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## Measurement of 5-HT<sub>1A</sub> receptor binding in depressed adults before and after antidepressant drug treatment using PET and [<sup>11</sup>C]WAY-100635

Eydie L. Moses-Kolko<sup>1</sup>, Julie C. Price<sup>2</sup>, Michael E. Thase<sup>1</sup>, Carolyn Cidis Meltzer<sup>1,3,4,5,6</sup>, David J. Kupfer<sup>1</sup>, Chester A. Mathis<sup>2</sup>, Wendy D. Bogers<sup>1,7</sup>, Susan R. Berman<sup>1</sup>, Patricia R. Houck<sup>1</sup>, Trisha N. Schneider<sup>1</sup>, and Wayne C. Drevets<sup>1,7</sup>

<sup>1</sup>University of Pittsburgh, School of Medicine, Department of Psychiatry, Pittsburgh, PA

<sup>2</sup>University of Pittsburgh, School of Medicine, Department of Radiology, Pittsburgh, PA

<sup>3</sup>University of Pittsburgh, School of Medicine, Department of Neurology, Pittsburgh, PA

<sup>4</sup>Emory University School of Medicine, Department of Radiology, Atlanta, GA

<sup>5</sup>Emory University School of Medicine, Department of Neurology, Atlanta, GA

<sup>6</sup>Emory University School of Medicine, Department of Psychiatry and Behavioral Sciences, Atlanta, GA

<sup>7</sup>NIH/NIMH/Section on Neuroimaging in Mood and Anxiety Disorders, Bethesda, MD

### Abstract

**Objective**—To assess effects of chronic antidepressant drug treatment on serotonin type-1A receptor (5-HT<sub>1A</sub>R) binding potential (BP) in major depressive disorder.

**Methods**—Depressed subjects (n=27) were imaged using PET and [<sup>11</sup>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<sub>1A</sub>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<sub>1A</sub>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).

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Corresponding Author: Eydie L. Moses-Kolko, MD, 410 Oxford Building, 3811 O'Hara Street, Pittsburgh, PA 15213 Phone: 412-246-5346 Fax: 412-246-6960.

Conflicts of Interest: David J. Kupfer serves on the advisory board of Eli Lilly & Company and is a consultant for Servier Amerique. Michael E. Thase is a consultant and on the speakers bureau for AstraZeneca, Eli Lilly & Company, GlaxoSmithKline, Bristol-Myers Squibb, and Wyeth Pharmaceuticals and also is a consultant for Organon, Inc., Cephalon, Inc., Forest Pharmaceuticals, Inc., Janssen Pharmaceutica, Novartis, and Pfizer Pharmaceutical. Chester A. Mathis receives royalty payments and is an advisor to GE Healthcare.

**Conclusions**—Chronic antidepressant drug treatment did not significantly change cerebral 5-HT<sub>1A</sub>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<sub>1A</sub>R density. Higher baseline 5-HT<sub>1A</sub>R binding was associated with poorer response to treatment.

### Keywords

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

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### Introduction

Alterations in serotonin type-1A receptor (5-HT<sub>1A</sub>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<sub>1A</sub>R binding potential (BP; proportional to B<sub>max</sub> × affinity, where B<sub>max</sub> = receptor density) in depressives versus controls using PET and [*carbonyl*-<sup>11</sup>C]WAY-100635 ([<sup>11</sup>C]WAY). There has been minimal study, however, of whether antidepressant treatment reverses the 5-HT<sub>1A</sub>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<sub>1A</sub>R density and mRNA expression in experimental animals, SRI effects in depressed humans may be unique. For example, the down-regulation of 5-HT<sub>1A</sub>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<sub>1A</sub>R BP using [<sup>11</sup>C]WAY-PET (Sargent et al. 2000), no treatment-associated changes in BP were evident in regions where the 5-HT<sub>1A</sub> receptor is expressed postsynaptically. In the raphe, where 5-HT<sub>1A</sub>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<sub>1A</sub>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<sub>1A</sub>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<sub>1A</sub>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<sub>1A</sub>R binding in the pretreatment, baseline condition. Most studies of MDD found abnormal reductions in the postsynaptic 5-HT<sub>1A</sub>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-HT<sub>1A</sub>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-HT<sub>1A</sub>R binding prior to treatment will benefit most from the potentially compensatory effect of enhancing postsynaptic 5-HT<sub>1A</sub>R transmission. We tested this hypothesis by comparing the pretreatment 5-HT<sub>1A</sub>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 (HRSD<sub>17</sub>) score  $\geq 18$ . 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 HRSD<sub>17</sub> 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*-<sup>11</sup>C]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 [<sup>11</sup>C]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

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 [<sup>11</sup>C]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, ROITool (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 ROI were chosen on the basis of association with 5-HT<sub>1A</sub>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<sub>1A</sub>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<sub>1A</sub>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<sub>1A</sub>R distribution volumes (DV). Regional measures of 5-HT<sub>1A</sub>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<sub>1A</sub>R density,  $K_D$  is the equilibrium dissociation constant,  $f_2$  is the free fraction of [<sup>11</sup>C]WAY in tissue,  $k_3$  is the association rate of [<sup>11</sup>C]WAY to 5-HT<sub>1A</sub>R, and  $k_4$  is the dissociation rate of [<sup>11</sup>C]WAY from 5-HT<sub>1A</sub>R (Lammertsma et al. 1996; Mintun et al. 1984).

Statistical inference for 5-HT<sub>1A</sub>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<sub>17</sub> scores and the 5-HT<sub>1A</sub>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<sub>17</sub> 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<sub>1A</sub>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  $x > \text{mean} \pm 3(\text{SD})$ ]. 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 [<sup>11</sup>C]WAY BP values derived using SRTM appear in table II, and the mean [<sup>11</sup>C]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 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 ( $3.82 \pm 0.39$  versus  $3.20 \pm 0.55$ ; exact  $MWU=88$ ;  $p=0.01$ ) and right orbital cortex ( $3.83 \pm 0.33$  versus  $3.26 \pm 0.55$ ; 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 ( $p<0.001$ ).]

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 ( $p>$

10) than CMOD 90 min BP values as follows: LLO 3%, MTC 4.7%, OCC 3.7%, PCG 2.3%, RLO 5.5%, RN 7.3%.]

## Discussion

The mean 5-HT<sub>1A</sub>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 [<sup>11</sup>C]WAY-PET. These negative results are consistent with Sargent et al. (2000), who found no significant changes in [<sup>11</sup>C]WAY 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<sub>1A</sub>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<sub>1A</sub> 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, [<sup>11</sup>C]WAY binding is insensitive to competition from endogenous 5HT (Hume et al. 2001; Parsey et al. 1998), and as a lipophilic, high-affinity 5-HT<sub>1A</sub>R antagonist, [<sup>11</sup>C]WAY 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<sub>1A</sub>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<sub>1A</sub>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 [<sup>11</sup>C]WAY by Gunn et al. (1998). When Parsey et al. (2000) reported evidence that the SRTM approach to analyzing [<sup>11</sup>C]WAY 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<sub>1A</sub>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<sub>1A</sub>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<sub>1A</sub>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-HT<sub>1A</sub>R 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-HT<sub>1A</sub>R binding reported in MDD, such treatments may nevertheless compensate for deficient 5-HT<sub>1A</sub>R function in depression. By desensitizing the presynaptic 5-HT<sub>1A</sub> 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-HT<sub>1A</sub>R 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-HT<sub>1A</sub>R 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-HT<sub>1A</sub>R function is noteworthy in view of our finding that the *pre-treatment* 5-HT<sub>1A</sub>R 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-HT<sub>1A</sub>R 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-HT<sub>1A</sub> promoter region polymorphism showed *decreased* response rates to SSRI treatment (Lemondé et al. 2004) and *increased* 5-HT<sub>1A</sub>R BP in one study (Parsey et al. 2006), although a second study could not confirm the association between this polymorphism and regional 5-HT<sub>1A</sub>R 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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## References

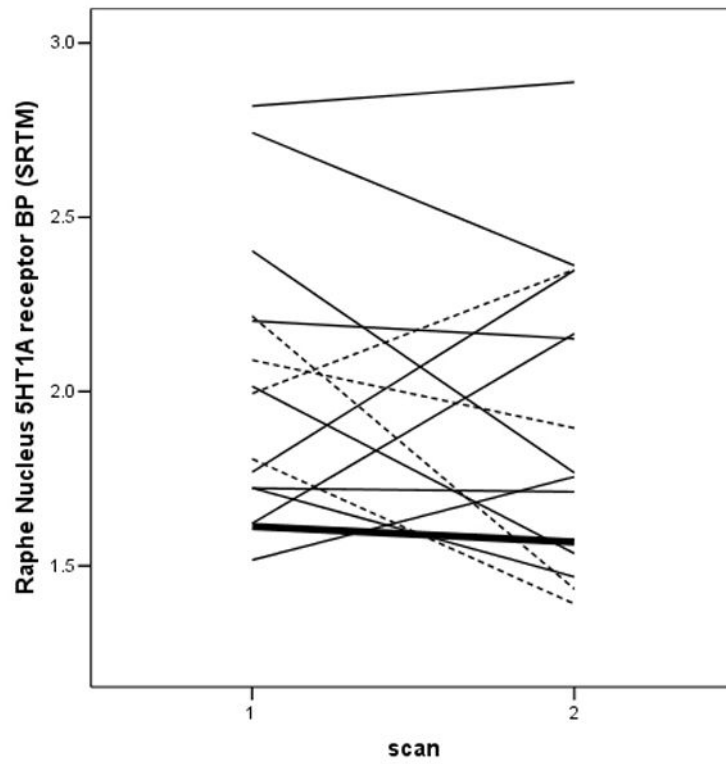
- Arango V, Underwood M, Gubbi A, et al. Localized alterations in pre- and postsynaptic serotonin binding sites in the ventrolateral prefrontal cortex of suicide victims. *Brain Research*. 1995; 688:121–33. [PubMed: 8542298]
- Arango V, Underwood MD, Boldrini M, et al. Serotonin 1A receptors, serotonin transporter binding and serotonin transporter mRNA expression in the brainstem of depressed suicide victims. *Neuropsychopharmacology*. 2001; 25:892–903. [PubMed: 11750182]
- Artigas F, Romero L, de Montigny C, et al. Acceleration of the effects of selected antidepressant drugs in major depression by 5-HT<sub>1A</sub> antagonists. *Trends Neurosci*. 1996; 19:378–83. [PubMed: 8873352]



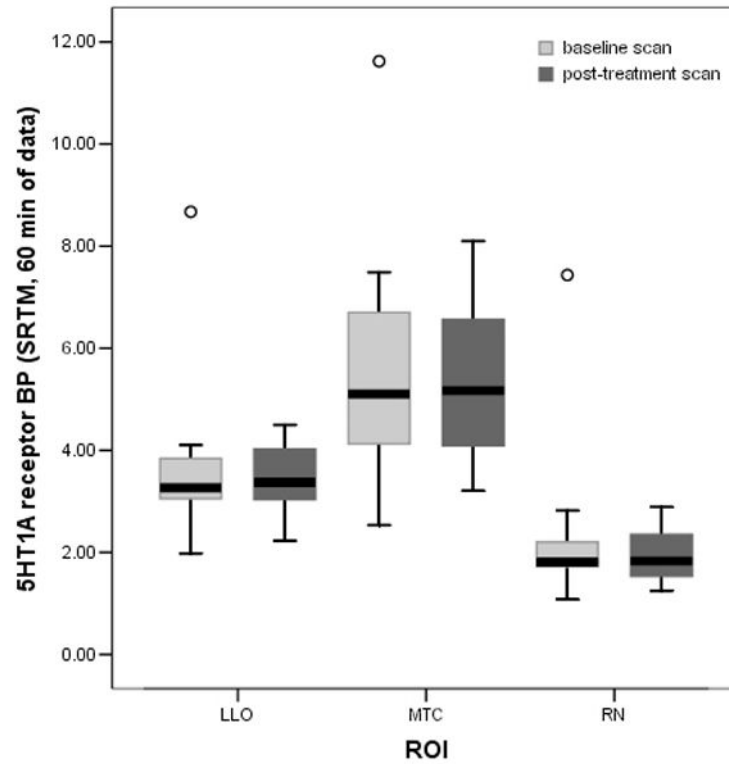
- Bailer UF, Frank GK, Henry SE, et al. Altered brain serotonin 5-HT<sub>1A</sub> receptor binding after recovery from anorexia nervosa measures by positron emission tomography and [<sup>11</sup>C]WAY 100635. *Arch Gen Psychiatry*. 2005; 62:1032–41. [PubMed: 16143735]
- Beique J, de Montigny C, Blier P, et al. Effects of sustained administration of the serotonin and norepinephrine reuptake inhibitor venlafaxine: I. in vivo electrophysiological studies in the rat. *Neuropharmacology*. 2000; 39(10):1800–12. [PubMed: 10884561]
- Blier P, de Montigny C. Electrophysiological investigations on the effect of repeated zimelidine administration on serotonergic neurotransmission in the rat. *J Neurosci*. 1983; 3:1270–8. [PubMed: 6304261]
- Blier P, de Montigny C, Azzaro AJ. Modification of serotonergic and noradrenergic neurotransmissions by repeated administration of monoamine oxidase inhibitors: electrophysiological studies in the rat central nervous system. *J Pharmacol Exp Ther*. 1986; 237:987–94. [PubMed: 2423685]
- Bowen DM, Najlerahim A, Procter AW, et al. Circumscribed changes of the cerebral cortex in neuropsychiatric disorders of late life. *Proc Natl Acad Sci*. 1989; 86:9504–8. [PubMed: 2574463]
- Brown, H.; Prescott, R. *Applied mixed models*. Chichester: John Wiley & Sons, LTD; 1999. Repeated measures data; p. 199-261.
- Carli M, Afkhami-Dastjerdian S, Reader TA. [<sup>3</sup>H]8-OH-DPAT binding and serotonin content in rat cerebral cortex after acute fluoxetine, desipramine, or pargyline. *J Psychiatry Neurosci*. 1996; 21:114–22. [PubMed: 8820177]
- Chaput Y, de Montigny C. Effects of the 5-hydroxytryptamine receptor antagonist, BMY 7378, on 5-hydroxytryptamine neurotransmission: electrophysiological studies in the rat central nervous system. *J Pharmacol Exp Ther*. 1988; 246:359–70. [PubMed: 2839669]
- Chaput Y, de Montigny C, Blier P. Presynaptic and postsynaptic modifications of the serotonin system by long-term administration of antidepressant treatments. An in vivo electrophysiologic study in the rat. *Neuropsychopharmacology*. 1991; 5:219–29. [PubMed: 1839498]
- Cowen PJ. Psychopharmacology of 5HT<sub>1A</sub> Receptors. *Nuclear Medicine and Biology*. 2000; 27:437–9. [PubMed: 10962247]
- David SP, Murthy NV, Rabiner EA, et al. A functional genetic variation of the serotonin (5-HT) transporter affects 5-HT<sub>1A</sub> receptor binding in humans. *Journal of Neuroscience*. 2005; 25(10):2586–90. [PubMed: 15758168]
- Debonnel G, Saint-Andre E, Hebert C, et al. Differential physiological effects of a low dose and high doses of venlafaxine in major depression. *Int J Neuropsychopharmacol*. 2006 Epub ahead of print.
- Drevets WC, Frank E, Price JC, et al. Serotonin Type-1A receptor imaging in depression. *Nuclear Med Biology*. 2000; 27(5):499–507.
- Drevets WC, Frank E, Price JC, et al. PET imaging of serotonin 1A receptor binding in depression. *Biol Psychiatry*. 1999; 46:1375–87. [PubMed: 10578452]
- Frazer, A.; Hensler, JG. 5-HT<sub>1A</sub> receptors and 5-HT<sub>1A</sub>-mediated responses: effect on treatments that modify serotonergic neurotransmission. In: Whitaker-Azmitia, PM.; Peroutka, SJ., translators and editors. *The Neuropharmacology of Serotonin*. New York: The New York Academy of Sciences; 1990. p. 460-75.
- Gunn RN, Sargent PA, Bench CJ, et al. Tracer kinetic modeling of the 5-HT<sub>1A</sub> receptor ligand [carbonyl-<sup>11</sup>C]WAY-100635 for PET. *Neuroimage*. 1998; 8:426–40. [PubMed: 9811559]
- Haddjeri N, Blier P, De Montigny C. Long-term antidepressant treatments result in tonic activation of forebrain 5HT<sub>1A</sub> receptors. *J Neuroscience*. 1998; 18(23):10150–6.
- Harvey AT, Rudolph RL, Preskorn SH. Evidence of the dual mechanisms of action of venlafaxine. *Archives of General Psychiatry*. 2000; 57(5):503–9. [PubMed: 10807491]
- Hensler JG. Regulation of 5HT<sub>1A</sub> receptor function in brain following agonist or antidepressant administration. *Life Science*. 2003; 72:1665–82.
- Hensler JG, Kovachich GB, Frazer A. A quantitative autoradiographic study of serotonin 1A receptor regulation. Effect of 5, 7-dihydroxytryptamine and antidepressant treatments. *Neuropsychopharmacology*. 1991; 4:131–44. [PubMed: 2025379]

- Hume S, Hirani E, Opacka-Juffry J, et al. Effect of 5-HT on binding of [(11)C] WAY 100635 to 5-HT(1A) receptors in rat brain, assessed using in vivo microdialysis and PET after fenfluramine. *Synapse*. 2001; 41(2):150–9. [PubMed: 11400181]
- Lammertsma A, Bench C, Hume S, et al. Comparison of methods for analysis of clinical [(11)C]raclopride studies. *J Cereb Blood Flow Metab*. 1996; 16:42–52. [PubMed: 8530554]
- Laruelle M. Imaging synaptic neurotransmission with in vivo binding competition techniques: A critical review. *Journal of Cerebral Blood Flow and Metabolism*. 2000; 20:423–51. [PubMed: 10724107]
- Lemondé S, Du L, Bakish D, et al. Association of the C(-1019)G 5-HT1A functional promoter polymorphism with antidepressant response. *International Journal of Neuropsychopharmacology*. 2004; 7(4):501–6. [PubMed: 15447813]
- Lopez JF, Chalmers DT, Little KY, et al. Regulation of serotonin 1A, glucocorticoid, and mineralocorticoid receptor in rat and human hippocampus: Implications for the neurobiology of depression. *Biological Psychiatry*. 1998; 43:547–73. [PubMed: 9564441]
- McCarron JA, Turton D, Pike VW, et al. Remotely controlled production of the 5HT1A receptor radioligand, [carbonyl-11C]WAY-100635, via 11C-carboxylation of an immobilized Grignard reagent. *J Labelled Comp Radiopharm*. 1996; 38:941–53.
- Meltzer CC, Drevets WC, et al. Gender-Specific Aging Effects on the Serotonin 1A Receptor. *Brain Research*. 2001; 895(1–2):9–17. [PubMed: 11259754]
- Meltzer CC, Price JC, Mathis CA, et al. Serotonin 1A receptor binding and treatment response in late-life depression. *Neuropsychopharmacology*. 2004a; 29(12):2258–65. [PubMed: 15483563]
- Meltzer CC, Price JC, Mathis CA, et al. Serotonin 1A receptor binding and treatment response in late-life depression. *Neuropsychopharmacology*. 2004b; 29(12):2258–65. [PubMed: 15483563]
- Mintun MA, Raichle ME, Kilbourn MR, et al. A quantitative model for the in vivo assessment of drug binding sites with positron emission tomography. *Ann Neurol*. 1984; 15:217–27. [PubMed: 6609679]
- Parsey RV, Arango V, Olvet DM, et al. Regional heterogeneity of 5-HT1A receptors in human cerebellum as assessed by positron emission tomography. *J Cereb Blood Flow Metab*. 2005; 25:785–93. [PubMed: 15716853]
- Parsey RV, Hwang D, Simpson N, et al. Kinetic derivation of serotonin 5-HT1A receptors binding potential with [C-11]Carbonyl-Way 100635 and competition studies with endogenous serotonin. *J Nuclear Med*. 1998; 39(5 Suppl):167P.
- Parsey RV, Oquendo MA, Ogden RT, et al. Altered serotonin 1A binding in major depression: a [carbonyl-C-11]WAY 100635 positron emission tomography study. *Biol Psychiatry*. 2006; 59(2):106–13. [PubMed: 16154547]
- Parsey RV, Slifstein M, Hwang DR, et al. Validation and Reproducibility of Measurement of 5HT1A Receptor Parameters With [carbonyl-11C]WAY-100635 in Human: Comparison of Arterial and Reference Tissue Input Functions. *Journal of Cerebral Blood Flow and Metabolism*. 2000; 20:1111–33.
- Price JC, Kelley DE, Ryan CM, et al. Evidence of Increased Serotonin-1A Receptor Binding in Type 2 Diabetes: A Positron Emission Tomography Study. *Brain Res*. 2002b; 927(1):97–103. [PubMed: 11814436]
- Price LH, Charney DS, Delgado PL, et al. Effects of desipramine and fluvoxamine treatment on the prolactin response to tryptophan. *Arch Gen Psychiatry*. 1989; 46:625–31. [PubMed: 2500111]
- Sargent PA, Kjaer KH, Bench CJ, et al. Brain serotonin 1A receptor binding measured by positron emission tomography with [(11)C]WAY-100635: Effects of depression and antidepressant treatment. *Arch Gen Psychiatry*. 2000; 57:174–80. [PubMed: 10665620]
- Spurlock G, Buckland P, O'Donovan M, et al. Lack of effect of antidepressant drugs on the levels of mRNAs encoding serotonergic receptors, synthetic enzymes and 5HT transporter. *Neuropharmacology*. 1994; 33:433–40. [PubMed: 7984281]
- Stockmeier CA, Shapiro LA, Dilley GE, et al. Increase in serotonin-1A autoreceptors in the midbrain of suicide victims with major depression-Postmortem evidence for decreased serotonin activity. *J Neuroscience*. 1998; 18(18):7394–401.

- Welner SA, DeMontigny C, Desroches J, et al. Autoradiographic quantification of serotonin1A receptors in rat brain following antidepressant drug treatment. *Synapse*. 1989; 4:347–52. [PubMed: 2532423]
- Woods RP, Mazziotta JC, Cherry SR. MRI-PET registration with automated algorithm. *J Comput Assist Tomogr*. 1993; 17:536–46. [PubMed: 8331222]
- Zimmer L, Riad M, Rbah L, et al. Toward brain imaging of serotonin 5-HT1A autoreceptor internalization. *NeuroImage*. 2004; 22:1421–6. [PubMed: 15219613]



**Figure 1.** Pattern of 5-HT<sub>1A</sub> 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 5HT<sub>1A</sub> receptor BP before and following SRI treatment for data obtained from the entire study sample**

This graph shows pre- and post-treatment 5-HT<sub>1A</sub> 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

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

\* post-treatment HRSD missing for four subjects who discontinued medications before completion of a therapeutic trial

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TABLE II

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

ROI	Entire Sample (n=15)			SSRI alone (n=10)			Venlafaxine +/- SSRI (n=5)		
	Pre-treatment	Post-treatment	W; p-value <sup>b</sup>	Pre-treatment	Post-treatment	W; p-value <sup>b</sup>	Pre-treatment	Post-treatment	W; p-value <sup>b</sup>
MTC <sup>a</sup>	5.62 ± 1.37	5.14 ± 1.39	-0.85;0.43	5.59 ± 1.63	5.11 ± 1.51	-0.53;0.65	5.68 ± 0.90	5.19 ± 1.29	-0.67;0.63
RN	2.02 ± 0.40	1.92 ± 0.44	-0.97;0.36	2.05 ± 0.47	2.02 ± 0.45	-0.36;0.77	1.94 ± 0.24	1.73 ± 0.40	-1.21;0.31
LLO	3.44 ± 0.51	3.50 ± 0.71	-0.28;0.80	3.35 ± 0.55	3.38 ± 0.73	-0.15;0.92	3.61 ± 0.43	3.74 ± 0.67	-0.67;0.63
RLO	3.51 ± 0.48	3.53 ± 0.65	-0.06;0.98	3.42 ± 0.52	3.54 ± 0.71	-0.46;0.70	3.69 ± 0.37	3.51 ± 0.59	-0.94;0.44
OCC-PC	2.02 ± 0.40	2.11 ± 0.57	-1.08;0.30	2.08 ± 0.35	2.13 ± 0.50	-0.46;0.70	1.91 ± 0.52	2.10 ± 0.77	-0.94;0.44
PCG	2.77 ± 0.59	2.90 ± 0.68	-0.85;0.42	2.54 ± 0.41	2.74 ± 0.66	-0.87;0.43	3.23 ± 0.67	3.23 ± 0.64	-0.14;1.00

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.

<sup>a</sup> one subject's MTC-BP data were excluded because the model failed to provide stable curve fits for this region's time-activity concentrations.

<sup>b</sup> W=Wilcoxon signed ranks test statistic.

TABLE III

Mean regional [ $^{11}\text{C}$ ]WAY distribution volume (DV) and binding potential (BP) values in depressed subjects, pre and post-treatment derived using compartmental modeling (CMOD) and arterial input functions [mean  $\pm$  SD; paired data, n=6].

ROI	CMOD DV			CMOD BP		
	Pre-treatment	Post-treatment	W; p-value	Pre-treatment	Post-treatment	W; p-value
CER	0.44 $\pm$ 0.12	0.51 $\pm$ 0.11	-0.73;0.56	n.a.	n.a.	n.a.
MTC <sup>a</sup>	7.50 $\pm$ 2.98	6.81 $\pm$ 1.95	-0.73;0.63	15.67 $\pm$ 2.74	11.36 $\pm$ 4.21	-1.46;0.25
RN	2.03 $\pm$ 0.68	2.11 $\pm$ 0.50	-0.11;1.00	3.68 $\pm$ 1.62	3.21 $\pm$ 1.09	-0.52;0.69
LLO	2.86 $\pm$ 0.85	3.14 $\pm$ 0.88	-0.52;0.69	5.47 $\pm$ 1.40	5.17 $\pm$ 1.34	-0.73;0.56
RLO	2.78 $\pm$ 0.74	3.11 $\pm$ 0.53	-0.1.15;0.31	5.41 $\pm$ 1.59	5.21 $\pm$ 1.28	-0.31;0.84
OCC-PC	1.79 $\pm$ 0.60	2.00 $\pm$ 0.50	-0.94; 0.44	3.06 $\pm$ 1.20	2.95 $\pm$ 0.78	-0.31;0.84
PCG	2.29 $\pm$ 0.69	2.60 $\pm$ 0.49	-0.94;0.44	4.17 $\pm$ 0.96	4.17 $\pm$ 1.01	-0.11;1.00

<sup>a</sup> two subjects's 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