 1998; Savitz et al., 2009). In randomized, controlled clinical trials of bipolar depression, subjects receiving lithium plus placebo showed rates of improvement and durable recovery that did not differ significantly from those seen in subjects receiving lithium plus conventional antidepressant agents (Nemeroff et al., 2001; Sachs et al., 2007). The evidence reviewed above that lithium and divalproex enhance post-synaptic 5-HT_{1A} receptor neurotransmission along with our finding that treatment with these mood stabilizers is associated with increased post-synaptic 5-HT_{1A} receptor BP_P thus appear compatible with the effects of other agents that exert antidepressant effects. Furthermore, it is noteworthy that in rats, the addition of lithium to the chronic administration of a variety of antidepressant drugs resulted in increased tonic activation of hippocampal 5-HT_{1A} receptors (Haddjeri et al., 1998). This finding was hypothesized to underlie the clinical observation that, in MDD, lithium augments the antidepressant response to conventional antidepressant drugs from multiple pharmacological classes (Bauer et al., 2010).

Several limitations of our study merit comment. A primary limitation was the small sample size. Nevertheless, based upon the magnitude of the effect sizes observed, even this small sample provided adequate power to detect changes in BP_P associated with mood stabilizer treatment. Our sample size was insufficient, however, to support direct comparisons between treatment responders and non-responders. A further limitation is that our cohort was almost entirely female. This limits the generalizability of the results to the BD population as a whole, and further studies in more balanced samples are warranted. A related limitation is that we chose not to fix the time of scanning with the menstrual phase of female subjects so that treatment of acutely depressed subjects was not delayed. Studies have previously investigated the effect of the menstrual phase on 5-HT_{1A} receptor binding, and although there is evidence for increased BP in the dorsal raphe in the luteal as compared to the follicular phase, no significant differences were found across menstrual phase in areas where 5-HT_{1A} receptor expression is post-synaptic (Jovanovic et al., 2006, 2009). Thus, it is unlikely that a systematic difference in menstrual phase between scan sessions would have influenced our finding in the MTC. Another limitation is that subjects were treated with two different agents, or a combination of agents. Unfortunately, there were not enough subjects in each group to co-vary for specific drug regimen. Further studies are needed to evaluate

differential effects between mood stabilizers. A limitation of the PET methodology is that [^{18}F]FC, the primary metabolite of the tracer [^{18}F] FCWAY, is predominantly taken up by bone. Thus, due to spatial resolution limitations, we could not accurately measure BP_P in cortical regions situated near the skull that otherwise would have been of interest in BD, such as the orbitofrontal cortex and ventrolateral prefrontal cortex. Nevertheless, this study provides compelling evidence for increased 5-HT_{1A} BP following mood stabilizer treatment in deep regions such as the MTC and cingulate cortex, and future studies with larger sample sizes are warranted.

In summary, although the results should be considered preliminary due to the small sample size, this study provides evidence that 12 weeks of treatment with lithium and/or divalproex in subjects with BD was associated with increased post-synaptic 5-HT_{1A} receptor BP_P in the MTC and, when controlling for mood state, in other areas of the cortex as well. Without controlling for mood state, the MTC emerged as the site where the significant increase in BP_P remained significant after applying corrections for multiple comparisons, potentially indicating that increased 5-HT_{1A} receptor function in this region contributes to the serotonergic mechanisms of mood stabilizer treatment. In addition, confirmatory results were obtained in the secondary analysis examining BP_F, indicating that our finding was robust across multiple modeling approaches. This study is the first to provide in vivo evidence that treatment with mood stabilizers increases post-synaptic 5-HT_{1A} receptor binding, and provides new evidence for the neurobiological effects of these agents in BD.

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HM and CAZ are listed as co-inventors on a patent for the use of ketamine in major depression and have assigned their patent rights on ketamine to the US government. HM and WCD are currently employees of Johnson & Johnson Pharmaceuticals. WCD has consulted for Pfizer Pharmaceuticals, Johnson and Johnson Pharmaceuticals, Eisai, Inc., and Myriad/ Rules Based Medicine, Inc.

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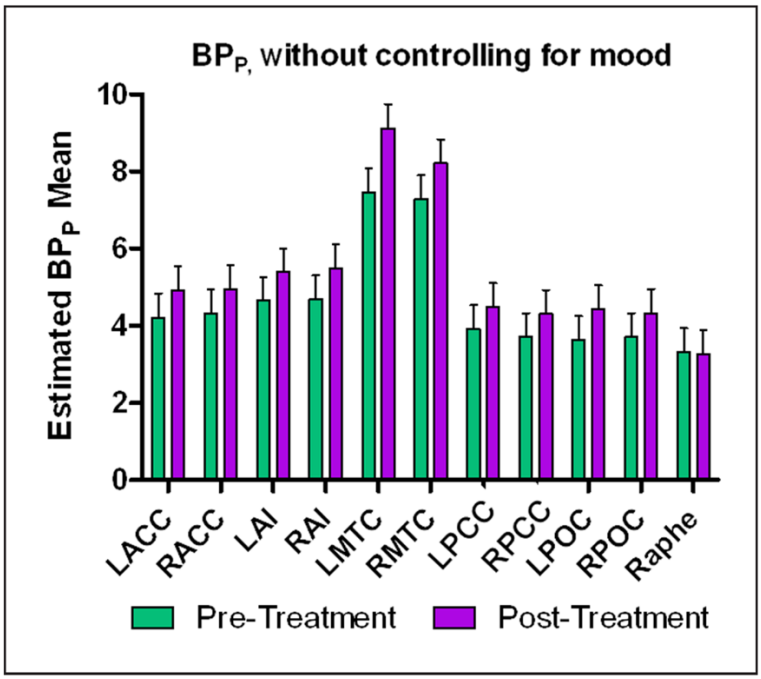

Figure 1.

Graph of means derived from the mixed model of binding potential (BP_P) pre- and post-treatment without controlling for mood scores. The significant increase in BP_P before and after treatment in the left mesiotemporal cortex (MTC) survived Bonferroni and false discovery rate (FDR) correction for multiple comparisons. Error bars represent standard error.

LACC: left anterior cingulate cortex; LAI: left anterior insula; LMTC: left mesiotemporal cortex; LPOC: left parieto-occipital cortex; RACC: right anterior cingulate cortex; RAI: right anterior insula; RMTC: right mesiotemporal cortex; RPOC: right parieto-occipital cortex.

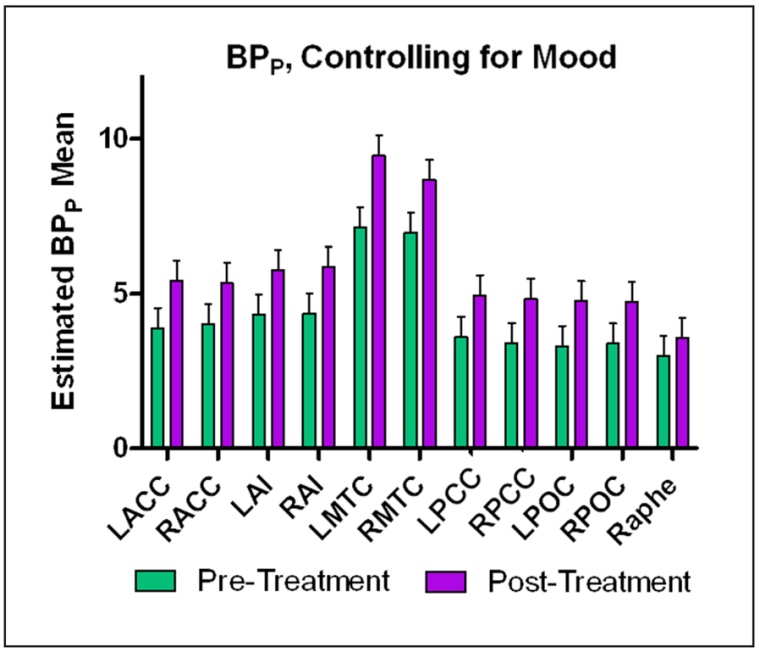

Figure 2.

Graph of means derived from the mixed model of binding potential (BP_P) pre- and post-treatment controlling for mood scores. All regions except for the raphe showed significant differences before and after treatment, Bonferroni corrected for multiple comparisons. Error bars represent standard error.

LACC: left anterior cingulate cortex; LAI: left anterior insula; LMTC: left mesiotemporal cortex; LPOC: left parieto-occipital cortex; RACC: right anterior cingulate cortex; RAI: right anterior insula; RMTC: right mesiotemporal cortex; RPOC: right parieto-occipital cortex.

Table 1

Demographic information for included subjects, means (standard deviations) are given.

	n	Age	Gender	Onset age	Time off meds (wks) *n*=8[a]	MADRS	YMRS	Injected dose (mCi)	Free fraction	Ref V_T
Pre-treatment	10	34 (11.4)	9 F (90%)	16 (4.9)	54 (54.0) range: 7–145	23 (5.8) range: 12–32	9 (5.1) (*n*=9) range: 0–10	7.91 (0.67)	0.117 (0.047)	0.486 (0.292)
Post-treatment	-	-	-	-	-	13 (10.6) (*n*=9) range: 1–25	5 (3.6) (*n*=9) range 3–18	7.98 (0.10)	0.113 (0.045)	0.482 (0.255)

MADRS: Montgomery-Asberg Depression Rating Scale; V_T: distribution volume; YMRS: Young Mania Rating Scale.

[a]We were unable to establish time off medications for one subject; however, the subject met the minimum time off medications allowable by the study (three weeks).

Table 2

Unweighted means from the mixed model for binding potential (BP_P) pre- and post-treatment. Means are given for the mixed model both with and without using Montgomery-Asberg Depression Rating Scale (MADRS) as a covariate.

BPP	Without MADRS covariate		With MADRS covariate	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
LACC	4.213	4.922	3.893	5.415[a]
RACC	4.333	4.948	4.012	5.339[a]
LAI	4.653	5.391	4.332	5.752[a]
RAI	4.684	5.483	4.363	5.869[a]
LMTC	7.456	9.121[a]	7.136	9.455[a]
RMTC	7.286	8.219[b]	6.966	8.678[a]
LPCC	3.918	4.485	3.597	4.944[a]
RPCC	3.710	4.312	3.390	4.823[a]
LPOC	3.624	4.424	3.304	4.756[a]
RPOC	3.702	4.333	3.382	4.730[a]
Raphe	3.314	3.257	2.993	3.580

LACC and RACC: left and right anterior cingulate cortex; LAI and RAI: left and right anterior insula; LMTC and RMTC: left and right mesiotemporal cortex; LPCC and RPCC: left and right posterior cingulate cortex, LPOC and RPOC: left and right parieto-occipital cortex. MADRS: Montgomery-Asberg Depression Rating Scale.

[a]Indicates that post-treatment value is significantly different from pre-treatment value at $p<0.05$ after both FDR and Bonferroni correction for multiple comparisons.

[b]Indicates that post-treatment value trended towards a significant difference from pre-treatment value at $0.05<p<0.1$ after FDR correction for multiple comparisons.

Table 3

Unweighted means from the mixed model for distribution volume (V_T) and binding potential (BP_F) pre- and post-treatment. Means are given for the mixed model both with and without using Montgomery-Asberg Depression Rating Scale (MADRS) as a covariate.

BP_F	Without MADRS covariate		With MADRS covariate	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
LACC	38.463	44.729	40.576	44.896
RACC	38.743	45.457	40.855	45.031
LAI	41.855	48.937	43.967	48.388
RAI	42.406	49.085	44.519	48.647
LMTC	67.957	83.475[a]	70.070	83.920[a]
RMTC	67.280	77.953	69.393	79.239
LPCC	36.146	40.747	38.259	40.571
RPCC	33.925	38.885	36.038	38.964
LPOC	31.926	39.852	34.039	38.801
RPOC	32.747	38.653	34.860	37.952
Raphe	28.583	30.163	30.695	28.816

LACC: left anterior cingulate cortex; LAI: left anterior insula; LMTC: left mesiotemporal cortex; LPCC: left posterior cingulate cortex; LPOC: left parieto-occipital cortex; MADRS: Montgomery-Asberg Depression Rating Scale; RACC: right anterior cingulate cortex; RAI: right anterior insula; RMTC: right mesiotemporal cortex; RPCC: right posterior cingulate cortex; RPOC: right parieto-occipital cortex.

[a]Indicates that post-treatment value is significantly different from pre-treatment value at $p<0.05$ after both false discovery rate (FDR) and Bonferroni correction for multiple comparisons.