ORIGINAL ARTICLE

Brain Serotonin$_{1A}$ Receptor Binding Measured by Positron Emission Tomography With [^{11}C]WAY-100635

Effects of Depression and Antidepressant Treatment

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Background: Pharmacological and postmortem investigations suggest that patients with major depressive disorder have alterations in function or density of brain serotonin$_{1A}$ (5-HT$_{1A}$) receptors. The aim of the present study was to use positron emission tomography with the selective 5-HT$_{1A}$ receptor antagonist [^{11}C]WAY-100635 to measure 5-HT$_{1A}$ receptor binding in depressed patients before and during treatment with selective serotonin reuptake inhibitors.

Methods: Positron emission tomographic scans with [^{11}C]WAY-100635 were performed on 25 patients with major depressive disorder. These included 15 unmedicated depressed patients. Ten of these unmedicated patients were scanned again during selective serotonin reuptake inhibitor treatment. A further 10 patients with major depressive disorder were scanned on one occasion only while taking selective serotonin reuptake inhibitors. Comparisons were made with [^{11}C]WAY-100635 positron emission tomographic scans in 18 healthy volunteer subjects. Region of interest analysis and statistical parametric mapping were performed on binding potential images generated using a reference tissue model.

Results: Binding potential values were reduced across many of the regions examined, including frontal, temporal, and limbic cortex in both unmedicated and medicated depressed patients compared with healthy volunteers. Binding potential values in medicated patients were similar to those in unmedicated patients.

Conclusions: Major depressive disorder is associated with a widespread reduction in 5-HT$_{1A}$ receptor binding. This reduced 5-HT$_{1A}$ receptor binding was not changed by selective serotonin reuptake inhibitor treatment.

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EVIDENCE FROM preclinical and clinical studies suggests that major depressive disorder may be associated with decreased serotonin (5-hydroxytryptamine, 5-HT) neurotransmission.[1,2] However, the precise nature of this putative deficit has remained elusive.

Alterations of 5-HT receptors may be a possible cause of this deficit. These receptors exist as different subtypes having different pharmacological properties. Neuroendocrine challenge studies with 5-HT$_{1A}$ receptor agonists in unmedicated depressed patients have suggested that the sensitivity of both presynaptic 5-HT$_{1A}$ autoreceptors and postsynaptic 5-HT$_{1A}$ receptors may be decreased in major depressive disorder.[3-5] However, results from postmortem brain studies of 5-HT$_{1A}$ receptor binding have been inconsistent, with several studies finding no change in 5-HT$_{1A}$ receptor binding in suicides, some of whom met criteria for major depression.[6-11] Other studies have reported increased 5-HT$_{1A}$ receptor binding in discrete cortical regions, notably in the ventrolateral prefrontal cortex.[12,13] A recent autoradiographic investigation also found increased numbers of 5-HT$_{1A}$ receptors in the raphe region in suicides who had major depression.[14]

Animal studies suggest increases in neurotransmission at postsynaptic 5-HT$_{1A}$ receptors may mediate the therapeutic effects of different classes of antidepressant drugs.[15-17] In the case of selective serotonin reuptake inhibitors (SSRIs), this effect is mediated by desensitization of cell body 5-HT$_{1A}$ autoreceptors and some studies in rodents suggest that this functional down-regulation is accompanied by a decrease in 5-HT$_{1A}$ receptor binding in the raphe nuclei,[18,19] although other studies have found no change in 5-HT$_{1A}$ receptor binding in this region.[20-22] Pharmacological challenge studies in humans also provide indirect evidence that repeated SSRI treatment lowers the functional responsiveness of 5-HT$_{1A}$ autoreceptors.[23,24]

The affiliations of the authors appear in the acknowledgment section at the end of the article.

SUBJECTS, MATERIALS, AND METHODS

SUBJECTS

Twenty-five patients with major depressive disorder were included in the study (**Table 1**). Depressed subjects were recruited from general practices and psychiatric outpatient clinics in Oxford and London, England. Depressed patients met *DSM-IV* criteria[28] for major depressive disorder, having undergone a Structured Clinical Interview for *DSM-IV*. Exclusion criteria included current physical illness, a history of bipolar affective disorder, a history of current alcohol dependence, current or previous treatment with mood stabilizers or antipsychotic medication, and current treatment with benzodiazepines.

Of the 25 depressed patients in the study, 10 patients (all men) were scanned before treatment and again after 6 weeks of treatment with the SSRI paroxetine hydrochloride (modal daily dose, 20 mg; range, 20-40 mg). Five further depressed patients (all men) were scanned once only while drug free. In addition, we scanned a further 10 patients (7 men and 3 women) established on SSRI treatment. Six of these patients were taking paroxetine hydrochloride (modal daily dose, 30 mg; range, 20-40 mg) and 4 were taking sertraline hydrochloride (modal daily dose, 100 mg; range, 100-150 mg).

The 15 unmedicated depressed patients were aged between 19 and 66 years (mean ± SD age, 37.7 ± 13.7 years). Their mean 17-item Hamilton Depression Rating Scale (HDRS) score of at the time of scanning was 21.8 ± 5.3 (range, 17-34). All unmedicated patients met *DSM-IV* criteria for current major depressive disorder at the time of scanning. Seven patients were antidepressant drug naive, and 8 patients had been antidepressant drug free for a median of 63 weeks (range, 12-1196 weeks).

The 20 SSRI-treated patients were aged between 20 and 69 years (mean ± SD age, 43.1 ± 14.8 years). Their median duration of treatment was 14 weeks (range, 5-182 weeks) and their mean HDRS score at the time of scanning was 8.4 ± 7.5 (range, 0-28). All of the SSRI-treated patients had met *DSM-IV* criteria for major depressive disorder during the current depressive episode, although treatment responders were no longer fully symptomatic at the time of scanning. Of the 10 patients who had PET scans before and during SSRI treatment, 5 were treatment responders (HDRS score $\leq$7) and 5 were nonresponders (HDRS score $\geq$8). In the 10 patients studied only while receiving SSRI treatment, 5 were responders and 5 were nonresponders.

PET scans were performed on 18 healthy volunteers (17 men and 1 woman) aged between 27 and 56 years (mean ± SD age, 36.4 ± 8.3 years). There were no significant differences in age between control subjects and either the untreated depressed patients or the SSRI-treated depressed patients ($P<.05$, unpaired t test). Healthy volunteers were recruited from hospital staff and advertisements in the press. Healthy volunteers were screened for psychiatric disorders by a routine clinical interview and the Structured Clinical Interview for *DSM-IV*.

All subjects gave informed written consent to the study, which was approved by local ethics committees and permission was obtained from the Administration of Radioactive Substances Advisory Committee of the United Kingdom.

PET SCANNING PROTOCOL

PET scans were performed on an ECAT 935B PET camera (CTI, Knoxville, Tenn) at the Medical Research Council Cyclotron Unit, Hammersmith Hospital, London. This scanner acquires 31 planes of data with an axial field of view of 10.5 cm. Subjects were positioned in the scanner, parallel to the orbitomeatal line, so as to include the cerebellum and the brainstem in the field of view.

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A major limitation of clinical investigations has been the difficulty of examining 5-HT_{1A} receptors directly in the living human brain. However, the development of [*carbonyl*-^{11}C]WAY-100635, a selective 5-HT_{1A} receptor antagonist,[25,26] in conjunction with positron emission tomography (PET) now allows assessment of 5-HT_{1A} receptor binding in vivo.[27] We used this technique to measure 5-HT_{1A} receptor binding in depressed patients before and during SSRI treatment.

On the basis of the neuroendocrine studies in man and the preclinical data, we hypothesized that 5-HT_{1A} receptor binding would be decreased in depressed subjects relative to control subjects, both at presynaptic sites in the raphe nuclei, and at postsynaptic sites in cortical regions and that long-term SSRI treatment would further reduce 5-HT_{1A} receptor binding in the raphe nuclei.

RESULTS

ROI ANALYSIS

There was a mean reduction in BP of 10.8% ± 4.6% across the 21 ROIs sampled in the unmedicated depressed patients compared with healthy volunteers. In the SSRI-treated patients there was a mean reduction in BP of 11.6% ± 4.1% across the 21 brain regions compared with the healthy volunteers (Table 2).

An ANOVA of BP values for the volunteers vs unmedicated depressed patients found a main effect of group ($F_{1,31}$ = 5.26; P = .03), a main effect of region ($F_{8.14,252.26}$ = 136.54; P <.001), and a group-by-region interaction ($F_{8.14,252.26}$ = 2.37; P = .02). Post hoc unpaired t tests demonstrated BP values to be significantly different between the 2 groups in 11 of the 21 brain regions (Table 2). At P = .05 we would expect 1 in 20 comparisons to be significantly different by chance (false-positives); however, significant differences in 11 of 21 regions indicate a true change in the majority of regions.

Likewise, there was a main effect of group in the ANOVA of BP values for the volunteers and SSRI-treated patients ($F_{1,36}$ = 7.98; P = .008), a main effect of region ($F_{8.61,310.05}$ = 181.59; $P<.001$), and a group-by-region interaction ($F_{8.61,310.05}$ = 2.83; P = .004). Post hoc unpaired t tests demonstrated BP values to be significantly different between the 2 groups in 14 of the 21 brain regions (Table 2).

An ANOVA of BP values for the 10 depressed patients scanned before and during treatment with parox-

[*carbonyl*-^{11}C]WAY-100635 was prepared at the Medical Research Council Cyclotron Unit.[29] A 10-minute transmission scan was acquired in 2-dimensional mode for correction of tissue attenuation. All subjects then received [^{11}C]WAY-100635 injected intravenously over 30 seconds. Dynamic PET data was acquired in 3-dimensional mode for 90 minutes after injection.[30] The emission data was scatter corrected[31] and reconstructed using a reprojection algorithm.[32]

KINETIC MODELING OF [^{11}C]WAY-100635

Quantitative tracer kinetic modeling was performed using a reference tissue compartmental model.[30,33] Cerebellum was used as the reference tissue. The model allows the estimation of R_1 (the relative delivery of radioligand normalized to the cerebellum), and binding potential ($BP = f_2 B_{MAX}/\{K_D[1 + \Sigma_i F_i/K_{Di}]\}$), where f_2 is the "free fraction" of unbound radioligand, B_{MAX} is the concentration of binding sites, K_D is the dissociation constant for the radioligand, and F_i and K_{Di} are the free concentration and the dissociation constant of competing endogenous ligand, respectively. Parametric images of BP and R_1 were calculated as described previously.[30,34]

IMAGE ANALYSIS

Regions of interest (ROIs) were defined using image analysis software (Analyze AVW v2.5; Biodynamics Research Unit, Mayo Foundation, Rochester, Minn). The ROIs were determined by inspection of the PET images with reference to the brain atlas of Talairach and Tournoux.[35] Two investigators (P.A.S. and K.H.K.), masked to the identity of the scans, agreed on the ROI positions. Cerebellar reference regions were defined on 4 planes of images of summated activity for the first 20 minutes after injection of the radiotracer. All other ROIs were defined on images of summated activity from 20 to 90 minutes after injection.

Regions of interest were defined for 21 brain regions (**Table 2**). Regional BP values were obtained by applying the ROIs to the parametric BP images and taking the mean voxel value.

Statistical analysis of the regional BP and R_1 data was performed using repeated-measures analysis of variance (ANOVA) with Greenhouse-Geisser correction using SPSS software (SPSS Inc, Chicago, Ill). Three separate comparisons of BP values were made with ANOVA: (1) healthy volunteers vs unmedicated depressed patients, (2) healthy volunteers vs SSRI-treated patients, and (3) 10 of the depressed patients before and during SSRI treatment. Where significant group-by-region interactions were obtained with ANOVA, post hoc *t* tests were performed for BP values in individual ROIs. All statistical tests were 2 tailed and reported at $P<.05$.

Pearson and Spearman correlation coefficients (for parametric and nonparametric data) were obtained for the mean BP value across all ROIs against PET and clinical variables, including total injected activity, specific activity, unlabeled ("cold") WAY-100635, WAY-100634 (precursor), age, length of illness, family history, HDRS score, and treatment response.

In addition to the ROI analysis, an exploratory analysis of parametric images of BP and R_1 was undertaken using statistical parametric mapping (SPM 96)[36,37] to confirm the findings of the ROI analysis. As this was a hypothesis-led analysis, *P* was thresholded at less than .01, uncorrected ($z = 2.33$). The BP and R_1 images were spatially normalized into Montreal Neurological Institute stereotactic space using a [^{11}C]WAY-100635 template as previously described.[38] Normalized BP images were smoothed with a gaussian filter to 8 mm full-width half-maximum, and R_1 images (which are statistically noisier) were smoothed to 16 mm full-width half-maximum. The same 3 comparisons were made using SPM as for the ROI analysis. Covariance of BP with PET and clinical variables (as above) was also performed within SPM.

etine demonstrated no main effect of treatment ($F_{1,9} = 1.01$; $P = .34$); however, there was a main effect of region ($F_{4.68,42.13} = 60.83$; $P<.001$) but no treatment-by-region interaction ($F_{4.75,42.72} = 0.96$; $P = .45$). Although BP values in the raphe were reduced following treatment with paroxetine, this did not reach statistical significance (**Figure 1**).

Unpaired *t* tests demonstrated no significant differences in BP between treatment responders (mean ± SD BP value for all ROIs = 4.66 ± 0.92) and treatment nonresponders (mean ± SD BP value for all ROIs = 4.52 ± 0.98) among the 20 SSRI-treated patients. Similarly, there was no significant difference in the changes in BP in the 10 patients scanned before and after SSRI treatment, between treatment responders (mean ± SD change in BP value for all ROIs = 0.16 ± 0.22) and treatment nonresponders (mean ± SD change in BP value for all ROIs = 0.31 ± 0.35).

There were no significant correlations ($P<.05$) of mean BP values with any PET or clinical variables (data not shown).

For the ROI R_1 values, there was no main effect of group or group-by-region interaction with 2-way ANOVA, either for volunteers vs unmedicated depressed patients (group $F_{1,31} = 0.01$, $P = .92$; group-by-region $F_{2.04,63.24} = 0.80$, $P = .46$) or for volunteers vs SSRI-treated patients (group $F_{1,36} = 0.46$, $P = .50$; group-by-region $F_{1.80,64.88} = 2.67$, $P = .08$). Power analysis showed that we could have detected a 10% change in R_1 with our subject numbers (power = 0.8, $P = .05$, 2 tailed).

SPM ANALYSIS

The results obtained using a hypothesis-led SPM analysis of BP images were similar to those obtained with ROI analysis. Significant reductions of BP in unmedicated depressed patients and SSRI-treated patients compared with control subjects were seen in most brain regions except for the occipital cortex (**Figure 2**). In contrast, no changes in R_1 were seen between the control subjects and the depressed patients, except for a reduction in the medial orbitofrontal cortex between the control subjects and the SSRI-treated patients only (data not shown). Global BP values (obtained from SPM) were lower in the depressed groups compared with the control group: 2.69 ± 0.38 (healthy volunteers) vs 2.44 ± 0.37 (unmedi-

Table 1. Group Characteristics*

Characteristic	Healthy Volunteer Subjects (n = 18)	Unmedicated Depressed Patients (n = 15)	Medicated Depressed Patients (n = 20)
Age, mean ± SD (range), y	36.4 ± 8.3 (27-56)	37.7 ± 13.7 (19-66)	43.1 ± 14.8 (20-69)
Sex, M/F	17/1	15/0	17/3
HDRS score	. . .	21.8 (17-34)	8.4 (0-28)
BDI score	. . .	23 (10-41)	12 (0-31)
Age at onset of depressive disorder, y	. . .	33 (17-63)	36 (9-63)
No. of previous episodes	. . .	0.87 (0-3)	1.45 (0-3)
Length of illness, mo	. . .	62 (3-324)	88 (5-348)
Length of current episode, mo	. . .	13 (2-60)	16 (4-61)
Family history of mood disorder, No. of patients	. . .	8	8
Treatment responders, No.	. . .	. . .	10
Taking paroxetine hydrochloride/sertraline hydrochloride, No.	. . .	. . .	16/4
Length of treatment, median (range), wk	. . .	. . .	14 (5-182)
Activity injected, MBq	307 (151-385)	337 (184-376)	348 (163-407)
Specific activity, MBq/μmol	73 166 (22 885-121 021)	94 006 (34 286-174 809)	68 766 (32 119-156 646)
Weight of unlabeled WAY-100635, μg	2.0 (0.6-4.7)	1.9 (0.6-4.4)	2.4 (0.9-5.5)
Weight of WAY-100634, μg	9.2 (0.5-16.7)	5.2 (0.6-12.1)	6.1 (0.4-11.9)

*Data are given as mean (range) unless otherwise specified. HDRS indicates Hamilton Depression Rating Scale; BDI, Beck Depression Inventory; and ellipses, data not applicable.

Table 2. Binding Potential Values for Regions of Interest

Region	Side	Mean ± SE Binding Potential: Healthy Volunteer Subjects (n = 18)	Unmedicated Depressed Patients (n = 15)	Medicated Depressed Patients (n = 20)
Medial temporal cortex	Right	6.8 ± 0.2	6.1 ± 0.3*	5.9 ± 0.2†
	Left	6.8 ± 0.2	6.2 ± 0.3	6.0 ± 0.2*
Temporal pole	Right	5.7 ± 0.2	5.2 ± 0.2*	5.1 ± 0.2*
	Left	5.8 ± 0.2	5.1 ± 0.1*	5.1 ± 0.1*
Orbitofrontal cortex	Right	5.7 ± 0.2	4.8 ± 0.2‡	5.0 ± 0.2*
	Left	6.2 ± 0.2	5.4 ± 0.3*	5.4 ± 0.2*
Ventral anterior cingulate cortex	Right	5.3 ± 0.2	4.4 ± 0.3*	4.3 ± 0.2‡
	Left	5.6 ± 0.2	4.9 ± 0.3	4.9 ± 0.2*
Dorsal anterior cingulate cortex	Right	5.3 ± 0.2	4.5 ± 0.3*	4.5 ± 0.2†
	Left	5.7 ± 0.2	4.9 ± 0.2‡	5.2 ± 0.2*
Insula cortex	Right	7.0 ± 0.2	6.1 ± 0.3*	6.1 ± 0.2†
	Left	6.9 ± 0.2	6.0 ± 0.3*	5.8 ± 0.2‡
Ventrolateral prefrontal cortex	Right	4.0 ± 0.1	3.6 ± 0.2	3.5 ± 0.1*
	Left	4.1 ± 0.2	3.6 ± 0.2	3.7 ± 0.1
Dorsolateral prefrontal cortex	Right	4.3 ± 0.2	3.8 ± 0.2	4.0 ± 0.2
	Left	4.4 ± 0.2	3.9 ± 0.2*	4.0 ± 0.2
Inferior occipital cortex	Right	3.4 ± 0.2	3.5 ± 0.2	3.4 ± 0.1
	Left	3.5 ± 0.2	3.4 ± 0.2	3.2 ± 0.1
Angular gyrus	Right	4.2 ± 0.2	4.0 ± 0.3	3.8 ± 0.1
	Left	4.4 ± 0.2	4.0 ± 0.2	3.9 ± 0.1
Raphe		4.2 ± 0.2	3.6 ± 0.2	3.4 ± 0.1‡

*Significant post hoc unpaired t tests of healthy volunteers vs unmedicated or medicated depressed patients, $P<.05$.
†Significant post hoc unpaired t tests of healthy volunteers vs unmedicated or medicated depressed patients, $P<.01$.
‡Significant post hoc unpaired t tests of healthy volunteers vs unmedicated or medicated depressed patients, $P<.005$.

cated patients; $P = 0.06$) and 2.45 ± 0.32 (medicated patients; $P = 0.04$). Global R_1 (obtained from SPM) was not different between groups: 0.61 ± 0.05 (healthy volunteers) vs 0.61 ± 0.07 (unmedicated patients) and 0.61 ± 0.05 (medicated patients). None of the PET or clinical variables covaried significantly with BP in SPM.

COMMENT

Our findings indicate that BP values for [^{11}C]WAY-100635 binding to 5-HT_{1A} receptors are modestly but significantly decreased in unmedicated patients with major depressive disorder and remain so during SSRI

treatment. These changes were seen with both ROI and SPM analyses. Decreases in BP could result either from a reduction in the number of available 5-HT_{1A} receptors or a decrease in receptor affinity. The present data do not allow us to discriminate between these possibilities.

A number of potential confounding factors need to be considered. These include the influence of endogenous 5-HT, differences in tracer kinetics, changes in blood flow, and partial volume effects.

A reduction in the number of available binding sites might occur as a result of increased concentrations of endogenous 5-HT with long-term SSRI treatment. However, we found similar changes in BP in unmedicated patients who would be expected to have low or normal levels of 5-HT, making this explanation unlikely. Nevertheless, it is possible that SSRI-induced changes in free endogenous 5-HT could offset an actual effect of treatment on receptor number so as to give no apparent change in BP values. However, PET studies in rodents in this laboratory indicate that [^{11}C]WAY-100635 is not readily displaced by endogenous 5-HT. Fenfluramine (10 mg/kg intraperitoneally) had no significant effect on the specific binding of [^{11}C]WAY-100635 in the hippocampus, despite causing a 14-fold increase in extracellular 5-HT as measured by in vivo microdialysis (Susan Hume, PhD, oral communication, 1998).

Differences in tracer kinetics for the cerebellar reference tissue, used for calculation of BP values, could not account for the changes observed in depressed patients as the cerebellar tissue time activity curves did not differ significantly in the 3 groups (**Figure 3**).

Depressed patients may have alterations in regional cerebral blood flow compared with healthy control subjects.[39] However, the reduction of BP values in these patients is unlikely to be an effect of altered blood flow or extraction, as BP values are minimally dependent on tracer delivery (R_1) over the range of R_1 values obtained in this study.[33] Furthermore, although widespread reductions of BP were detected in the depressed groups, global R_1 did not differ between groups and there were no significant changes in R_1 in the 21 regions examined. With SPM, regional changes of R_1 were anatomically restricted (medial orbitofrontal cortex in medicated patients only).

While partial volume effects of systematic anatomical change on BP values cannot be excluded, such as might result from cerebral atrophy, this is unlikely due to the relatively young population examined and the lack of correlation of 5-HT_{1A} receptor binding with age in our sample.

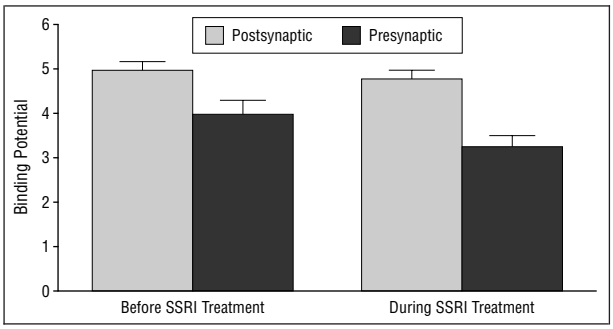

Figure 1. *Presynaptic (raphe) and postsynaptic (averaged cortical) binding potential values for the 10 depressed patients scanned before and during selective serotonin reuptake inhibitor (SSRI) treatment (error bars show SEM).*

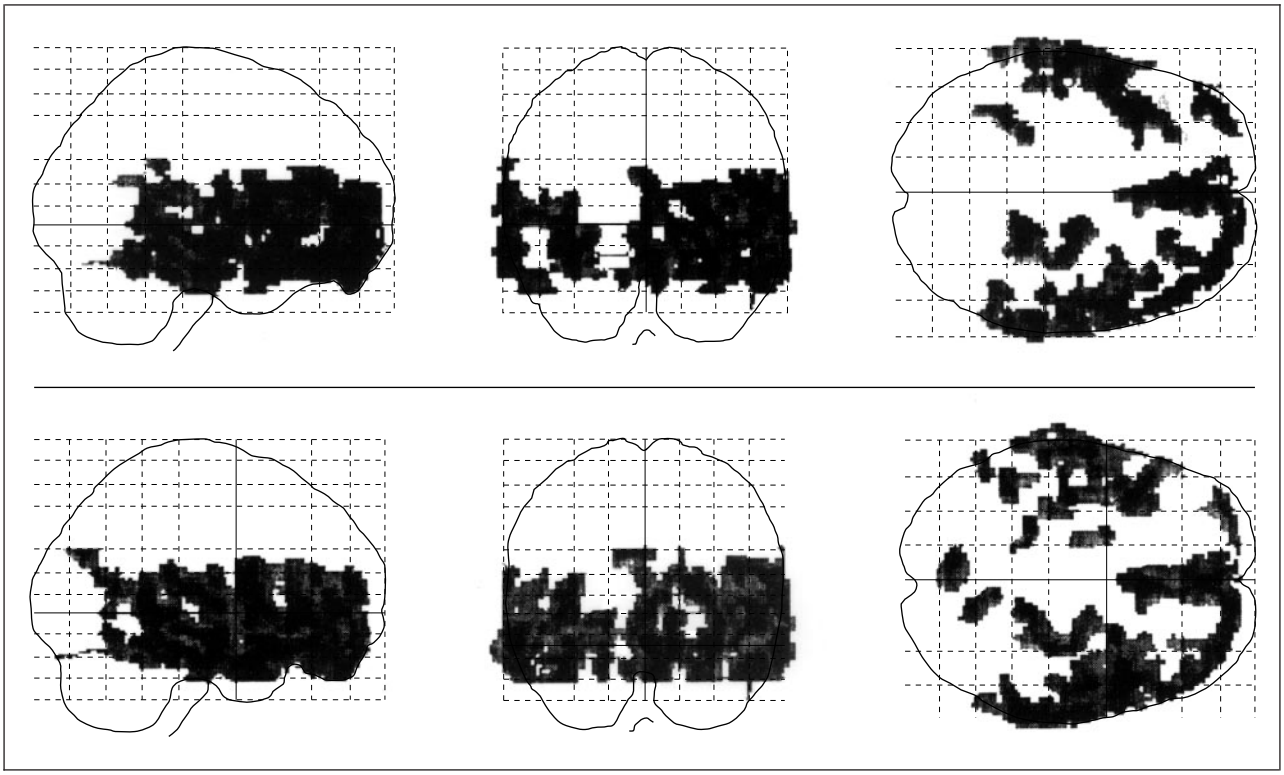

Figure 2. *Statistical parametric maps of binding potential images. Top, Reduced binding potential in unmedicated depressed patients (n = 15) compared with healthy volunteer subjects (n = 18). Bottom, Reduced binding potential in medicated patients (n = 20) compared with healthy volunteer subjects (n = 18). Changes in binding potential values in both unmedicated and medicated patients compared with volunteer subjects are similar.*

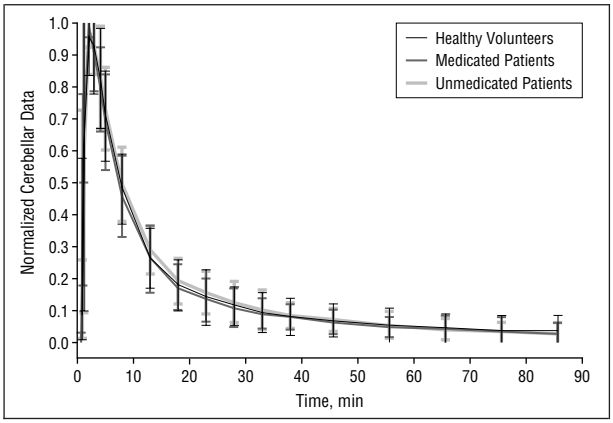

Figure 3. *Decay-corrected cerebellar time activity curves normalized to peak value for the healthy volunteer subjects (n = 18), unmedicated depressed patients (n = 15), and medicated depressed patients (n = 20) (error bars show 2 SDs).*

Where atrophy has been reported in depressed patients, this has tended to be in older patient populations.[40]

We observed widespread reductions in 5-HT_{1A} receptor binding in unmedicated depressed patients. Some areas where reduced binding was found, for example, orbitofrontal cortex and cingulate cortex, have been implicated by lesion studies and by functional imaging to form part of the neural circuitry underpinning clinical depression.[39,41]

The cause of the decrease in 5-HT_{1A} receptor binding in untreated depressed patients requires further investigation. The binding did not return to normal with a short period of treatment with antidepressant medication and there were no significant differences in BP values between treatment responders and nonresponders. It will be important to assess whether 5-HT_{1A} receptor binding is also diminished in recovered depressed patients once they are withdrawn from antidepressant drug treatment.

In this study, we found no robust evidence for a reduction in 5-HT_{1A} receptor number following SSRI treatment. Although the BP values in the raphe were reduced in the 10 patients scanned before and during SSRI treatment, this did not reach statistical significance (Figure 1). It is important to note, however, that animal studies suggest SSRI treatment may cause considerable changes in 5-HT_{1A} receptor function without necessarily altering the number of 5-HT_{1A} receptors.[42,43]

A number of methodological limitations of our study need to be recognized. The majority of patients were moderately depressed and we studied few subjects with severe illness. In addition, because of radiation exposure we did not include premenopausal women. The number of patients in the within-subject study of SSRI treatment was small and may therefore lack power to detect effects of SSRI treatment on 5-HT_{1A} receptor number. Finally, PET ligand studies cannot provide information about changes in receptor function that may be unaccompanied by alteration in BP.

In conclusion, our data suggest that major depression is associated with a decease in 5-HT_{1A} receptor binding in several brain regions. This could contribute toward the impairment in 5-HT_{1A} neurotransmission that has been detected in pharmacological challenge studies in depressed patients. Further studies will be needed to determine whether the decrease in 5-HT_{1A} receptor binding is specific for depression and whether changes normalize with long-term remission.

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