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Measurement of 5-HT\textsubscript{1A} receptor binding in depressed adults before and after antidepressant drug treatment using PET and [\textsuperscript{11}C]WAY-100635

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Abstract

Objective—To assess effects of chronic antidepressant drug treatment on serotonin type-1A receptor (5-HT\textsubscript{1A}R) binding potential (BP) in major depressive disorder.

Methods—Depressed subjects (n=27) were imaged using PET and [\textsuperscript{11}C]WAY-100635 at baseline and following a median of 9.4 weeks of treatment with selective serotonin reuptake inhibitor or dual reuptake inhibitor antidepressant agents. Fifteen subjects had complete pre- and post-treatment scan data. The 5-HT\textsubscript{1A}R BP was derived from the tissue time-radioactivity concentrations from regions-of-interest defined a priori using a simplified reference tissue model (SRTM), and in a subset of subjects, compartmental modeling (CMOD).

Results—Chronic treatment had no effect on pre- or postsynaptic 5-HT\textsubscript{1A}R BP, as confirmed by both the SRTM and CMOD analyses. These results were unaffected by treatment response status and were consistent across brain regions. Among the 22 subjects for whom the clinical response-to-treatment was established, the treatment non-responders (n=7) had higher baseline BP values in the left (p=0.01) and right orbital cortex (p=0.02) than the responders (n=15).
Conclusions—Chronic antidepressant drug treatment did not significantly change cerebral 5-HT\textsubscript{1A}R binding, consistent with preclinical evidence that the alterations in serotonergic function associated with antidepressant drug administration are not accompanied by changes in 5-HT\textsubscript{1A}R density. Higher baseline 5-HT\textsubscript{1A}R binding was associated with poorer response to treatment.

Keywords
raphe nucleus; hippocampus; major depression; selective serotonin reuptake inhibitor

Introduction
Alterations in serotonin type-1A receptor (5-HT\textsubscript{1A}R) function have been associated with the pathophysiology (Arango et al. 2001; Bowen et al. 1989; Drevets et al. 2000; Lopez et al. 1998; Stockmeier et al. 1998) and treatment (Artigas et al. 1996; Chaput et al. 1991; Cowen 2000; Frazer et al. 1990; Haddjeri et al. 1998) of major depressive disorder (MDD). Several groups (Drevets et al. 1999; Meltzer et al. 2004a; Sargent et al. 2000), but not all (Parsey et al. 2006), reported abnormal reductions of in vivo pre- and postsynaptic 5-HT\textsubscript{1A}R binding potential (BP; proportional to B\textsubscript{max} x affinity, where B\textsubscript{max} = receptor density) in depressives versus controls using PET and [carbonyl-\textsuperscript{11}C]WAY-100635 ([\textsuperscript{11}C]WAY). There has been minimal study, however, of whether antidepressant treatment reverses the 5-HT\textsubscript{1A}R binding abnormalities observed in MDD. Although serotonin reuptake inhibitor (SRI) induced increases in intrasynaptic 5HT concentrations are not associated with increases in 5-HT\textsubscript{1A}R density and mRNA expression in experimental animals, SRI effects in depressed humans may be unique. For example, the down-regulation of 5-HT\textsubscript{1A}R mRNA expression and density in MDD has been hypothesized to result from glucocorticoid hormone hypersecretion, a process which may be interrupted by antidepressant drug treatment (Lopez et al. 1998).

In one study of selective SRI (SSRI) treatment effects on human 5-HT\textsubscript{1A}R BP using \textsuperscript{11}C]WAY-PET (Sargent et al. 2000), no treatment-associated changes in BP were evident in regions where the 5-HT\textsubscript{1A} receptor is expressed postsynaptically. In the raphe, where 5-HT\textsubscript{1A}R expression occurs presynaptically, the BP showed a nonsignificant trend toward being lower in the post-SRI-scans (effect size of 0.26). This latter observation was notable because the presynaptic 5-HT\textsubscript{1A}R population becomes desensitized during chronic SRI administration (see Discussion). The present study investigated the effects of SRI treatment in an independent MDD sample, using both a reference tissue model and an arterial input function-based kinetic model to quantify 5-HT\textsubscript{1A}R BP. Preliminary data also were acquired in a subgroup of subjects treated with venlafaxine, an agent expected to inhibit the reuptake of norepinephrine as well as serotonin (Beique et al. 2000; Debonnel et al. 2006; Harvey et al. 2000), based upon preclinical evidence that antidepressant agents with potent norepinephrine reuptake inhibiting effects proved more effective than SSRI at preventing stress-induced decreases in 5-HT\textsubscript{1A}R binding and mRNA expression (Lopez et al. 1998).

In addition, we characterized the relationship between the clinical response to antidepressant drug treatment and the regional 5-HT\textsubscript{1A}R binding in the pretreatment, baseline condition. Most studies of MDD found abnormal reductions in the postsynaptic 5-HT\textsubscript{1A}R receptor
binding in unmedicated depressed patients (Bowen et al. 1989; Drevets et al. 1999; Sargent et al. 2000; Lopez et al. 1998). It is thus noteworthy that chronic administration of antidepressant agents from various drug classes increases post-synaptic 5-HT1A R function (without altering receptor density) in rodents (Chaput et al. 1991; Haddjeri et al. 1998). If this effect also extends to depressed humans, then it is conceivable that the depressed subjects with the greatest reduction in post-synaptic 5-HT1A R binding prior to treatment will benefit most from the potentially compensatory effect of enhancing postsynaptic 5-HT1A R transmission. We tested this hypothesis by comparing the pretreatment 5-HT1A R binding between the subjects who proved responsive to antidepressant treatment versus those who did not.

**Materials and Methods**

Subjects were enrolled between January 1998 and October 2002, after being recruited through media advertisements and psychiatric services (inpatient/outpatient/emergency) at the University of Pittsburgh. Subjects provided written informed consent as approved by the University of Pittsburgh Biomedical IRB. Subjects were included if they met DSM-IV criteria for recurrent MDD based upon an unstructured interview with a psychiatrist and the Structured Clinical Interview for DSM IV, and had a 17-item Hamilton Rating Scale for Depression (HRSD17) score ≥ 18. Subjects were excluded if they had medical or neurological illnesses likely to affect cerebral physiology or anatomy, gross abnormalities of brain structure evident in MRI scans, suicidal intent, substance abuse within 1 year, lifetime history of substance dependence (other than nicotine), or exposure to psychotropic or other medications likely to alter cerebral physiology or monoamine function within 3 weeks (8 weeks for fluoxetine).

Twenty-seven depressed subjects (55.6% female; mean age=34.3±8.7 yrs) were imaged at unmedicated baseline. Seven subjects withdrew from the study after the baseline scan (5 discontinued treatment, one continued treatment but failed to return for rescanning, and one elected to receive a non-SRI antidepressant drug). The remaining 20 subjects were imaged after a median of 9.4 weeks (range: 7 to 63 weeks) of treatment. Medication-naïve subjects and prior SSRI responders were treated with citalopram (n=14; mean dose=41±9.5 mg/d, range 20–60 mg). Prior SSRI non-responders were treated with venlafaxine (n=4; doses were 187.5, 225, 375, and 375 mg/d). An additional subject was treated with combined citalopram 20 mg/d plus venlafaxine 225 mg/d. Treatment response was defined as a 50% reduction in HRSD17 score.

The PET scans were acquired on an ECAT HR+ PET scanner (CTI-PET systems, Knoxville, TN) in 3D mode [63 transaxial planes 2.4-mm thick; in-plane resolution=4.1 mm full-width at half-maximum (FWHM) over a 15.2-cm field-of-view]. Radiosynthesis of [carbonyl-11C]WAY was performed as described by (McCarron et al. 1996). A transmission scan was obtained to correct the PET emission scan for attenuation effects. A dynamic emission scan (29 frames of increasing length over 60 min) then was initiated following i.v. bolus administration of 9 to 19 mCi of high specific activity [11C]WAY (1.58 +/- 0.71 mCi/ nmol at time of injection). Thirty minutes of additional post-injection emission data (total scan duration=90 min) was collected in a subset of 8 subjects to ensure the comparability of

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the results obtained using either scan length (Parsey et al. 2000). Arterial blood was sampled and corrected for radiolabeled metabolites to compute the plasma input function of $[^{11}\text{C}]\text{WAY}$ in 17 of the 27 subjects pretreatment, and in 8 subjects post-treatment.

To provide an anatomical framework for analysis of the PET data, MRI scans were obtained using a 1.5 T GE Medical Systems (Milwaukee, WI) Signa Scanner and a 3D spoiled gradient recalled (SPGR) sequence. The MRI and PET images were aligned using automated image registration (AIR; Woods et al. 1993). Regions-of-interest (ROI) were manually traced on the MRI scan using a modified version of the IDL-based (Interactive Data Language, Boulder, CO) computer program, ROI TOOL (CTI PET Systems; Knoxville, TN). The ROIs were defined in the raphe nucleus (RN), the mesiotemporal cortex [MTC; hippocampus, amygdala, and parts of the parahippocampal and periamygdaloid cortices; Brodmann area (BDA) 34/27/28], the right (RLO; BDA 45/47) and left lateral orbital (LLO; BDA 45/47) cortex, the postcentral gyrus (PCG; BDA 1/2/3) and the occipital cortex-posterior cingulate gyrus (OCC-PC; BDA 17/18/31), as previously described (Drevets et al. 1999). These ROIs were chosen on the basis of association with 5-HT$_{1A}$R reductions in prior PET (Drevets et al. 1999; Sargent et al. 2000) and post mortem studies of depression (Arango et al. 1995; Bowen et al. 1989; Lopez et al. 1998). A reference region for assessing nonspecifically bound and free radioligand was defined in the cerebellar gray matter (CER) using anatomical guidelines that excluded the vermis (Parsey et al. 2005) and minimized the influence of spill-in effects from the temporal-occipital cortex (Bailer et al. 2005; Drevets et al. 1999; Meltzer et al. 2001; Meltzer et al. 2004b; Price et al. 2002b). Because the RN is inadequately visualized in MR images, the ROI for this structure was defined on summed late PET image frames which predominantly reflect 5-HT$_{1A}$R-specific binding on 7 planes spanning the pontine and midbrain raphe nuclei (see Drevets et al. 1999).

Tissue time-activity concentrations were obtained from the dynamic PET image for each ROI. Regional 5-HT$_{1A}$R-BP values were determined using a simplified reference tissue method (SRTM; Gunn et al. 1998; Lammertsma et al. 1996). In subjects for whom arterial blood was sampled, a 2-tissue compartmental model (CMOD) was applied to the arterial input function and regional tissue time-activity concentrations to derive the 5-HT$_{1A}$R distribution volumes (DV). Regional measures of 5-HT$_{1A}$R BP were determined for the compartmental model as $BP = (DV_{ROI}/DV_{CER}) - 1 = (B_{max}/K_D)f_2 = k_3/k_4$ (equivalent to SRTM BP measure), where $B_{max}$ is the available 5-HT$_{1A}$R density, $K_D$ is the equilibrium dissociation constant, $f_2$ is the free fraction of $[^{11}\text{C}]\text{WAY}$ in tissue, $k_3$ is the association rate of $[^{11}\text{C}]\text{WAY}$ to 5-HT$_{1A}$R, and $k_4$ is the dissociation rate of $[^{11}\text{C}]\text{WAY}$ from 5-HT$_{1A}$R (Lammertsma et al. 1996; Mintun et al. 1984).

Statistical inference for 5-HT$_{1A}$R BP was conducted with the Wilcoxon signed ranks test or the Mann-Whitney $U$ test, for related and independent samples respectively, with SPSS (SPSS Software Version 13, SPSS Inc, Chicago, IL). Possible relationships between the baseline HRSD$_{17}$ scores and the 5-HT$_{1A}$R-BP values and between the treatment-associated changes in these measures also were explored using Spearman’s rho correlation coefficients. Mixed-effects statistical analysis with repeated measures was performed post-hoc on the SRTM-derived BP data using SAS Proc Mixed (SAS/STAT Software Version 8 2000 SAS institute, Cary, NC), with subjects as the random term. This method offered the benefit of
employing the maximal sample size (Brown et al. 1999) to test treatment-by-region, treatment-by-gender, and treatment-by-response interactions in the SRTM-derived BP data. The SRTM- and CMOD-derived BP values for the 60 and 90 minute dynamic scans were compared to assess the possibility of bias, and were correlated within subjects using Pearson correlation coefficients.

**Results**

The demographic and clinical data for the subjects are listed in table I. Comorbid disorders present in the depressed sample were: panic disorder (2), bulimia (1), alcohol/substance abuse in remission >1 year (11), specific phobia (4), post-traumatic stress disorder (2), and social phobia (2). Of the 27 subjects entered, 22 (81.5%) had sufficient clinical data obtained during the treatment phase to determine response status (these included the 20 cases scanned both pre- and post-treatment plus two cases who withdrew before re-scanning). Of these, 15 (68%) were treatment responders (>50% reduction in HRSD_17 score). The mean interscan interval did not differ between responders (16±16 wks) and nonresponders (16±11 wks; p=0.99). The interscan intervals were not correlated with the changes in 5HT_1A_R BP measured using SRTM. The subgroups with and without post-treatment scan data were demographically and clinically similar.

Of the 20 subjects scanned both pre- and post-treatment, the pretreatment scans were excluded from analysis for 2 subjects due to excessive movement and for 1 subject for showing outlying values [defined as x > mean ± 3(SD)]. The post-treatment scans from 2 additional subjects were excluded due to excessive movement. A complete set of technically usable pre- and post-treatment images thus was obtained for 15 subjects. In the subjects for whom arterial blood was sampled both pre- and post-treatment (n=8), the arterial input function from one subject’s pretreatment scan and the image reconstruction from another subject’s post-treatment scan proved unusable due to technical problems. Thus, 6 subjects had complete pre- and post-treatment scan data with technically usable arterial input functions.

From the paired analyses, the mean [¹¹C]WAY BP values derived using SRTM appear in table II, and the mean [¹¹C]WAY DV and BP values derived via CMOD appear in table III. The pre- and post-treatment BP or DV values did not differ significantly in any ROI in either analysis (Tables I & II; Figure 1). Inclusion of the outlier (see above) in the SRTM analysis did not alter these results. When the subjects treated with venlafaxine were excluded from the paired analysis, the SSRI alone group (n=10) showed no significant differences in the pre- versus post-treatment BP values in any region (Table II; Figure 1). In subjects treated with venlafaxine (n=5), there also were no significant differences in the pre-versus post-treatment BP values in any region (Table II).

Analysis of the data from the entire intention-to-treat sample (n=27) using the mixed-effects model also revealed no significant effects of treatment on the SRTM-derived BP values in any region either when including [F(1,14) = 2.07, p = 0.17; Figure 2] or excluding the subjects treated with venlafaxine ([F(1,9)=2.99, p=.12]. There also were no significant
treatment-by-region interactions [F(5,69)=0.05, p=1.00] or treatment-by-gender interactions evident in the these analyses [F(1,13)=1.51, p=0.24].

The regional BP values did not differ significantly between pre- and post-treatment scans for the treatment responsive subgroup alone, and the mean treatment-associated changes in BP did not differ significantly between responders and nonresponders. The interactions between treatment response status and treatment-associated changes in regional BP were not significant [F(1,13)=3.10, p=0.10]. Changes in the HRSD$_{17}$ scores did not correlate with changes in SRTM-derived BP values in any ROI (RN: r=0.004, p=0.99; LLO: r_=-0.34, p=0.22; RLO: r =-0.18; p=0.53; OCC-PC: r =0.06, p=0.82; PCG: r =-0.11, p=0.69; MTC: r=_-0.37, p=0.20).

Among the 22 subjects for whom the clinical response-to-treatment was established, the treatment non-responders (n=7) had higher baseline BP values in the left (3.82 ± 0.39 versus 3.20 ± 0.55; exact MWU =88; p=0.01) and right orbital cortex (3.83 ± 0.33 versus 3.26 ± 0.55; exact MWU =71; p=0.02) than the treatment-responders (n=15). The baseline BP values did not differ significantly between responders and nonresponders in the PCG (p=0.08), OCC-PC (p=0.12), RN (p=0.97) or MTC (p=0.98). The baseline BP values were not correlated with baseline HRSD$_{17}$ scores in any region (RN: r= 0.29, p=0.17; LLO: r= 0.06, p=0.78; RLO: r= 0.18, p=0.39; OCC-PC: r = 0.17, p=0.44; PCG: r =-0.09, p=0.67; MTC: r= 0.16, p=0.49).

For the scans for which technically usable arterial input functions were available (n=15), the CMOD-derived BP values were positively correlated with the SRTM-derived BP values (r; 95% confidence interval; p value) in RN (0.83; 0.54–0.94; <0.001), LLO (0.83; 0.54–0.94; <0.001) RLO (0.81; 0.50–0.93; <0.001), OCC-PC (0.85; 0.60–0.95; <0.001), PCG (0.81; 0.52–0.94; <0.001), and MTC (0.59; 0.02–0.87;0.045; n=12). The SRTM-derived BP-values were biased toward being lower than the CMOD-derived BP-values, as previously described (Parsey et al 2000). [SRTM BP values were lower than CMOD BP values in every ROI (p<.001).]

In the subjects with 90 min emission scans (n=6), the SRTM-derived BP values obtained using the 90 min time-radioactivity concentration curves correlated tightly with those obtained using only the 60 min curves in all regions, as follows (r; 95% confidence interval; p value): RN (0.99; 0.91–1.0; <0.001), LLO (0.99; 0.91–1.0; <0.001), RLO (0.96; 0.67–1.0; 0.003), OCC-PC (0.96; 0.67–1.0; 0.003), PCG (0.99; 0.91–1.0; <0.001), and MTC (0.98; 0.82–1.0;0.001). [SRTM 60 min BP values were lower than SRTM 90 min BP values as follows: LLO 4%, p=.063; MTC 11%, p=.031; OCC 0.2%, NS; PCG 3.8%, p=.031; RLO 4.4%, p=.063; RN 9.4%, p=.094.]

In subjects for whom both 90 min emission scans and arterial input functions were obtained (n=7), the CMOD derived BP values also were highly correlated between the 60 and 90 min data in RN (0.94; 0.62–0.99; <0.002), LLO (0.93; 0.61–0.99; p<0.002), RLO (r=0.87; 0.35–0.98; <0.01), OCC-PC (0.96; 0.75–0.99; p<0.001), PCG (r=0.75; 0.0–0.96; <0.05), and MTC (0.91;0.50–0.99; 0.004). [CMOD 60 min BP values were non-significantly lower (p>.
Discussion

The mean 5-HT\textsubscript{1A}R binding did not change significantly following chronic SRI treatment in the orbital, mesiotemporal, parietal, or occipital cortices or the midbrain/pontine raphe nuclei, as measured using \textsuperscript{[11]}CWAY-PET. These negative results are consistent with Sargent et al. (2000), who found no significant changes in \textsuperscript{[11]}CWAY binding in MDD subjects following chronic paroxetine (n=16) or sertraline (n=4) treatment. These data also appear compatible with preclinical evidence that postsynaptic 5-HT\textsubscript{1A}R density and mRNA expression remain unchanged during SRI-induced increases in intrasynaptic serotonin concentrations (Carli et al. 1996; Hensler et al. 1991; Spurlock et al. 1994; Welner et al. 1989), and that the SRI-induced 5-HT\textsubscript{1A} autoreceptor desensitization occurs through receptor internalization or G-protein changes (Hensler 2003; Zimmer et al. 2004) rather than through alterations in receptor density (Frazer & Hensler 1990). Notably, \textsuperscript{[11]}CWAY binding is insensitive to competition from endogenous 5HT (Hume et al. 2001; Parsey et al. 1998), and as a lipophilic, high-affinity 5-HT\textsubscript{1A}R antagonist, \textsuperscript{[11]}CWAY is likely to bind internalized receptors without showing significant changes in site affinity (Laruelle 2000).

A limitation of our study was that the sample for which usable pre- and post-treatment scan data were available consisted of only 15 subjects, so we could not rule out the possibility that the small and nonsignificant differences observed in tables II and III might become significant in a much larger sample. However, the small effect sizes across regions for the full sample (0.01 – 0.35; 0.5 – 9% changes) suggests that any treatment-associated effect may be within the range of measurement variability. Too few subjects (n=5) were re-imaged following venlafaxine treatment in order to establish whether NRI agents alter the 5-HT\textsubscript{1A}R BP, however. A future study involving a larger subject sample treated with NRI agents thus may be warranted.

The negative results obtained with respect to changes in 5-HT\textsubscript{1A}R binding were primarily based upon BP values derived using SRTM and 60 min emission scan data. Our study was initiated using this approach as validated for \textsuperscript{[11]}CWAY by Gunn et al. (1998). When Parsey et al. (2000) reported evidence that the SRTM approach to analyzing \textsuperscript{[11]}CWAY images introduced bias (consistently underestimating BP) and that longer dynamic scans were needed to reach equilibrium conditions in some regions, we revised our methods to add arterial blood sampling and increase the scan duration. Nevertheless, the bias introduced by the SRTM method (Parsey et al. 2000) is inconsequential to the comparisons of pre- versus post-treatment 5-HT\textsubscript{1A}R BP data, because both measures are subject to identical bias. Moreover, the greater test-retest reliability of the SRTM method compared to CMOD or other approaches (Parsey et al. 2000) enhanced the sensitivity of our pre-versus post-treatment comparisons. Moreover, the SRTM- and CMOD-derived 5-HT\textsubscript{1A}R BP values were correlated in the subset of subjects for whom arterial blood was sampled, supporting the emphasis of the SRTM-derived BP values as the largest available data set of pre- and post-SRI treatment 5-HT\textsubscript{1A}R binding data (table II).
Another limitation of the current study was that the analyses were restricted to a few, relatively large, predefined ROIs. We thus could not exclude the possibility that SRI-induced changes in 5-HT₁AR BP may have occurred outside the regions sampled, or may have been limited to subsections of these ROI.

Although chronic SRI administration did not appear to correct the abnormal reduction in 5-HT₁AR binding reported in MDD, such treatments may nevertheless compensate for deficient 5-HT₁AR function in depression. By desensitizing the presynaptic 5-HT₁A autoreceptor and thereby increasing the amount of 5-HT release (Artigas et al. 1996; Blier et al. 1983; Blier et al. 1986; Chaput et al. 1988; Chaput et al. 1991) chronic SRI administration appears to increase postsynaptic 5-HT₁AR function (Chaput et al. 1991; Price et al. 1989). Likewise, chronic treatment with NRI or tricyclic antidepressant agents results in tonic activation of postsynaptic 5-HT₁AR in the absence of alterations in receptor density (Chaput et al. 1991; Haddjeri et al. 1998).

These effects of antidepressant drugs of increasing postsynaptic 5-HT₁AR function is noteworthy in view of our finding that the pre-treatment 5-HT₁AR binding was lower in the orbital cortex in subjects who proved responsive to treatment versus subjects who proved nonresponsive (effect size of 1.3 in the LLO). This observation is compatible with a previous report that MDD cases with a lower raphe 5-HT₁AR binding in the pretreatment, baseline condition showed more rapid rates of symptom remission during antidepressant drug treatment (Meltzer et al. 2004a). Conversely, MDD cases who expressed the G allele of the C(−1019)G 5-HT1A promoter region polymorphism showed decreased response rates to SSRI treatment (Lemonde et al. 2004) and increased 5-HT₁AR BP in one study (Parsey et al. 2006), although a second study could not confirm the association between this polymorphism and regional 5-HT₁AR BP (David et al. 2005). Nevertheless, concurrent assessment of genotype, treatment response and neuroimaging binding measures ultimately may provide fruitful research directions for elucidating pathophysiology and guiding treatment development.

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Figure 1.
Pattern of 5-HT$_{1A}$ receptor BP changes in the raphe nucleus during treatment with selective serotonin reuptake inhibitors (SSRI; solid lines), venlafaxine alone (dashed lines), or venlafaxine plus an SSRI (heavy solid line).
Figure 2. Boxplots of observed 5HT1A receptor BP before and following SRI treatment for data obtained from the entire study sample

This graph shows pre- and post-treatment 5-HT1A receptor BP in three representative regions-of-interest using all available pre and post-treatment SRTM data (including the outlier). LLO = left lateral orbital cortex; baseline scan n=26, post-treatment scan n=18. MTC = mesiotemporal cortex; baseline scan n=24, post-treatment scan n=16. RN = raphe nucleus: baseline scan n=26, post-treatment scan n=18). ○ denotes the outlier.
# TABLE I

Demographic and clinical characteristics of subjects

<table>
<thead>
<tr>
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<th>All Subjects</th>
<th>Usable Post-treatment scan data</th>
<th>Unusable or unavailable Post-treatment scan data</th>
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<tr>
<td>N</td>
<td>27</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>Proportion of females (%)</td>
<td>55.6</td>
<td>50</td>
<td>66.7</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>34.3 (8.7)</td>
<td>34.8 (7.8)</td>
<td>33.2 (10.7)</td>
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<tr>
<td>Baseline HRSD$_{17}$ [mean (SD), range]</td>
<td>21.0 (4.3), 14–31</td>
<td>21.1 (3.8), 14–28</td>
<td>20.8 (5.4), 17–31</td>
</tr>
<tr>
<td>Post-treatment HRSD$_{17}$ [mean (SD), range]</td>
<td>9.5 (8.5), 0–28 (n=22)</td>
<td>8.6 (8.0), 0–28</td>
<td>11.0 (11.1), 0–28 (n=4)*</td>
</tr>
</tbody>
</table>

*Post-treatment HRSD missing for four subjects who discontinued medications before completion of a therapeutic trial
### TABLE II

Paired comparisons of regional 5-HT$_{1A}$R binding potential (BP) values (mean±SD) derived using simplified reference tissue modeling in the pre- versus post-treatment conditions.

<table>
<thead>
<tr>
<th>ROI</th>
<th>Entire Sample (n=15)</th>
<th>SSRI alone (n=10)</th>
<th>Venlafaxine +/- SSRI (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-treatment</td>
<td>Post-treatment</td>
<td>W; p-value$^b$</td>
</tr>
<tr>
<td>MTC$^a$</td>
<td>5.62 ± 1.37</td>
<td>5.14 ± 1.39</td>
<td>−0.85;0.43</td>
</tr>
<tr>
<td>RN</td>
<td>2.02 ± 0.40</td>
<td>1.92 ± 0.44</td>
<td>−0.97;0.36</td>
</tr>
<tr>
<td>LLO</td>
<td>3.44 ± 0.51</td>
<td>3.60 ± 0.71</td>
<td>−0.28;0.80</td>
</tr>
<tr>
<td>RLO</td>
<td>3.51 ± 0.48</td>
<td>3.53 ± 0.65</td>
<td>−0.06;0.98</td>
</tr>
<tr>
<td>OCC-PC</td>
<td>2.02 ± 0.40</td>
<td>2.11 ± 0.57</td>
<td>−1.08;0.30</td>
</tr>
<tr>
<td>PCG</td>
<td>2.77 ± 0.59</td>
<td>2.90 ± 0.68</td>
<td>−0.85;0.42</td>
</tr>
</tbody>
</table>

Abbreviations: ROI=region of interest; MTC=mesiotemporal cortex; RN=raphe nucleus; LLO=left lateral orbital cortex; RLO=right lateral orbital cortex; OCC-PC=occipital cortex-posterior cingulate gyrus; PCG=post central gyrus.

- $^a$ one subject’s MTC-BP data were excluded because the model failed to provide stable curve fits for this region’s time-activity concentrations.
- $^b$ W=Wilcoxon signed ranks test statistic.
<table>
<thead>
<tr>
<th>ROI</th>
<th>CMOD DV</th>
<th></th>
<th>CMOD BP</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-treatment</td>
<td>Post-treatment</td>
<td>W; p-value</td>
<td>Pre-treatment</td>
</tr>
<tr>
<td>CER</td>
<td>0.44 ± 0.12</td>
<td>0.51 ± 0.11</td>
<td>−0.73;0.56</td>
<td>n.a.</td>
</tr>
<tr>
<td>MTCa</td>
<td>7.50 ± 2.98</td>
<td>6.81 ± 1.95</td>
<td>−0.73;0.63</td>
<td>15.67 ± 2.74</td>
</tr>
<tr>
<td>RN</td>
<td>2.03 ± 0.68</td>
<td>2.11 ± 0.50</td>
<td>−0.11;1.00</td>
<td>3.68 ± 1.62</td>
</tr>
<tr>
<td>LLO</td>
<td>2.86 ± 0.85</td>
<td>3.14 ± 0.88</td>
<td>−0.52;0.69</td>
<td>5.47 ± 1.40</td>
</tr>
<tr>
<td>RLO</td>
<td>2.78 ± 0.74</td>
<td>3.11 ± 0.53</td>
<td>−0.11;1.00</td>
<td>5.41 ± 1.59</td>
</tr>
<tr>
<td>OCC-PC</td>
<td>1.79 ± 0.60</td>
<td>2.00 ± 0.50</td>
<td>−0.94;0.44</td>
<td>3.06 ± 1.20</td>
</tr>
<tr>
<td>PCG</td>
<td>2.29 ± 0.69</td>
<td>2.60 ± 0.49</td>
<td>−0.94;0.44</td>
<td>4.17 ± 0.96</td>
</tr>
</tbody>
</table>

aTwo subjects’ MTC-BP data were excluded because the model failed to provide stable curve fits for this region’s time-activity concentrations.

Abbreviations as in Table II