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Elevated Serotonin 1A Binding in Remitted Major Depressive Disorder: Evidence for a Trait Biological Abnormality

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Abstract

Background—Several biological abnormalities in major depressive disorder (MDD) persist during episode remission, including altered serotonin neurotransmission, and may reflect underlying pathophysiology. We previously described elevated brain serotonin 1A (5-HT_{1A}) receptor binding in antidepressant-naïve subjects with MDD within a major depressive episode (MDE) compared to healthy controls using positron emission tomography (PET). In the current study, we measured 5-HT_{1A} receptor binding in unmedicated subjects with MDD during sustained remission, hypothesizing higher binding compared with healthy controls, and binding comparable to currently depressed antidepressant-naïve subjects, indicative of a biologic trait.

Methods—We compared 5-HT_{1A} binding potential (BP_F) assessed through PET scanning with [^{11}C]WAY-100635 in 15 subjects with recurrent MDD in remission for ≥12 months and off antidepressant medication for ≥ six months, 51 healthy controls, and 13 antidepressant-naïve MDD subjects in a current MDE. Metabolite-corrected arterial input functions were acquired for estimation of BP_F.

Results—Remitted depressed subjects had higher 5-HT_{1A} BP_F than healthy controls; this group difference did not vary significantly in magnitude across brain regions. 5-HT_{1A} BP_F was comparable in remitted and currently depressed subjects.

Conclusions—Elevated 5-HT_{1A} BP_F among subjects with remitted MDD appears to be a trait abnormality in MDD, which may underlie recurrent major depressive episodes. Future studies should evaluate the role of genetic and environmental factors in producing elevated 5-HT_{1A} BP_F and MDD, and examine whether 5-HT_{1A} BP_F is a vulnerability factor to MDEs that could have a role in screening high-risk populations for MDD.

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Keywords

depression; serotonin; 5-HT1A receptor; remission; PET; trait

Introduction

Biological abnormalities in major depressive disorder (MDD) that are trait phenomena may be more likely to be part of the etiology of MDD predisposing to recurrent episodes of major depression, in contrast to homeostatic mechanisms or stress responses occurring only during acute illness (Bhagwagar and Cowen, 2008). There is evidence of trait serotonergic abnormalities in MDD. Acute tryptophan depletion provokes depressive symptoms in remitted depressed subjects and in relatives of depressed subjects, an effect not seen in healthy controls (Ruhe *et al*, 2007). In addition, acute challenges with serotonergic agents such as citalopram or fenfluramine result in blunted neuroendocrine responses in remitted depressed subjects (Bhagwagar *et al*, 2002, Flory *et al*, 1998).

The 5-HT_{1A} receptor is located on the soma and proximal dendrites of serotonergic neurons in the brainstem raphe nuclei, where it serves as an auto-receptor, and postsynaptically in the cortex and terminal fields all over the brain (Aghajanian, 2002). We have previously reported that antidepressant-naïve (AN) MDD subjects during a major depressive episode (MDE) have higher 5-HT_{1A} receptor binding *in vivo* than healthy controls as assessed by positron emission tomography (PET; outcome measure BP_F, = B_{avail}/K_D, where B_{avail} is the receptor density available for binding and $1/K_D$ is the affinity of radioligand) (Parsey *et al*, 2006d). This is consistent with reports of elevated 5-HT_{1A} brain receptors in animal models of depression, including 5-HT_{1A} elevations in mice bred for helplessness on the tail suspension test (Naudon *et al*, 2002) and hippocampal 5-HT_{1A} elevations among behaviorally depressed cynomolgus macaques in a post-mortem quantitative receptor autoradiography study (Shively *et al*, 2007), although a PET imaging study by this group using the outcome measure BP_P revealed discrepant findings (Shively *et al*, 2006). Studies of neuroendocrine responses to 5-HT_{1A} receptor agonists in MDD have been inconsistent (reviewed in (Navines *et al*, 2007)). There are also discrepancies in PET imaging findings regarding 5-HT_{1A} abnormalities in MDD (Drevets *et al*, 1999, Drevets *et al*, 2007, Hirvonen *et al*, 2008, Meltzer *et al*, 2004, Moses-Kolko *et al*, 2007b, Sargent *et al*, 2000); divergent findings may be partly related to methodological differences and patient samples (see discussion for further detail). Post-mortem studies of 5-HT_{1A} receptor binding in depression and/or suicide have variously reported increases, no changes, or decreases (reviewed in (Stockmeier, 2003); see also (Boldrini *et al*, 2008)). To our knowledge, no post-mortem study has examined 5-HT_{1A} receptor binding among subjects with remitted depression.

A previous PET study found persistent 5-HT_{1A} receptor abnormalities during remission from MDD among 14 male subjects compared to 18 controls using the outcome measure BP_{ND} (Bhagwagar *et al*, 2004). In the current study, we assessed 5-HT_{1A} binding among 15 remitted depressed subjects using cerebellar white matter as the reference region to estimate the outcome measure BP_F. Based on our findings among currently depressed subjects, we hypothesized that 5-HT_{1A} BP_F would be higher in subjects with recurrent MDD in sustained

remission compared with healthy controls, consistent with a trait abnormality. As a secondary aim, we hypothesized that 5-HT_{1A} BP_F would not differ significantly between subjects with MDD in sustained remission and AN subjects with MDD in a current MDE.

In an exploratory manner, we genotyped subjects for a functional C-1019G promoter polymorphism of the 5-HT_{1A} gene (Lemonde *et al*, 2003). The G allele has been associated with greater expression in raphe neuron cell cultures *in vitro* (Lemonde *et al*, 2003), with greater raphe nucleus binding *in vivo* (Parsey *et al*, 2006d), with the diagnosis of MDD and with diminished response to antidepressant treatment (reviewed in (Le François *et al*, 2008). Therefore, while the current study was underpowered for genetic analyses, we explored the hypothesis that the G allele would be less frequent among remitted MDD subjects compared to current MDD subjects, among whom only a portion will eventually achieve remission.

Patients and Methods

Subjects

15 subjects who met criteria for MDD in full remission, 51 healthy controls, and 13 AN currently depressed subjects with MDD were included. This study draws on PET data from 42 healthy controls and 13 AN currently depressed MDD patients from a previous study (Parsey *et al*, 2006d); those subjects underwent PET scanning between 7/29/1999 and 3/25/2003. In the present study, 15 subjects with MDD in full remission and a second cohort of nine healthy controls underwent PET scanning with [^{11}C]WAY-100635 to quantify 5-HT_{1A} receptor binding. Remitted depressed subjects were scanned between 2/3/2004 and 12/11/2007; the second cohort of controls was scanned between 5/24/2000 and 10/2/2007. Clinical assessments, PET acquisition, reconstruction, and image processing did not differ between groups. There was no evidence of drift in PET camera performance over the study period based on quality control measurements including cross calibration factor (in this assay, which is performed bimonthly, the HR+ scanner is calibrated using a cylindrical phantom filled with ^{18}F. The phantom is scanned using the HR+ for 30 minutes. Ten samples of the activity (2ml each) are taken from the phantom and measured in a Wallac 1480 Wizard well counter (PerkinElmer Lifescience). The cross calibration factor is the ratio of detected counts between the scanner and the well counter). After a comparison of first and second cohorts of healthy controls revealed no differences in 5-HT_{1A} BP_F considering all regions of interest ($F=0.38$, $df=1,49$, $p=0.54$), these cohorts were combined in subsequent analyses. Subjects were recruited through community advertisements; remitted depressed subjects were already in remission at the time of recruitment. Eligibility was assessed by psychiatric and medical history, chart review, Structured Clinical Interview for DSM-IV (SCID) (First *et al*, 1995), physical examination, routine blood tests, pregnancy test, and urine toxicology. The Beck Depression Inventory (BDI) (Beck *et al*, 1961), Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960), and Global Assessment Scale (GAS) (Endicott *et al*, 1976), and Beck Hopelessness Scale (Beck *et al*, 1974), assessed depression severity and functional impairment.

Inclusion criteria for remitted depressed subjects were: 1) DSM-IV criteria for MDD, in full remission for at least one year; 2) ≥ two prior MDEs; 3) 17-item HAM-D <8 upon screening; 4) absence of psychotropic medication use for ≥6 months before the PET scan (to

minimize the effects of prior antidepressant treatment on 5-HT_{1A} BP_F (Parsey *et al*, 2006d, Spindelegger *et al*, 2008)); 5) age 18–65 years; 6) no current or lifetime history of alcohol or other drug abuse or dependence; 7) absence of lifetime exposure to 3,4-methylenedioxymethamphetamine; 8) absence of significant current medical conditions; 9) absence of pregnancy; and 10) capacity to provide informed consent. We required a minimum of two prior MDEs given findings of greater biological abnormalities in recurrent as opposed to single episode MDD (Basso and Bornstein, 1999, Kupfer *et al*, 1991, Thase, 1992, Thase *et al*, 1995), with at least one difference persisting into remission (Jindal *et al*, 2002). Healthy controls met inclusion criteria five through ten, had no psychiatric history, and had no history of a mood or psychotic disorder in their first-degree relatives. AN subjects with current MDD met DSM-IV criteria for a current MDE and had never taken antidepressant medication; these subjects met inclusion criteria five through ten above. Comorbid disorders among remitted depressed subjects, which were in remission, included post-traumatic stress disorder (n=1) and attention-deficit hyperactivity disorder (n=1). Among AN currently depressed subjects, comorbid disorders included panic disorder (n=4), post-traumatic stress disorder (n=2), dysthymia (n=3), and social anxiety disorder (n=1). This study was approved by the Institutional Review Board of the New York State Psychiatric Institute. All subjects gave written informed consent after explanation of the study.

Radiochemistry

[^{11}C]WAY100635 was prepared as previously described (Parsey *et al*, 2000). Remitted depressed subjects had lower mean injected dose and mass of [^{11}C]WAY100635 than healthy controls (injected dose: remitted depressed = 4.6±1.2mCi, controls = 8.0±3.4mCi, T=3.75, DF=64, p = 0.0004; injected mass: remitted depressed = 1.7±1.6 μg, controls = 2.0±2.0μg, T=2.17, DF=64, p=0.033). This was intentional, as the majority of remitted depressed subjects were scanned following publication of a dosimetry study for [^{11}C]WAY100635 recommending reductions in injected dose and mass for human studies (Parsey *et al*, 2005b). [^{11}C]WAY100635 equilibrium distribution volume (V_T) should be insensitive to changes in injected mass if receptor occupancy is below 10% (Slifstein and Laruelle, 2001). Indeed, there was not a significant correlation between injected mass or dose and V_T in any region of interest (representative pre- and post-synaptic regions: raphe nucleus and injected mass: r=0.075, p=.51; raphe nucleus and injected dose: r=0.025, p=.82; hippocampus and injected mass: r=0.14, p=.20; hippocampus and injected dose: r=0.11, p=.36).

Measurement of the arterial input function, plasma free fraction (f_P), and metabolites was conducted as described previously (Parsey *et al*, 2000). f_P was lower among remitted depressed than controls, but did not differ between remitted depressed and AN currently depressed subjects (remitted depressed = 0.062±0.026, controls = 0.081±0.024, t=2.66, df=64, p=0.01; AN currently depressed = 0.066±0.023; remitted vs. AN currently depressed: t=0.46, df=26, p=0.65).

PET and MRI Acquisition

After placement of an arterial and venous catheter, PET imaging was performed on an ECAT EXACT HR+ (Siemens/CTI, Knoxville, TN) (63 slices covering an axial field of view of 15.5 cm, axial sampling of 2.46 mm, in 3D mode. A 10 min transmission scan was acquired prior to injection of [^{11}C]WAY-100635 as an i.v. bolus over 45 seconds. Emission data were collected for 110 minutes as 20 successive frames of increasing duration. Images were reconstructed using the 3D-RP algorithm implemented on a vector processor (CTI, Knoxville, TN) to a 128×128 matrix (pixel size of 1.7 × 1.7 mm^2) with attenuation correction and a Shepp 0.5 filter (cutoff 0.5 cycles/projection rays) resulting in an in-plane and axial resolution (i.e. full width half-maximum) of 4.4 mm and 4.1 mm in air and at the center of the field of view (Brix *et al*, 1997). Scatter correction was performed using the technique implemented by the manufacturer (Watson *et al*, 1995).

Acquisition of T1-weighted MRI for co-registration of PET images and identification of regions of interest was performed as previously described using a 1.5 T Signa Advantage or a 3 T Signa HDx system (General Electric Medical Systems, Milwaukee, WI) (Parsey *et al*, 2000).

Image Analysis

Image analysis was performed using MATLAB 2006b (The Mathworks, Natick, MA) with extensions to the following open source packages: Functional Magnetic Resonance Imaging of the Brain's Linear Image Registration Tool (FLIRT) v5. (Jenkinson and Smith, 2001), Brain Extraction Tool (BET) v1.2 (Smith, 2002), as well as Statistical Parametric Mapping (SPM5) normalization (Ashburner and Friston, 1999) and segmentation routines (Ashburner and Friston, 2005). No attempt was made to correct for transmission-emission mismatch. To correct for subject motion, de-noising filter techniques were applied to all PET images starting at frame five. The eighth frame was used as a reference to which all other frames were aligned using rigid body FLIRT. Motion correction was assessed visually by comparing movies of pre- and post-motion correction scans. Motion was evaluated for drift between frames and across the entire scan duration, separately. A mean of motion corrected frames eight through eighteen for each subject was registered to that subject's T1-weighted MRI using FLIRT.

Regions of interest were hand drawn on individual subjects' T1-weighted MRI images by experienced technicians trained to reliably approximate these regions using brain atlases (Duvernoy, 1991, Talairach and Tournoux, 1988) and published reports (Kates *et al*, 1997, Killiany *et al*, 1997). ROIs included the ventral prefrontal cortex (PFC), medial PFC, dorsolateral PFC, anterior cingulate, body of the cingulate (posterior to anterior cingulate), amygdala, hippocampus, parahippocampal gyrus, insular cortex, temporal cortex, parietal cortex, and occipital cortex. A fixed volume elliptical ROI (2 cm^3) was placed on the raphe nuclei in the dorsal midbrain: a composite of mostly the dorsal and median raphe nuclei, on a mean PET image for each subject since the boundaries of this structure cannot be identified on MRI. A cylindrical ROI was drawn in the cerebellar white matter, which was used as the reference region for this study, as it has been previously shown to have the lowest concentration of 5-HT$_{1A}$ receptors within the cerebellum, and is adequately modeled

by a one-tissue compartment model (Parsey *et al*, 2005a). For comparison purposes, a cylindrical ROI was drawn in the cerebellar gray matter. The segmented MRI image was used to refine the contours of the ROI to more accurately reflect the gyral pattern and differences between the PET and MRI fields of view.

Quantitative Analysis

Regional distribution volumes of [^{11}C]WAY-100635 were derived from kinetic analysis using the arterial input function and a two tissue compartment (2T) model as the general framework (see (Parsey *et al*, 2000) for details). V_{ND} and V_S are defined as the distribution volumes of the nondisplaceable and specific compartments, respectively (Laruelle *et al*, 1994, Mintun *et al*, 1984). V_T, the total regional equilibrium distribution volume, is equal to $V_{ND} + V_S$. The primary outcome measure for this study was binding potential ($BP_F = B_{avail}/K_D$). Time activity curves were fit with a 2T model which has the K_1/k_2 ratio fixed to that of the cerebellar white matter (reference region). BP_F was calculated as $(V_{T(ROI)} - V_{T(CER)})/f_P$ or $(V_T - V_{ND})/f_P$. For comparison purposes, the outcome measure BP_{ND} was calculated using the simplified reference tissue model (SRTM) (Lammertsma and Hume, 1996), using both the cerebellar white and gray matter, as was the outcome measure BP_P ($= V_T - V_{ND} = f_p B_{avail}/K_D$). The contribution of plasma total activity to regional activity was calculated assuming a 5% blood volume in the ROI and was subtracted prior to analysis. Kinetic parameters were derived by nonlinear regression using a Levenberg-Marquart least squares minimization procedure implemented in MATLAB (The Math Works, Inc., South Natick, MA).

Genotyping

Genotyping of the C(-1019)G polymorphism of the 5-HT_{1A} receptor gene was performed using allele-specific polymerase chain reaction (PCR) amplification as previously described (Parsey *et al*, 2006d).

Statistical Analysis

To properly account for correlations among measurements made on the same subject, we applied mixed-effects modeling methods and analyzed the data for the 13 regions simultaneously, with region and diagnostic group as fixed effects and subject as the random effect. Standard errors (SE) were computed for each estimated BP_F value using a bootstrap algorithm that takes into account errors in metabolite, plasma, and brain data (Ogden and Tarpey, 2006). Observations were weighted accordingly in the linear mixed-effects models in order to increase precision in group estimates. Analyses were performed on natural log-transformed values. Log transformation is commonly used to remedy problems with skewness and unequal variance, both of which are generally issues with PET data. It has specifically been used in previous PET studies by our group and others to address these issues (Hirvonen *et al*, 2008, Miller *et al*, 2008, Oquendo *et al*, 2007, Parsey *et al*, 2006a, Parsey *et al*, 2006b, Parsey *et al*, 2006c, Parsey *et al*, 2006d, Sullivan *et al*, 2005). Other groups have used related statistical approaches, including linearizing transformation (Rabiner *et al*, 2002b) and non-parametric testing (Meltzer *et al*, 2004) to address these issues in analyzing PET data. As the natural log is a monotone transformation,

demonstrating a difference in log(BP_F) is equivalent to demonstrating a difference (in the same direction) in BP_F. Figure 1 presents raw BP_F values. Reported p values were not adjusted for multiple comparisons. Linear mixed effects models of binding and Fisher's exact tests were performed in R 2.1.0 (http://cran.r-project.org). T-tests were performed in Excel (Microsoft, 2003).

Results

Clinical Characteristics

Clinical characteristics of the study sample are presented in Table 1. The remitted MDD group had depression severity ratings that were modestly greater than healthy volunteers and only 10% that of the acutely depressed MDD group for the BDI. Both MDD groups had a comparable number of prior MDEs; the remitted group had been free from an episode for a mean of three years at the time of study participation. About 60% of both MDD groups had a first degree relative with MDD. Clinical assessments reported here were obtained within an average of 3.7±5.2 days of PET scanning.

Comparison of 5-HT_{1A} BP_F Between Groups

Remitted depressed subjects had higher 5-HT_{1A} BP_F than healthy controls including all brain regions in the model (Figure 1; F=4.99, df=1,90, p=0.028). As we have found an inverse relationship between aggression (Brown-Goodwin Aggression scale) and 5-HT_{1A} BP_F, as well as a sex effect, with higher 5-HT_{1A} BP_F among females (Parsey *et al*, 2002), sex and aggression score were included as covariates in linear mixed effects models. The difference between remitted depressed subjects and healthy controls remained statistically significant with inclusion of sex and aggression as covariates in the model (F=8.45, df=1,86, p=0.0046). The magnitude of difference between these groups did not vary across brain regions (region-by-diagnosis interaction: F=1.36, df=12,756, p=0.18).

5-HT_{1A} BP_F did not differ between remitted MDD and AN acutely depressed MDD subjects (Figure 1; F=0.065, df=1,90, p=0.80), even after inclusion of sex and aggression as covariates in the model (F=0.003, df=1,86, p=0.95). 5-HT_{1A} BP_F was higher among AN acutely depressed MDD subjects than the combined cohort of healthy controls (F=6.65, df=1,62, p=0.012), even after inclusion of sex and aggression as covariates in the model (F=7.51, df=1,58, p=0.0081).

Alternative Outcome Measures

In order to compare our findings with other studies, we repeated the primary analysis comparing remitted depressed subjects to healthy controls using outcome measure BP_{ND}, estimated via the simplified reference tissue method (Slifstein *et al*, 2000), consistent with methods used in a previous publication examining 5-HT_{1A} binding in remitted depression (Bhagwagar *et al*, 2004). We performed this comparison using two different reference regions, cerebellar white matter and cerebellar gray matter. When using the cerebellar white matter as reference region, BP_{ND} was an average of 11.4% higher across all regions of interest among remitted depressed subjects than controls, although this difference was not statistically significant (F=1.66, DF=1,61, p=0.20). In contrast, when the cerebellar gray

matter was used as the reference region, which has appreciable 5-HT_{1A} binding (Parsey *et al*, 2005a), BP_{ND} was an average of 22.6% *lower* across all regions of interest among remitted depressed subjects than controls (F=10.78, DF=1,61, p=0.002). While the V_T of the reference region used for our primary analyses, the cerebellar white matter, did not differ significantly between remitted depressed and control subjects (remitted depressed: 0.25±0.10, controls: 0.29±0.11, T=1.16, DF=64, p=0.25), there was a trend toward higher V_T in the alternative reference region of cerebellar gray matter among remitted depressed subjects compared to controls (remitted depressed: 0.57±0.25, controls: 0.47±0.19, T=1.71, DF=64, p=0.092).

When we re-analyzed our data using the outcome measure BP_P (= $V_T - V_{ND} = f_P B_{avail}/K_D$), which requires the assumption of equivalent f_P between groups but which therefore does not require f_P measurement, using cerebellar white matter as the reference region, differences in 5-HT_{1A} BP_P between remitted depressed subjects and controls were not statistically significant (F=0.38, df=1,64, p=0.54).

5-HT_{1A} Receptor Promoter Polymorphism

For genetic analysis, we included antidepressant-exposed with antidepressant-naïve currently depressed subjects from the currently depressed MDD cohort (described in (Parsey *et al*, 2006d)), as prior medication status does not affect genotype, comparing these 28 currently depressed subjects with remitted depressed subjects and healthy volunteers for the C(-1019)G polymorphism in the 5-HT_{1A} receptor gene. Considering all three groups simultaneously (healthy controls, remitted MDD, and currently depressed MDD), there was a difference in genotype between groups, with higher frequency of the GG genotype of the in the MDD groups (Table 2; Fisher's exact, p=0.019). In pair-wise group comparisons of genotype frequency, the only two groups that differed significantly in genotype were currently depressed and control groups (Fisher's exact, p=0.005); there were not significant differences between controls and remitted depressed (Fisher's exact, p=0.54) or between remitted depressed and currently depressed groups (Fisher's exact, p=0.23). The G allele was similarly more frequent in the current MDD group than the control group (Fisher's exact, p=0.038).

Discussion

We find higher 5-HT_{1A} BP_F across all studied brain regions in subjects with recurrent MDD in sustained remission and off antidepressant medications for at least six months compared with healthy controls. In addition, we do not find a significant difference in 5-HT_{1A} BP_F between remitted and currently depressed MDD subjects. These findings are consistent with a trait abnormality in 5-HT_{1A} receptor BP_F in MDD.

While the current findings may appear at odds with a report of lower 5-HT_{1A} BP_{ND} among remitted depressed subjects as compared to controls (Bhagwagar *et al*, 2004), that study used the entire cerebellum as the reference region, and estimated the outcome measure BP_{ND}. Inclusion of the cerebellar vermis and gray matter in a reference region may lead to bias in resulting binding estimates, given detectable 5-HT_{1A} binding in these subregions (Parsey *et al*, 2005a). Small differences in reference region distribution volume (V_{ND}) can

have large effects on BP_{ND}, as BP_{ND} is equal to $(V_T-V_{ND})/V_{ND}$, and V_{ND} is typically <1. When we re-analyzed our data using the cerebellar gray matter as reference region, estimating BP_{ND} via the simplified reference tissue model, BP_{ND} was an average of 22.6% *lower* across all regions of interest among remitted depressed subjects than controls, consistent with (Bhagwagar *et al*, 2004). In contrast, when BP_{ND} was estimated using the cerebellar white matter as reference region, mean BP_{ND} was 11.4% higher across all regions of interest among remitted depressed subjects than controls, although this difference was not statistically significant. This difference was driven by a trend toward higher V_T in the alternative reference region of cerebellar gray matter among remitted depressed subjects compared to controls, consistent with our reports of appreciable 5-HT_{1A} receptor binding in the cerebellar gray matter (Parsey *et al*, 2005a). This result reconciles seemingly disparate findings, and emphasizes the importance of considering specific methodology, including the reference region and outcome measure used, in interpreting PET findings (Parsey *et al*, 2000).

We used BP_F as the outcome measure in this study as it is the closest measure to B_{avail} among the existing outcome measures for PET studies (BP_F, BP_P, and BP_{ND}). However, estimating BP_F requires measurement of f_P, which is particularly low with [^{11}C]WAY-100635. When we re-analyzed our data using the outcome measure BP_P (= $V_T - V_{ND} = f_P B_{avail}/K_D$), which requires the assumption of equivalent f_P between groups but which therefore does not require f_P measurement, 5-HT_{1A} BP_P was numerically higher among remitted depressed subjects than controls (an average of 9.2% higher across all regions of interest), although this difference was not statistically significant. This suggests that the observed difference in BP_F between groups is partially dependent on f_P. We observed lower f_P among remitted depressed subjects than controls; we had previously found non-significantly lower f_P among currently depressed subjects than controls (Parsey *et al*, 2006d). If such a peripheral marker were found to reliably correlate (inversely) with cerebral 5-HT_{1A} binding potential, it could be used clinically as a less invasive surrogate marker for cerebral 5-HT_{1A} binding. However, there is significant overlap in [^{11}C]WAY-100635 f_P between groups, and f_P is insensitive to regional heterogeneity in brain receptor binding. Of note, Hirvonen *et al* previously compared antidepressant-naïve currently depressed subjects to healthy controls using the outcome measure BP_P, reporting lower 5-HT_{1A} BP_P among currently depressed subjects than controls (Hirvonen *et al*, 2008); that study did not examine remitted depressed subjects. Differences in methodology include their use of atlas-based methods for automated ROI labeling. In addition, it is possible that frequencies of the C-1019G 5-HT_{1A} receptor polymorphism differed between samples, although this was not reported in their study, which may also have contributed to discrepant findings in comparing *currently* depressed subjects to controls.

Our findings are consistent with broadly-distributed elevations in 5-HT_{1A} receptor binding as a trait abnormality in MDD. Based on these results, we propose the following model to integrate several recent findings by our group and others regarding longitudinal 5-HT_{1A} expression in major depression (Figure 2). Due to genetics, childhood experiences, or gene-environment interactions, AN subjects with MDD have higher 5-HT_{1A} BP_F than healthy controls by the time of the onset of a first MDE. If this receptor difference is important

causally, one would predict that 5-HT_{1A} receptor differences precede the development of depressive symptomatology, a question for future study. Chronic treatment with antidepressants may then lead to reductions in 5-HT_{1A} BP_F, although data are not conclusive. We find lower 5-HT_{1A} BP_F among MDD subjects who have received previous antidepressant treatment compared with medication naïve MDD subjects, providing cross-sectional evidence of medication effects (Parsey *et al*, 2006d). A reduction in 5-HT_{1A} BP_{ND} following ≥12 weeks of treatment with escitalopram was reported in subjects with social phobia or panic disorder, indicating receptor down-regulation with chronic SSRI use (Spindelegger *et al*, 2008). Consistent with these human findings, mice that have been stressed by housing in isolation show increased 5-HT_{1A} receptor binding, which is reversed post-synaptically by chronic treatment with the SSRI citalopram (Gunther *et al*, 2008). In contrast, other human studies have not observed changes in 5-HT_{1A} binding after shorter SSRI courses in major depression (Moses-Kolko *et al*, 2007a, Sargent *et al*, 2000). Finally, we find higher 5-HT_{1A} BP_F in remitted depressed subjects off antidepressant medications for a minimum of six months compared to controls, suggesting that 5-HT_{1A} BP_F increases again over time after stopping antidepressant medication, returning to elevated pre-treatment levels without return of MDE, and that it remains persistently elevated into remission among subjects not taking antidepressant medication.

Trait elevations in 5-HT_{1A} binding potential in MDD could be partly explained by a genetic model of over-representation of the G allele of the 5-HT_{1A} C(-1019)G polymorphism among subjects with MDD (Albert, 2004). This would lead to higher 5-HT_{1A} autoreceptor binding in the raphe nucleus (Parsey *et al*, 2006d), leading to greater inhibition of serotonergic neuronal firing and decreased serotonin release in the terminal field of serotonin neurons, potentially leading to compensatory upregulation of 5-HT_{1A} receptors in the terminal field. Whether less serotonin release related to this polymorphism would result in post-synaptic 5-HT_{1A} receptor upregulation to compensate for serotonergic deficit is not known (Cahir *et al*, 2007), although a neurodevelopmental model would be required to test this hypothesis thoroughly.

This genetic model is limited, as we did not observe an association between C(-1019)G polymorphism and 5-HT_{1A} binding among the modest sample of remitted depressed subjects in the current study ($f=1.34$, $df=2,9$, $p=0.31$) although such an association was previously observed when considering a larger sample of 42 healthy controls and 28 currently depressed MDD subjects (Parsey *et al*, 2006d). In addition, many subjects who develop MDD do not carry the G allele of this polymorphism, and differences in genotype frequency were only significant comparing *currently* depressed subjects to controls. The fact that allelic frequencies at this locus for remitted depressed subjects were intermediate between healthy controls and currently depressed subjects, but not significantly different from either group, may simply be due to the small size of this sample for genetic studies. Alternatively, while speculative, it is possible that subjects with MDD who achieve sustained remission have a lower frequency of the G allele than other MDD subjects (Le François *et al*, 2008), predisposing them to better antidepressant response and greater likelihood of sustained remission. Larger sample sizes are clearly needed to test this hypothesis thoroughly.

While we did not observe region-by-diagnosis interactions when comparing remitted depressed subjects to either controls or AN currently depressed subjects, there are some regions in which remitted depressed 5-HT_{1A} BP_F appears closer to controls than to AN currently depressed subjects (Fig 1). This suggests the need for replication studies with larger sample sizes to study whether 5-HT_{1A} BP_F may normalize partially in a regionally specific manner during sustained remission from MDD.

There were some clinical and demographic differences between groups. Lifetime aggression (which has been associated with 5-HT_{1A} BP_F) was higher among remitted depressed subjects than controls. Differences in 5-HT_{1A} BP_F between remitted depressed and controls remained highly significant after aggression was included as a co-variate. The remitted depressed group had a higher proportion of Caucasian individuals than controls or AN currently depressed, and was more highly educated than the AN currently depressed group. There was also a trend toward a lower unemployment rate among remitted depressed than AN currently depressed (13% vs. 50%, p=0.08). These factors were all associated with a higher likelihood of remission with citalopram treatment in the STAR*D trial (Trivedi *et al*, 2006), consistent with the frequencies observed in our sample. While we are not aware of any studies reporting differences in 5-HT_{1A} binding as a function of race or ethnicity, group differences in ethnicity may have affected allelic frequencies of the 5-HT_{1A} receptor promoter polymorphism examined. Though not statistically significant, remitted depressed subjects were six years younger than healthy controls on average. We and others have previously found no effect of age on 5-HT_{1A} binding (Parsey *et al*, 2002, Rabiner *et al*, 2002a, Sargent *et al*, 2000). Similarly, we found no correlation between age and 5-HT_{1A} BP_F in any region in the current cohort. While others have described age-related decline in 5-HT_{1A} binding (Bhagwagar *et al*, 2004, Cidis Meltzer *et al*, 2001, Moller *et al*, 2007, Tauscher *et al*, 2001), the magnitude of these reported effects is not sufficient to explain our findings, given the small difference in age between groups. There was a higher incidence of comorbid anxiety disorders among AN currently depressed subjects than remitted depressed subjects. While panic disorder and social anxiety disorder have been associated with lower 5-HT_{1A} receptor binding (Lanzenberger *et al*, 2007, Nash *et al*, 2008, Neumeister *et al*, 2004), the small number of subjects with these comorbidities in the current sample prevented statistical analysis of such effects.

This study has some limitations. It has a modest sample size of remitted depressed subjects. In addition, remitted depressed subjects reported past antidepressant-exposure, but this exposure was on average 3 years earlier, and hence is unlikely to have had persistent effects on 5-HT_{1A} BP_F. Any residual effects of past antidepressant medication on 5-HT_{1A} receptors among remitted depressed subjects would be expected to lead to *lower* 5-HT_{1A} BP_F (Parsey *et al*, 2006d), and thereby an *underestimation* of the magnitude of the difference we report between remitted depressed subjects and healthy controls. Remitted depressed subjects were recruited once they were already in sustained remission; their clinical history was therefore based on subjects' retrospective reports of prior depressive episodes and symptoms. Future studies could identify subjects prospectively by following individuals assessed during a current MDE into periods of sustained remission. Finally, PET data from some healthy controls and all AN depressed subjects in comparator groups were drawn from a previous

study (Parsey *et al*, 2006d). This is unlikely to have influenced the results reported here, as PET acquisition, processing, and data analysis did not differ between groups. There was no difference in 5-HT_{1A} BP_F between the first and second cohorts of controls, making temporal drift an unlikely explanation of our findings. While T1-weighted MRIs used for identification of ROIs were performed on 1.5T and 3T cameras, we observed no difference in the volume of a representative ROI, the dorsolateral prefrontal cortex, as a function of MRI camera (comparison among remitted depressed: t=0.90, df=13, p=0.38; comparison among healthy controls: t=1.08, df=49, p=0.29). Similarly, regional [^{11}C]WAY-100635 V_T values did not differ as a function of MRI camera when comparing age- and sex- matched controls considering all ROI's (F=0.004, df= 1,11.87, p=0.95).

5-HT_{1A} BP_F may serve as a biological marker in populations at-risk for the development of MDD (including those with a family history of mood disorder), which could be used for the purposes of screening and primary prevention. Future studies should examine genetic and nongenetic causes of elevated 5-HT_{1A} receptor binding potential in MDD, its relationship to treatment outcome, and the effect of treatment on binding.

In summary, this study provides evidence of persistently elevated 5-HT_{1A} receptor binding potential among subjects with MDD in sustained remission, consistent with a trait serotonergic abnormality in MDD. Apparent discrepancies between this finding and previously published findings are reconciled through a close analysis of PET acquisition and analysis methodologies.

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Disclosure/Conflicts of Interest

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Dr. Sullivan has been on speakers' bureaus for Pfizer and GSK, has consulted for Jazz Pharmaceuticals and Krele Pharmaceuticals, previously owned stock in Pfizer, and has a patent application for use of tianeptine, all unrelated to the current manuscript.

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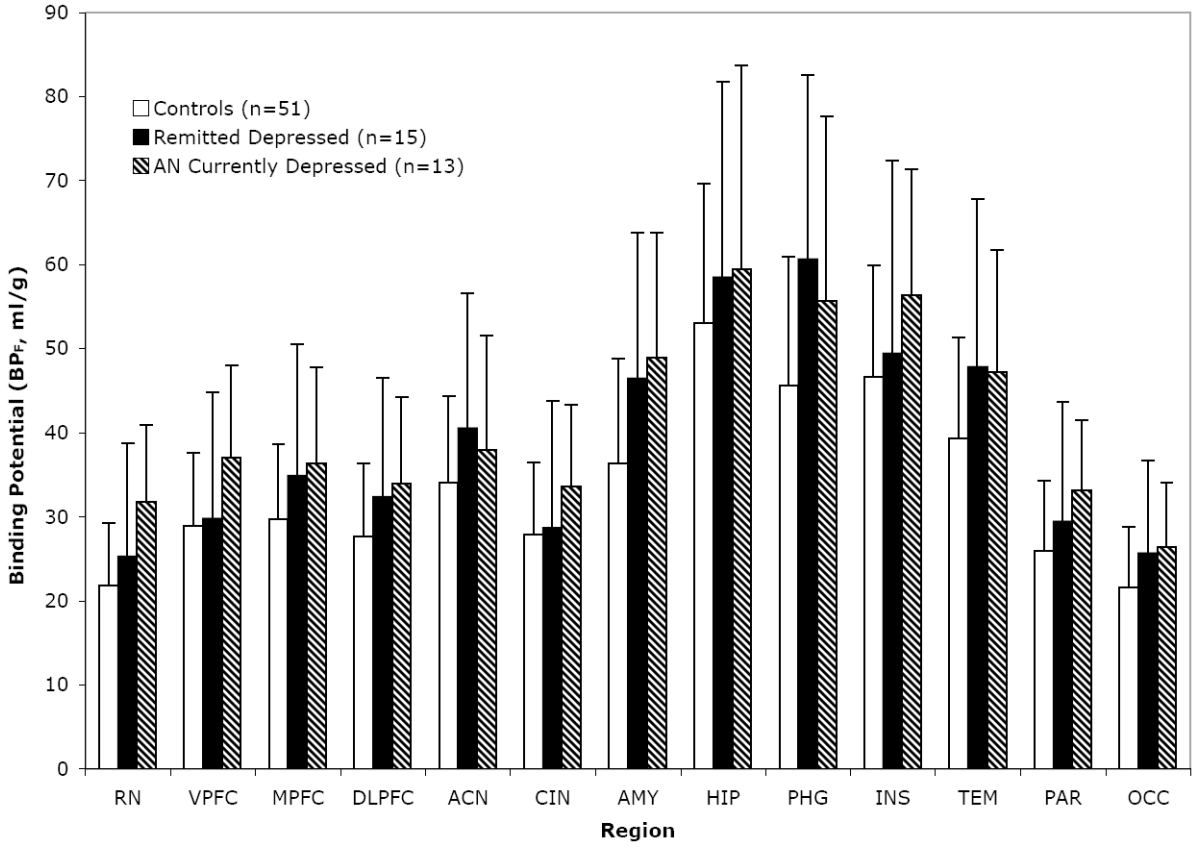

Figure 1.

Remitted depressed subjects have higher serotonin 1A receptor binding potential (BP_F) than healthy controls and do not differ significantly from antidepressant-naïve currently depressed subjects, considering all regions simultaneously. Regions: RN, raphe nuclei; VPFC, ventral prefrontal cortex; MPFC, medial PFC; DLPFC, dorsolateral PFC; ACN, anterior cingulate; CIN, cingulate cortex (posterior to ACN); AMY, amygdala; HIP, hippocampus; PHG, parahippocampal gyrus; INS, insular cortex; TEM, temporal cortex; PAR, parietal cortex; OCC, occipital cortex. Linear mixed effects model comparing remitted depressed to controls: F=4.99, df=1,90, p=0.028. Comparing remitted depressed to currently depressed: F=0.065, df=1,90, p=0.80. Bar heights indicate weighted mean BP_F for each ROI; error bars represent the corresponding equivalent of the standard deviation of the weighted mean for each ROI.

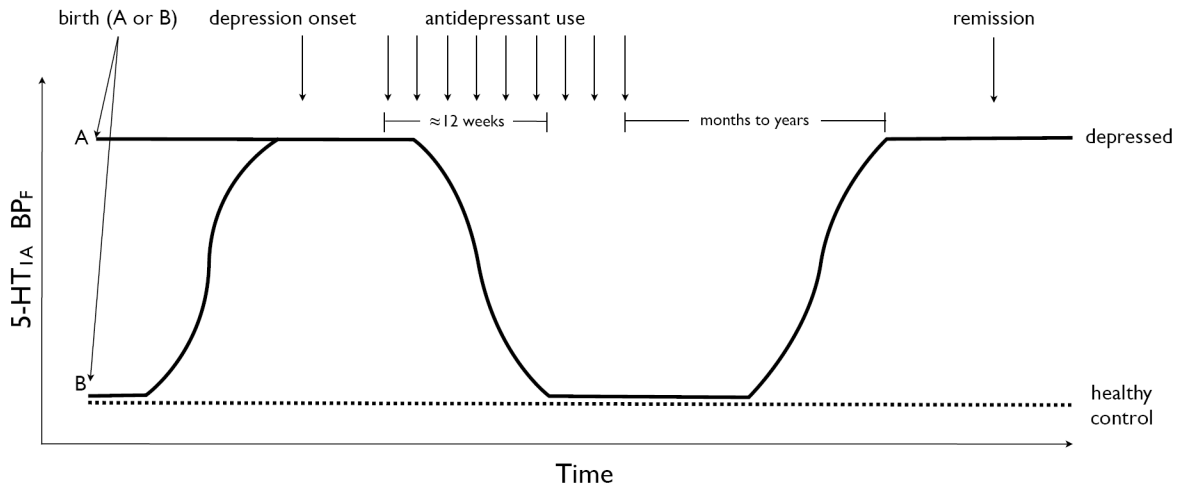

Figure 2.

Chronological model of serotonin 1A receptor binding potential over the life span among subjects with major depressive disorder as compared to healthy controls.

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Table 1

Clinical and Demographic Characteristics of the Sample

	Controls (n=51)	Remitted depressed (n=15)	Antidepressant-naive (AN) currently depressed (n=13)	Remitted Depressed vs. Controls	Remitted Depressed vs. AN Currently Depressed
Continuous Variables	mean (S.D.)			p-value (2-tailed t-test)	
Age	37.4±14.5	31.8±10.9	35.9±12.3	0.17	0.36
24-Item Hamilton Depression Rating Scale	0.7±1.0	3.5±2.3	25.5±8.0	<0.0001	<0.0001
Beck Depression Inventory	1.6±2.5	2.6±2.9	26.9±8.1	0.19	<0.0001
Global Assessment Scale	90.1±4.6	86.3±7.5	52.5±12.8	0.02	<0.0001
Beck Hopelessness Scale	1.7±2.3	2.5±2.4	9.6±6.1	0.21	0.0003
Brown Goodwin Aggression Scale	13.6±4.1	18.±4.1	16.3±4.6	0.0006	0.3
Years of Education	16.6±2.9	16.1±1.0	13.3±4.2	0.49	0.02
Age of Onset	N/A	15.9±4.8	22.1±11.4	N/A	0.069
Median number of prior depressive episodes	N/A	3	4	N/A	0.88*
Length of current major depressive episode (days)	N/A	N/A	76.3±163.9	N/A	N/A
Duration of remission (years)	N/A	2.9±1.8	N/A	N/A	N/A
Categorical Variables	N (%)			p-value (fisher's exact)	
Female	29 (56.9)	10 (66.7)	10 (76.9)	0.56	0.69
Subjects with a history of prior suicide attempts	0 (0)	2 (13.3)	4 (30.8)	0.049	0.37
Subjects with a history of major depression in first-degree relative	0 (0)	9 (60)	8 (61.5)	<0.0001	1
Race/Ethnicity				0.035	0.0006
Asian	7 (13.7)	0 (0)	0 (0)		
African-American	8 (15.7)	1 (6.7)	1 (7.7)		
Caucasian	28 (54.9)	13 (86.7)	4 (30.8)		
Hispanic	8 (15.7)	0 (0)	7 (53.8)		
>1 Race	0 (0)	1 (6.7)	1 (7.7)		

* p-value associated with non-parametric Mann-Whitney test as some subjects reported "too numerous to count" prior depressive episodes.

Table 2

Genotypic and Allelic Frequencies of the C(-1019)G polymorphism in the 5-HT_{1A} receptor gene.

		Genotypes n (%)			Alleles n (%)	
	n	**CC**	**CG**	**GG**	**C**	**G**
Controls	50*	17 (34)	29 (58)	4 (8)	49 (59.8)	33 (40.2)
Remitted MDD	14*	3 (21.4)	9 (64.3)	2 (14.3)	15 (53.6)	13 (46.4)
Current MDD	28	6 (21.4)	11 (39.3)	11 (39.3)	23 (41.1)	33 (58.9)

* One control and one remitted MDD subject were not genotyped.