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Brain Serotonin 1A Receptor Binding as a Predictor of Treatment Outcome in Major Depressive Disorder

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Abstract

Background—We previously reported higher serotonin 1A receptor (5-HT1A) binding in subjects with major depressive disorder (MDD) during a major depressive episode using positron emission tomography imaging with [^{11}C]WAY-100635. 5-HT1A receptor binding is also associated with treatment outcome after nonstandardized antidepressant treatment. We examined whether pretreatment 5-HT1A binding is associated with treatment outcome following standardized escitalopram treatment in MDD. We also compared 5-HT1A binding between all MDD subjects in this cohort and a sample of healthy control subjects.

Methods—Twenty-four MDD subjects in a current major depressive episode and 51 previously studied healthy control subjects underwent positron emission tomography scanning with [^{11}C]WAY-100635, acquiring a metabolite-corrected arterial input function and free-fraction measurement to estimate 5-HT1A binding potential ($BP_F = B_{max}/K_D$, where B_{max} = available receptors and K_D = dissociation constant). Major depressive disorder subjects then received 8 weeks of treatment with escitalopram; remission was defined as a posttreatment 24-item Hamilton Depression Rating Scale <10 and ≥50% reduction in Hamilton Depression Rating Scale.

Results—Remitters to escitalopram had 33% higher baseline 5-HT1A binding in the raphe nuclei than nonremitters ($p = .047$). Across 12 cortical and subcortical regions, 5-HT1A binding did not differ between remitters and nonremitters ($p = .86$). Serotonin 1A receptor binding was higher in MDD than control subjects across all regions ($p = .0003$). Remitters did not differ from nonremitters in several relevant clinical measures.

Conclusions—Elevated 5-HT1A binding in raphe nuclei is associated with subsequent remission with the selective serotonin reuptake inhibitor escitalopram; this is consistent with data

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from a separate cohort receiving naturalistic antidepressant treatment. We confirmed our previous findings of higher 5-HT1A binding in current MDD compared with control subjects.

Keywords

Antidepressant; depression; PET imaging; prediction; serotonin 1A receptor; treatment outcome

Psychiatrists currently lack tools that predict antidepressant response to specific treatments for major depressive disorder (MDD). The National Institutes of Health has identified personalized medicine as one of its primary research goals (1), and several efforts are currently underway to characterize moderators and mediators of treatment outcome in MDD (2-4).

The serotonin 1A (5-HT1A) receptor has been implicated in the pathophysiology of MDD in both animal models and human studies (5). We have found elevated 5-HT1A binding in the brain in current MDD in two previous samples (6,7) and also in a separate remitted MDD sample (8), using positron emission tomography (PET) imaging with [^{11}C]WAY-100635. This receptor serves an autoinhibitory role on serotonergic neurons in the raphe nuclei. Evidence also indicates a role for the 5-HT1A autoreceptor in the mechanism of action of selective serotonin reuptake inhibitors (SSRIs). In rodent models, SSRI exposure initially leads to reduced firing of serotonergic neurons via 5-HT1A autoreceptor stimulation. After approximately 14 days of SSRI exposure, the 5-HT1A receptor desensitizes and serotonergic neuronal firing rate is restored, leading to a net increase in intrasynaptic serotonin (9). This timing coincides with the clinically observed delay in SSRI antidepressant action.

We previously reported that higher baseline 5-HT1A receptor binding is associated with nonremission to naturalistic (open, nonstandardized) treatment for MDD (10). Since that publication, we have developed a method to increase precision of estimation in PET imaging, and therefore statistical power, by weighting observations according to their measurement precision, using standard errors estimated by a bootstrapping algorithm (11) (Supplement 1). The bootstrap algorithm incorporates errors associated with fitting the metabolite curve, input function, and time activity curve for each region of interest (ROI). When we reanalyzed data from this naturalistic study, weighting observations by bootstrap error, the direction of the finding was reversed in the raphe nuclei alone, with 29.5% higher raphe binding in remitters compared with nonremitters (p = .082) (12). Quantification of 5-HT1A binding in raphe nuclei may benefit particularly from incorporation of bootstrap errors, as small regions are particularly susceptible to measurement noise. This distinct finding in raphe nuclei compared with other brain regions is consistent with its distinct role as an autoreceptor in raphe nuclei (13).

In the current study, we compared baseline 5-HT1A binding between MDD remitters and nonremitters with 8 weeks of standardized pharmacotherapy with the SSRI escitalopram. Based on our naturalistic study, we hypothesized that remission would be associated with higher baseline 5-HT1A autoreceptor binding in the raphe nuclei and lower baseline binding across 12 cortical and subcortical regions in the terminal field.

The G allele of a functional promoter polymorphism in the serotonin 1A receptor gene (HTR1A, C-1019G) has been associated with increased 5-HT1A expression in raphe nucleus neurons both in vitro (14) and in vivo using PET (6,7,15). Some previous studies, including our previous naturalistic treatment study (10), have reported associations between the G allele and nonresponse to antidepressant medications (reviewed in [16]). In the current study, we examined HTR1A genotype in MDD escitalopram remitters and nonremitters, hypothesizing higher allelic frequency of the G allele among nonremitters. Finally, we compared this new cohort of MDD subjects with a sample of 51 historical control subjects (6), hypothesizing elevated 5-HT1A binding across all brain regions examined, based on our previous findings (6,7).

Methods and Materials

Sample

Participants were recruited through online or print advertisements and through referrals from neighboring outpatient clinics. Eligibility was assessed by psychiatric and medical history, chart review, physical examination, routine blood tests, pregnancy test, and urine toxicology. Axis I diagnoses were based on the Structured Clinical Interview for DSM-IV (17), conducted by doctoral- or masters'-level psychologists and reviewed in a consensus conference of research psychologists and psychiatrists. Inclusion criteria included: 1) age 18 to 65 years; 2) DSM-IV criteria for MDD in a current major depressive episode; 3) 17-item Hamilton Depression Rating Scale (HDRS) score ≥17; 4) ability to provide informed consent; and 5) ability to discontinue anticoagulant treatment, except for aspirin, for 10 days. Exclusion criteria included: 1) significant medical conditions; 2) lifetime history of alcohol abuse or dependence; 3) substance abuse or dependence (other than nicotine; Table 1) unless in complete remission for >6 months; 4) ecstasy or intravenous drug use more than two times; 5) presence of major psychiatric disorders, including schizophrenia (comorbid anxiety disorders allowed); 6) comorbid anorexia or bulimia nervosa within the past year; 7) first-degree family history of schizophrenia, if subject was <33 years old; 8) inability to remain off all psychotropic drugs that interact with serotonin transporters and/or 5-HT1A receptors for a minimum of 3 weeks; 9) fluoxetine use within 6 weeks of PET scanning; 10) pregnancy, current lactation, plans to conceive during study participation, or abortion within 2 months of enrollment; 11) medical contraindication to antidepressants; 12) dementia; 13) neurological disease or previous head injury accompanied by loss of consciousness or motor deficits; 14) exposure to 5-HT1A receptor agonist within preceding 6 months; 15) failure of more than two SSRI or other antidepressant monotherapy trials of adequate dose and duration; 16) metal implants; 17) current or past exposure to radiation; 18) active suicidality or ideation requiring inpatient admission or medication intervention; and 19) history of significant clinical decompensation in response to prior medication washout.

Inclusion criteria for control subjects consisted of items 1, 4, and 5 listed above. Additionally, control subjects had no current or past psychiatric diagnosis, with the exception of specific phobia, and were medication and drug free. Exclusion criteria for control subjects were: 1) lifetime alcohol or substance use disorder other than nicotine; 2) first-degree relatives with history of major depression, schizophrenia, or suicide attempt or

more than two relatives with substance dependence; and 3) items 4, 10, 13, and 17 listed above.

Based on prior medication history elicited during a semi-structured interview, MDD subjects were characterized as antidepressant-exposed (AE) if they had been exposed to an antidepressant medication for ≥2 months at a therapeutic dosage within 4 years of the scan date and as not recently medicated (NRM) if they were antidepressant-naïve or had antidepressant exposure ≥4 years before the date of PET scanning. We used this definition of NRM, as we previously found no difference in 5-HT1A binding potential BP_F between antidepressant-naïve MDD subjects and MDD subjects off of antidepressants for ≥4 years (6).

Clinical Procedures

No MDD subjects were taking antidepressant medication at study enrollment. One MDD subject had stopped ineffective antidepressant medication (duloxetine) before study enrollment and remained off of medication for 23 days before PET imaging, with weekly clinical monitoring. Short-acting benzodiazepines were allowed for treatment of anxiety or insomnia up until 72 hours before scanning. Only one subject used benzodiazepines for this purpose; this subject discontinued benzodiazepines 4 days before PET scanning. Following baseline PET and magnetic resonance imaging (MRI), treatment was initiated with escitalopram at a dose of 10 mg daily for the first 4 weeks. After 4 weeks, escitalopram dose was increased to 20 mg for nonresponders (<50% decrease in HDRS) and was maintained at 10 mg for responders. At 6 weeks, subjects still taking escitalopram 10 mg who were nonremitters (HDRS ≥10 or <50% decrease in HDRS) had their escitalopram dose increased to 20 mg. The primary clinical outcome measure was remission status at 8 weeks.

Twenty-eight subjects underwent baseline PET imaging and began treatment. Two subjects were not analyzed due to 1) further history revealing a prior diagnosis of anorexia nervosa, and 2) lack of input function. Two subjects dropped out of the study before completing 4 weeks of treatment. Two subjects discontinued escitalopram after completing 6 weeks of treatment (due to intolerable side effects), and 22 subjects completed 8 weeks of treatment. We analyzed data from 24 subjects completing at least 6 weeks of SSRI treatment, using last observation carried forward to determine remission status for subjects who did not attend their week 8 visit (both were nonremitters). Three MDD subjects from the current sample were excluded from comparisons of binding between MDD and control subjects, as they overlapped with an MDD sample presented previously (6).

PET/MRI Imaging

[^{11}C]WAY-100635 was synthesized as previously described (18). A metabolite-corrected arterial input function was acquired for use in kinetic modeling (19,20). Plasma free fraction (f_P) was measured to allow estimation of the outcome measure BP_F (see modeling). Injected dose (ID), injected mass (IM), and f_P differed between MDD subjects and healthy control subjects but not between remitters and nonremitters (Table 2). Results from a human dosimetry study (21) necessitated a reduction in ID (and consequently IM), causing the differences between control subjects (scanned earlier) and MDD subjects (scanned later).

However, no correlation was found between BP_F and either ID or IM (ID: $F = .135$, $df = 1,75$, $p = .71$; IM: $F = .33$, $df = 1,75$, $p = .95$). A head holder (Soule Medical, Tampa, Florida) was molded around the subject's head to minimize motion. Positron emission tomography images were acquired on an ECAT EXACT HR+ camera (Siemens/CTI, Knoxville, Tennessee) in three-dimensional mode. Following a 10-minute transmission scan, [^{11}C]WAY-100635 was injected as an intravenous bolus and emission data were collected for 110 minutes. T1-weighted MRI images were acquired for co-registration with PET images, identification of ROIs, and tissue segmentation on a 1.5T Signa Advantage or a 3T Signa HDx scanner (General Electric Medical Systems, Milwaukee, Wisconsin).

Image Processing

Image analysis was performed within MATLAB 2006b (The MathWorks, Natick, Massachusetts) using extensions to FSL version 3.3 (including Functional Magnetic Resonance Imaging of the Brain's Linear Image Registration Tool [FLIRT] [22], Brain Extraction Tool [23]), as well as Statistical Parametric Mapping 5 normalization (24) and segmentation routines (25). Motion correction of PET data was achieved using de-noising filter applied to all PET images starting at frame five, as well as rigid-body FLIRT. Positron emission tomography/MRI co-registration was performed using FLIRT between a mean image of motion-corrected PET frames and the T1-weighted MRI as previously described (26).

Regions of interest were manually drawn onto individual subjects' T1-weighted MRI images by experienced technicians trained to reliably approximate these regions using brain atlases (27,28) and published reports (29,30). A fixed volume elliptical ROI (2 cm^3) was placed on raphe nuclei in the dorsal midbrain identified on a mean PET image for each subject. A cylindrical ROI was drawn in the cerebellar white matter, which was used as the reference region, because, compared with cerebellar gray matter, it has lower volume of distribution (V_T), comparable nonspecific binding, and less specific binding (6,20).

Quantitative Analysis

V_T values of [^{11}C]WAY-100635 were estimated for each ROI using kinetic analysis with an arterial input function and a two-tissue compartment constrained model (for more details, see [19]). Time activity curves were fit with a two-tissue compartment constrained model in which K_1/k_2 ratio was constrained to that of the reference region (REF, cerebellar white matter), which was fit with a one-tissue compartment model. The primary outcome measure for this study was binding potential ($BP_F = B_{avail}/K_D$) where B_{avail} is the total number of available receptors and $1/K_D$ is the affinity of the tracer for the receptor. BP_F was calculated as $(V_{T(ROI)} - V_{T(REF)})/f_P$. While we have previously provided evidence supporting the use of BP_F as the outcome measure of choice with [^{11}C]WAY-100635 (6), we repeated primary analyses with the alternative binding potential outcome measures BP_P, which does not correct for f_P, calculated as $V_{T(ROI)} - V_{T(REF)}$, and BP_{ND}, which assumes equivalent nondisplaceable uptake across groups, calculated as $[V_{T(ROI)} - V_{T(REF)}]/V_{T(REF)}$, for comparison with other findings.

Genotyping

Genotyping of the C-1019G polymorphism of the HTR1A receptor gene was performed as previously described with allele-specific polymerase chain reaction amplification (7).

Statistics

Group comparisons of BP_F (remitters vs. nonremitters, MDD vs. control subjects) were performed using mixed-effects modeling methods, with region and diagnostic group as fixed effects and subject as the random effect. Standard errors were computed for each estimated BP_F value, using a bootstrap algorithm taking into account errors in plasma, metabolite, and brain data (11). To improve precision in group estimates, observations were weighted by their associated standard errors in the linear mixed effects. To determine the extent to which pretreatment raphe BP_F predicted clinical outcome, linear regression was performed, using posttreatment HDRS as the dependent variable and both pretreatment HDRS and raphe BP_F as independent variables. To allow for testing of proportional differences in binding across regions and to stabilize variance across regions, all analyses involving multiple regions were performed on log-transformed data. Analyses on a single region (raphe nuclei) were performed on data in the original (nontransformed) scale. Log transformation is used commonly to address skewness and unequal variance of data, both of which are generally issues with PET data. We and others have used log transformation in multiple prior studies (7,10,31-37). Other groups have used related statistical approaches, including linearizing transformation (38) and non-parametric testing (39), 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.

Data are presented graphically using actual (not log-transformed) BP_F values. Reported p values were not adjusted for multiple comparisons. Threshold of statistical significance for all analyses was set at $p < .05$. 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, Redmond, Washington) and chi-square tests were done in SPSS Statistics (IBM Corp., Armonk, New York).

Results

Sample Characteristics

Clinical and demographic variables are presented in Table 1. There were no differences between MDD remitters and nonremitters in baseline measures of depression severity, chronicity, prior antidepressant exposure, or family history of depression. Remission rate in the sample was 46%. One MDD subject (a remitter) had past cannabis dependence in sustained remission. Three nonremitters suffered from current comorbid anxiety disorders (two with generalized anxiety disorder and one with social phobia). Five remitters suffered from current comorbid anxiety disorders (all with social phobia, one with comorbid panic disorder, and one with comorbid generalized anxiety disorder).

5-HT1A Binding and Remission Status

Remitters had higher 5-HT1A binding in the raphe nuclei compared with nonremitters (F = 4.43, df = 1, p = .047) (Figure 1, Table 3). In contrast, 5-HT1A binding did not differ between remitters and nonremitters across all other regions tested simultaneously (F = .033, df = 1,22, p = .86). We have previously shown that 5-HT1A binding is dependent on sex, 5-HT1A genotype, and prior medication status (7,40). Remitter/nonremitter contrasts were unchanged after including sex, genotype, and prior medication status as covariates (raphe nuclei: F = 5.36, df = 1, p = .033; other ROIs: F = .002, df = 1,17, p = .97). Reference region binding did not differ between remitters and nonremitters (Table 2).

Effect of Diagnosis on 5-HT1A Binding

Consistent with our findings in two previous cohorts, the MDD group had higher 5-HT1A BP_F than control subjects across all ROIs examined (F = 14.59, df = 1,69, p = .0003) (Figure 2). This finding was unchanged after including sex and genotype as covariates (F = 12.08, df = 1,65, p = .0009). To examine the effects of prior medication status on binding, we compared AE MDD, NRM MDD, and control subjects in a model simultaneously and found a difference in BP_F across these groups (F = 7.51, df = 2,68, p = .0011). Pair-wise post hoc testing demonstrated higher binding in NRM MDD subjects compared with healthy control subjects (F = 14.39, df = 1,68, p = .0003) but not compared with AE MDD subjects (F = .896, df = 1,68, p = .35). These results were unchanged with the inclusion of sex and genotype as covariates (three-group comparison: F = 7.46, df = 2,64, p = .0012; NRM MDD vs. control subjects: F = 14.55, df = 1,64, p = .0003; NRM MDD vs. AE MDD: F = .85, df = 1,64, p = .36). Reference region binding did not differ between MDD subjects and control subjects (Table 2).

Relationship between HTR1A Genotype and 5-HT1A Binding

Genotype at the C-1019G locus did not differ between remitters and nonremitters (Fisher's exact, p = .64; Table 1). Consistent with our previous studies, we examined the effects of genotype on 5-HT1A binding in raphe nuclei in NRM MDD subjects and control subjects, including diagnosis as a covariate in this analysis. 5-HT1A binding was associated with genotype, with highest binding in raphe nuclei among GG homozygotes (F = 7.36, df = 1, p = .0086). This finding was unchanged including sex as an additional covariate (F = 9.09, df = 1, p = .0038).

Alternative Outcome Measures

Comparisons of binding between remitters and nonremitters yielded similar results using the alternative outcome measure BP_P, but not BP_{ND} (Table 3, all with same covariates as BP_F analyses; BP_P: remitters vs. nonremitters in raphe: F = 5.24, df = 1, p = .035; remitters vs. nonremitters in other ROIs: F = .023, df = 1,17, p = .88; BP_{ND}: remitters vs. nonremitters in raphe: F = 3.51, df = 1, p = .40; remitters vs. nonremitters in other ROIs: F = .49, df = 1,17, p = .49). Comparisons of binding between MDD and control subjects yielded similar results using the alternative outcome measure BP_{ND}, but not BP_P (Table 3; BP_P: F = 2.31, df = 1,66, p = .13; BP_{ND}: F = 6.42, df = 1,66, p = .014).

Discussion

In this study, we found higher pretreatment 5-HT1A binding in raphe nuclei among MDD subjects who remit after 8 weeks of standardized SSRI treatment compared with nonremitters. We did not find differences in 5-HT1A binding between remitters and nonremitters in the other brain regions examined, where 5-HT1A is localized mostly on target neurons within the terminal field of serotonergic neurons. Finally, we found elevated 5-HT1A binding across all regions examined in this MDD cohort compared with a historical healthy volunteer comparison group, consistent with findings in two previous MDD cohorts (6,7). This is presented in Figure 3, showing binding in three independent cohorts of not recently medicated MDD subjects compared with healthy control subjects.

Higher pretreatment 5-HT1A binding in the raphe nuclei in MDD remitters is consistent with the trend we found in the same direction in a previous cohort that received naturalistic antidepressant treatment when analyzed using an equivalent analytic approach (10). In that study, we also found higher 5-HT1A binding across the terminal field of serotonergic neurons among nonremitters compared with remitters, a finding not replicated in the current prospective study. There are several differences between these two studies that may partially explain these discrepant findings: in the previous study, subjects received nonstandardized treatment, including a range of different pharmacologic and psychotherapeutic interventions, and remission status was assessed at 1 year (in contrast to the 8-week trial of standardized SSRI treatment in the current study). Moreover, the samples differed: the current study had a higher proportion of antidepressant-naïve individuals, which is relevant, as prior antidepressant exposure is associated with lower 5-HT1A binding (6,7).

We hypothesize the following model to explain the association between high 5-HT1A binding at baseline in raphe nuclei and subsequent remission following SSRI treatment. High 5-HT1A autoreceptor levels in raphe nuclei (seen in eventual SSRI remitters) causes lower basal firing rate of serotonergic neurons. With acute SSRI administration, serotonin reuptake inhibition activates autoreceptors in raphe nuclei, further lowering serotonergic neuron firing rate and serotonin (5-HT) release. When these raphe autoreceptors desensitize over weeks of SSRI treatment (9), there will be a progressive increase in serotonergic neuron firing rate and in 5-HT release, which combined with SSRI reuptake inhibition enhances serotonergic neurotransmission.

In contrast, relatively normal 5-HT1A autoreceptor levels in raphe nuclei (seen in eventual SSRI nonremitters) may lead to more normal firing of serotonergic neurons at baseline and therefore less serotonin deficiency. Chronic SSRI exposure in this case will cause a smaller pool of 5-HT1A autoreceptors to desensitize, causing less of an increase in serotonergic neuron firing rate and in net 5-HT release.

The long-term goal of this research is to move from identification of group differences (remitters vs. nonremitters) to prediction of outcome in individual patients. In an exploratory manner, we examined the capacity of raphe BP_F to predict posttreatment HDRS, while co-varying for pretreatment HDRS, using linear regression. Raphe BP_F predicted 13% of variance in posttreatment HDRS, although the regression coefficient was not significant (*p*

= .13). While a finding of this magnitude is not yet translatable to the clinic, it is consistent with findings from a separate sample, has face validity, and was achieved without requiring the use of statistical methodology such as support vector machine for prediction.

This is the third independent cohort of current MDD subjects in which we report higher 5-HT1A BP_F compared with healthy control subjects; we have also shown that the abnormality is present in unmedicated MDD in sustained remission (8). There is disagreement in the literature regarding the direction of 5-HT1A receptor abnormalities in major depression assessed by PET using [^{11}C]WAY-100635. As described in a recent review (41), the largest differences across these studies are not in differential sampling of clinical populations, but rather in differences in the PET outcome measures employed. For the reasons described below, we believe BP_F to be the optimal outcome measure for quantification of 5-HT1A receptors using [^{11}C]WAY-100635. This series of studies provides strong support for elevated 5-HT1A receptor levels in MDD, consistent with animal models of depression (42,43), genetic findings (44), and the effectiveness of 5-HT1A-modulating medications in treating MDD (45,46).

Other groups have also examined the relationship between 5-HT1A binding and treatment response in MDD. One study reported higher [^{11}C]WAY-100635 binding in orbitofrontal cortex in 7 treatment nonresponders compared with 15 responders following treatment with an SSRI or a serotonin-norepinephrine reuptake inhibitor using the PET outcome measure BP_{ND} (47). Another study in elderly MDD subjects found that higher pretreatment [^{11}C]WAY-100635 BP_{ND} in the dorsal raphe nucleus was associated with longer time to achieve remission with paroxetine at a trend level (39). One difference between those studies and the present finding is the outcome measure used (BP_F vs. BP_{ND}); the outcome measure BP_{ND} is most dependent on the assumption of equivalent nondisplaceable uptake between groups (48). BP_{ND} normalizes specific binding to the binding in the reference region, whereas BP_F, employed in the current study, normalizes specific binding to the plasma free fraction of radiotracer. In the case of [^{11}C]WAY-100635, reference-region binding is very low, making it particularly susceptible to noise from sources including radiometabolites and problems with scatter correction (6,41). Small differences in reference-region binding (distribution volume of nondisplaceable compartment, V_{ND}) can greatly influence the outcome measure BP_{ND}, which is defined as $(V_T - V_{ND})/V_{ND}$. Consistent with this, we found differences between remitters and nonremitters in raphe using both BP_F and BP_P, but not BP_{ND}. For more on outcome measure selection for [^{11}C]WAY-100635, see Parsey *et al.* (6). An additional methodological difference with previous studies is that the current study incorporated bootstrap errors to better account for measurement error, thereby reducing noise in estimates (11), of particular importance in small regions such as raphe nuclei.

Plasma free fraction differed between MDD and control groups in this study, although it did not differ between MDD remitters and nonremitters. The difference observed in raphe BP_F between remitters and nonremitters was not driven by f_P, as these differences persisted using BP_P, which does not correct for f_P. Plasma free fraction did differ between MDD subjects and control subjects, with lower f_P among MDD subjects. When using the alternative outcome measure BP_P, which does not account for f_P, we did not find differences between

MDD subjects and control subjects in the current sample. In a previous study, however, with a larger MDD sample, we found that higher [^{11}C] WAY BP_F in not recently medicated MDD subjects was not fully explained by the observed group differences in f_P, as BP_P also differed between MDD and control subjects (6). There is evidence of inflammatory processes being activated in depression, with increased levels of C-reactive protein expression and certain cytokines, including interleukin-6, among individuals with MDD (49,50). One possible (and speculative) mechanism explaining low f_P and possibly f_{ND} (free fraction in the nondisplaceable compartment) in MDD would be through greater nonspecific binding of radiotracer to cytokines or C-reactive protein in peripheral plasma and in the central nervous system in this group.

We did not find a significant relationship between the C1019G polymorphism in the HRT1A gene and remission status. This is a small sample for pharmacogenetic research, but at least in this study, the relationship between binding and treatment outcome is independent of this promoter polymorphism. Other factors may have led to higher raphe binding in remitters independent of C1019G genotype, including genetic variation at other regulatory sites and epigenetic factors. Larger samples would be required to more definitively test this conclusion.

Future studies will benefit from the use of a 5-HT1A agonist radioligand, such as [^{11}C]CUMI-101, which specifically identifies high-affinity 5-HT1A receptors (51), thereby capable of measuring desensitization and not just downregulation. This may therefore be a better measure of autoreceptor effects on firing rates and may better predict treatment outcome. It also remains to be determined whether baseline 5-HT1A autoreceptor binding can predict antidepressant outcome with nonserotonergic treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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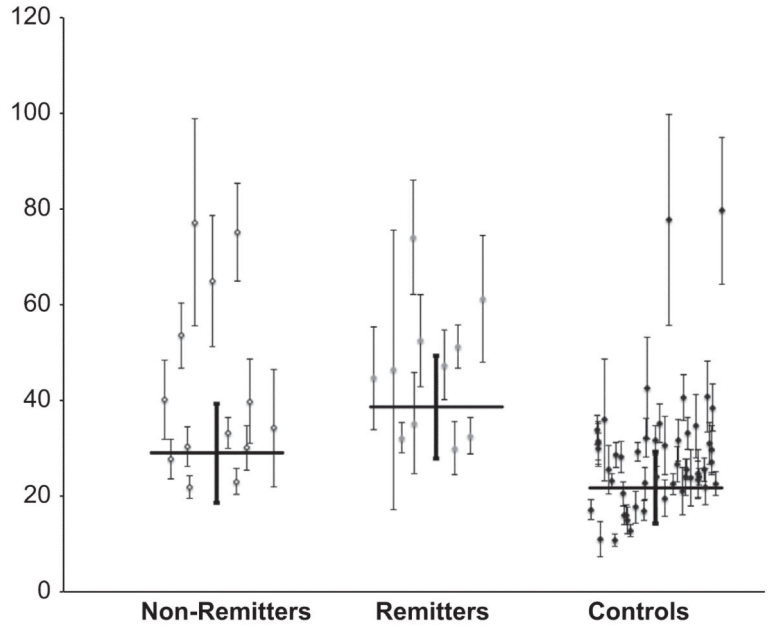

Figure 1.

Remitters to escitalopram have higher serotonin 1A binding potential (BP_F) in raphe nuclei than nonremitters (p = .047). Error bars represent standard errors computed using a bootstrap algorithm that takes into account errors in metabolite, plasma, and brain data. Horizontal bars represent weighted means.

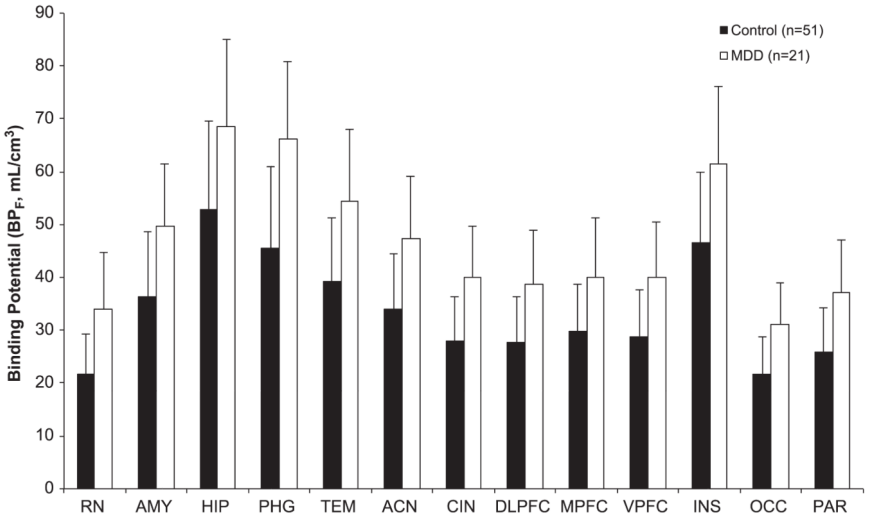

Figure 2.

Current major depressive disorder (MDD) subjects have higher serotonin 1A binding potential (BP_F) than healthy control subjects across all regions of interest examined ($p = .0003$). Bar heights represent the weighted means for each region of interest; error bars indicate the corresponding equivalent of the standard deviations of the weighted means. ACN, anterior cingulate; AMY, amygdala; CIN, cingulate cortex (posterior to ACN); DLPFC, dorsolateral prefrontal cortex; HIP, hippocampus; INS, insular cortex; MPFC, medial prefrontal cortex; OCC, occipital cortex; PAR, parietal cortex; PHG, parahippocampal gyrus; RN, raphe nuclei; TEM, temporal cortex; VPFC, ventral prefrontal cortex.

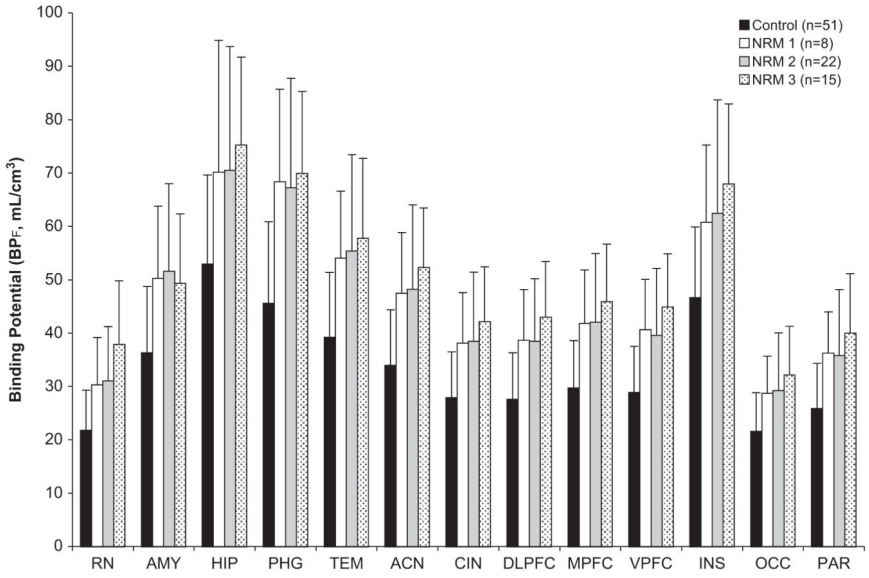

Figure 3.

Comparison of three independent cohorts of not recently medicated (NRM) current major depressive disorder subjects with healthy control subjects demonstrating consistent finding of elevated serotonin 1A binding potential (BP_F) in major depressive disorder across samples. ACN, anterior cingulate; AMY, amygdala; CIN, cingulate cortex (posterior to ACN); DLPFC, dorsolateral prefrontal cortex; HIP, hippocampus; INS, insular cortex; MPFC, medial prefrontal cortex; OCC, occipital cortex; PAR, parietal cortex; PHG, parahippocampal gyrus; RN, raphe nuclei; TEM, temporal cortex; VPFC, ventral prefrontal cortex.

Table 1

Clinical, Demographic, and Genetic Characteristics

	Control Subjects (*n* = 51)	Remitters (*n* = 11)	Nonremitters (*n* = 13)	Remitters Versus Nonremitters *p* Value
Age	37.3 ± 14.4	34.7 ± 14.0	35.2 ± 13.3	.92
Hamilton Depression Rating Scale (24-Item)	.7 ± 1.0	24.6 ± 6.2	24.6 ± 4.7	.99
Years of Education	16.6 ± 2.9	15.1 ± 2.3	15.5 ± 2.9	.74
Beck Depression Inventory	1.6 ± 2.5	23.3 ± 10.5	27.1 ± 10.2	.38
Global Assessment Scale	90.2 ± 4.8	60.4 ± 6.4	58.7 ± 5.3	.49
Beck Hopelessness Scale	1.6 ± 2.3	7.6 ± 8.1	9.5 ± 4.8	.53
Age of Onset	–	21.5 ± 9.2	26.8 ± 13.1	.28
Median Number of Major Depressive Episodes	–	2	2	.67[a]
% Female	29 (56.9%)	7 (63.6%)	10 (76.9%)	.66[b]
Number of Subjects with a Family History of Major Depressive Disorder	–	1	3	.60[b]
Number Not Recently Medicated Subjects (%)	–	10 (90.9%)	8 (61.5%)	.24[b]
Current Anxiety Disorder Comorbidity	–	5 (45.5%)	3 (23.1%)	.39[b]
Final Escitalopram Dose (mg)	–	15 ± 5.9	18.5 ± 3.8	.10
Current Nonsmoker (%)	46 (90.2%)	9 (81.8%)	10 (76.9%)	1[b]
C(-1019)G HTR1A Promoter Polymorphism				
CC	17 (34.0%)	4 (36.3%)	2 (16.7%)	
CG	29 (58.0%)	5 (45.5%)	7 (58.3%)	
GG	4 (8.0%)	2 (18.2%)	3 (25.0%)	.644[b]

HTR1A, serotonin 1A.

[a] Mann-Whitney U Test *p*-value.

[b] Fisher's exact test *p* value.

Table 2

[^{11}C]WAY-100635 PET Scan Parameters

	Control Subjects (n = 51)	Remitters (n = 11)	Nonremitters (n = 13)	Remitters Versus Nonremitters p Value	Control Subjects Versus MDD p Value
Injected Dose (mCi)	7.99 ± 3.43	5.68 ± 1.34	5.56 ± 1.62	.85	.002
Injected Mass (μg)	2.98 ± 1.94	1.30 ± 1.28	1.29 ± .95	.98	<.001
Plasma Free Fraction (f_P)	8.09% ± 2.40%	6.49% ± 1.95%	6.34% ± 2.05%	.85	.004
Reference Region Binding (volume of distribution, $V_{T(REF)}$, Cerebellar White Matter)	.25 ± .011	.24 ± .023	.28 ± .024	.27	.60

MDD, major depressive disorder; PET, positron emission tomography.

Table 3

Comparison of Binding Potential Values (Weighted Means ± SD) Across MDD Remitters, MDD Nonremitters, and Controls

	RN	AMY	HIP	PHG	TEM	ACN	CIN	DOR	MED	VPFC	INS	OCC	PAR
BP_F													
Control subjects (51)	21.8 ± 7.5	36.3 ± 12.5	53.0 ± 16.7	45.6 ± 15.3	39.2 ± 12.1	34.0 ± 10.4	27.9 ± 8.6	27.6 ± 8.7	29.7 ± 8.9	28.9 ± 8.7	46.6 ± 13.3	21.6 ± 7.2	25.9 ± 8.4
Nonremitters (13)	29.0 ± 10.3	47.8 ± 14.8	59.9 ± 17.8	61.6 ± 18.4	49.8 ± 16.2	42.4 ± 13.8	36.6 ± 11.8	34.5 ± 11.4	35.8 ± 12.3	35.7 ± 12.0	54.2 ± 16.9	28.1 ± 9.8	33.8 ± 10.9
Remitters (11)	38.7 ± 10.7	48.8 ± 14.8	74.4 ± 19.3	66.8 ± 16.5	55.0 ± 16.4	50.2 ± 13.0	40.1 ± 12.0	40.3 ± 11.2	44.0 ± 11.5	41.5 ± 11.2	65.7 ± 18.7	29.8 ± 9.3	37.5 ± 11.6
MDD (21)[a]	34.1 ± 10.6	49.7 ± 11.8	68.6 ± 16.5	66.2 ± 14.7	54.5 ± 13.6	47.4 ± 11.8	40 ± 9.6	38.6 ± 10.3	39.9 ± 11.5	40 ± 10.5	61.4 ± 14.7	31.1 ± 7.9	37.2 ± 9.8
BP_P													
Control subjects (51)	1.73 ± .51	2.73 ± .81	3.92 ± 1.23	3.46 ± 1.05	2.80 ± .93	2.46 ± .80	2.00 ± .67	1.97 ± .67	2.16 ± .69	2.06 ± .69	3.40 ± 1.00	1.56 ± .55	1.85 ± .62
Nonremitters (13)	1.74 ± .68	2.86 ± .85	3.68 ± .94	3.66 ± 1.00	3.02 ± .85	2.63 ± .73	2.20 ± .61	2.18 ± .57	2.27 ± .64	2.21 ± .59	3.34 ± .89	1.76 ± .50	2.10 ± .55
Remitters (11)	2.62 ± .66	3.20 ± .93	4.58 ± 1.22	4.30 ± 1.08	3.64 ± .99	3.17 ± .91	2.67 ± .69	2.60 ± .71	2.83 ± .78	2.63 ± .72	4.20 ± 1.16	1.96 ± .58	2.50 ± .69
MDD (21)[a]	2.0 ± .79	3.04 ± .84	4.08 ± 1.06	3.95 ± 1.02	3.34 ± .88	2.87 ± .79	2.43 ± .62	2.4 ± .63	2.5 ± .72	2.42 ± .64	3.71 ± .98	1.94 ± .49	2.33 ± .6
BP_{NS}													
Control subjects (51)	6.28 ± 1.93	10.68 ± 2.18	15.41 ± 3.27	14.24 ± 2.50	11.82 ± 2.31	10.19 ± 2.08	8.24 ± 1.86	8.33 ± 1.84	8.94 ± 1.84	8.58 ± 1.94	13.78 ± 2.61	6.64 ± 1.43	7.93 ± 1.68
Nonremitters (13)	6.69 ± 2.11	11.23 ± 1.75	13.32 ± 3.23	13.81 ± 2.79	11.51 ± 2.75	9.64 ± 2.69	8.46 ± 2.01	7.95 ± 2.22	8.40 ± 2.65	8.06 ± 2.33	12.31 ± 3.11	6.62 ± 1.49	7.93 ± 1.91
Remitters (11)	8.56 ± 2.65	12.12 ± 2.26	17.81 ± 3.60	15.31 ± 3.62	13.31 ± 3.11	11.88 ± 2.71	9.22 ± 2.46	9.57 ± 2.48	10.69 ± 2.27	9.56 ± 2.58	14.45 ± 3.81	7.03 ± 2.05	8.88 ± 2.47
MDD (21)[a]	7.18 ± 2.43	11.54 ± 2.05	14.44 ± 3.8	14.23 ± 3.16	12.13 ± 3.03	10.29 ± 2.88	8.69 ± 2.23	8.41 ± 2.44	9.08 ± 2.75	8.49 ± 2.52	12.97 ± 3.55	6.77 ± 1.73	8.22 ± 2.17

ACN, anterior cingulate; AMY, amygdala; CIN, cingulate cortex (posterior to ACN); DOR, dorsolateral prefrontal cortex; HIP, hippocampus; INS, insular cortex; MDD, major depressive disorder; MED, medial prefrontal cortex; OCC, occipital cortex; PAR, parietal cortex; PHG, parahippocampal gyrus; RN, raphe nuclei; TEM, temporal cortex; VPFC, ventral prefrontal cortex.

[a] Three MDD subjects from the current sample were excluded from comparisons of binding between MDD and control subjects, as they overlapped with the MDD sample presented in a previous publication (6).

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