Correspondence

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Research Letter

Psychotherapy increases brain serotonin 5-HT$_{1A}$ receptors in patients with major depressive disorder

Introduction

The serotonin 5-HT$_{1A}$ receptor system is implicated in the pathophysiology of major depressive disorder (MDD) (Stockmeier, 2003) and serotonergic medications are currently widely used in the treatment of MDD. Previous molecular imaging studies in patients with MDD have provided evidence of a widespread decrease in the density of serotonin 5-HT$_{1A}$ receptors in the disease (Drevets et al. 1999; Sargent et al. 2000; Bhagwagar et al. 2004; Meltzer et al. 2004; Hirvonen et al. 2008, but see Parsey et al. 2006 for opposite results). Psychotherapy usually results in clinically identical outcomes with medication in the treatment of patients with mild to moderate MDD (Ebmeier et al. 2008). However, nothing is known about the molecular mechanisms mediating the effects of psychotherapy. To test and compare the effects of fluoxetine therapy. To test and compare the effects of fluoxetine (FLU, 20 mg/d, increased up to 40 mg/d if needed, $n=15$) for 16 weeks. Demographic and clinical characteristics of the patient groups are given in Table 1. Of the patients, 22 were completely antidepressant-naive, while one patient in the PSY group had been drug-free for 5 years. At baseline, the patients were evaluated by a psychiatrist, using the Structured Clinical Interview for DSM-IV Axis I disorders (First et al. 1997), 17-item Hamilton Depression Rating Scale (HAM-D; Hamilton 1967), and the Beck Depression Inventory (BDI; Beck et al. 1961). At this time, all patients underwent PET scanning for 5-HT$_{1A}$ receptors. We have previously published 5-HT$_{1A}$ receptor abnormalities in this sample at baseline (Hirvonen et al. 2008). After 16 weeks, all patients were re-evaluated by the same psychiatrist. Response to treatment was defined as a reduction of $\geq 50\%$ in HAMD total score, and remission was defined as a HAMD total score of $\leq 7$.

PET procedures

Preparation of the radioligand [carbonyl-11C]WAY-100635 and PET scanning procedures have been previously described in detail (Hirvonen et al. 2007). In brief, subjects were scanned twice with a whole-body 3D PET scanner (GE Advance, USA) and [carbonyl-11C]WAY-100635 before and after treatment. To examine the stability of the PET measurements in the long term, four healthy volunteers underwent two PET scans 383±134 days apart. There were no differences between the groups or between the scans in biochemical variables (Table 1).

Automated region of interest (ROI) analysis

An automated ROI analysis was performed as previously described (Hirvonen et al. 2008). ROIs in the standard space were applied onto each spatially normalized image using Imadeus software (version 1.2, Forima Inc., Finland). The ROI for raphe was drawn directly on the [carbonyl-11C]WAY-100635 template, since this small structure is not readily visible in MR images. Cerebellar white matter was used as the reference region (Parsey et al. 2005; Hirvonen et al. 2007).

Quantification of [carbonyl-11C]WAY-100635 binding

Binding potential (BP$_{ND}$) values, representing the ratio of specific and non-displaceable binding (Innis et al. 2007) were estimated using the simplified reference
tissue model (SRTM) with cerebellar white matter as the reference region (Lammertsma & Hume, 1996). The model did not converge in 10 subjects in the dorsal raphe, a small brain structure sensitive to, for example partial volume effects. Thus raphe was omitted from the primary analysis. A more simple area under curve (AUC) ratio method (Hirvonen et al. 2007) indicated that there were no statistically significant group repetition interactions in DRN (data not shown) but further studies with advanced high-resolution PET methodology are clearly needed.

Voxel-based analyses
To facilitate detailed visualization of the results, a confirmatory voxel-based analysis of parametric BP\textsubscript{ND} maps was performed as previously described (Hirvonen et al. 2008) using basis functions (Gunn et al. 1998) and SPM2 (Friston et al. 1995) running on Matlab 6.5 for Windows (Math Works, USA).

Statistical analyses of ROI-based data
Statistical analyses were carried out using SPSS 13.0 for Windows (release 13.0.1, copyright SPSS Inc., 1989–2004). The data were normally distributed, and were analysed by means of repeated-measures analysis of variance (rmANOVA) with repetition, region (ROI), and hemisphere as within-subject factors, and age as the between-subject predictor of BP\textsubscript{ND}. Group repetition interaction was modelled to investigate treatment-group differences in the change in BP\textsubscript{ND} values between the scans. This was followed by regional models. Sex entered the models as covariate. We also evaluated the reproducibility and reliability of the method of repeated scanning with [carbonyl-\textsuperscript{11}C]WAY-100635 in the four healthy volunteers, by means of absolute variability and intra-class correlation coefficients (ICC). Data are presented as mean ± standard deviation unless otherwise specified. 

\( p < 0.05 \) in all between-group comparisons unless otherwise apparent.

Results
The clinical outcome in both treatment groups was similar in terms of standard symptom ratings, and 59% of the subjects reached remission and 77% of the

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Fluoxetine</th>
<th>Psychotherapy</th>
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<tbody>
<tr>
<td>( n )</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>Age (years, mean ± s.d.)</td>
<td>39 ± 9</td>
<td>41 ± 10</td>
</tr>
<tr>
<td>Females (%)</td>
<td>66.7</td>
<td>37.5</td>
</tr>
<tr>
<td>Education level (mean ± s.d.)</td>
<td>1.80 ± 0.8</td>
<td>1.75 ± 0.9</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>22.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Body mass index (kg/m\textsuperscript{2}, mean ± s.d.)</td>
<td>25.5 ± 4.4</td>
<td>28.4 ± 4.2</td>
</tr>
<tr>
<td>Baseline HAMD total score (mean ± s.d.)</td>
<td>18.1 ± 3.2</td>
<td>19.9 ± 2.3</td>
</tr>
<tr>
<td>Change in HAMD total score (mean ± s.d.)</td>
<td>−10.9 ± 5.7</td>
<td>−14.3 ± 4.4</td>
</tr>
<tr>
<td>Baseline BDI total score (mean ± s.d.)</td>
<td>24.4 ± 8.7</td>
<td>22.4 ± 4.2</td>
</tr>
<tr>
<td>Change in BDI total score (mean ± s.d.)</td>
<td>−13.5 ± 5.8</td>
<td>−13.6 ± 7.1</td>
</tr>
<tr>
<td>Duration of current episode (weeks, mean ± s.d.)</td>
<td>21.7 ± 15.0</td>
<td>41.3 ± 40.0</td>
</tr>
<tr>
<td>Recurrent/first-episode MDD (n)</td>
<td>2/13</td>
<td>4/4</td>
</tr>
<tr>
<td>No. of episodes in recurrent MDD (mean ± s.d.)</td>
<td>0.13 ± 0.4</td>
<td>1.75 ± 3.4</td>
</tr>
<tr>
<td>Responders (%)</td>
<td>66.7</td>
<td>87.5</td>
</tr>
<tr>
<td>In remission (%)</td>
<td>60.0</td>
<td>50.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>[carbonyl-\textsuperscript{11}C]WAY-100635 radiochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injected dose, 1st PET (MBq, mean ± s.d.)</td>
</tr>
<tr>
<td>Injected dose, 2nd PET (MBq, mean ± s.d.)</td>
</tr>
<tr>
<td>Injected mass, 1st PET (( \mu )g, mean ± s.d.)</td>
</tr>
<tr>
<td>Injected mass, 2nd PET (( \mu )g, mean ± s.d.)</td>
</tr>
<tr>
<td>Specific radioactivity, 1st PET (MBq/nmol, mean ± s.d.)</td>
</tr>
<tr>
<td>Specific radioactivity, 2nd PET (MBq/nmol, mean ± s.d.)</td>
</tr>
<tr>
<td>Scan interval, days (mean ± s.d.)</td>
</tr>
<tr>
<td>Change in cerebellar AUC (%, mean ± s.d.)</td>
</tr>
</tbody>
</table>

AUC, Area under the curve; BDI, Beck Depression Inventory; HAMD, Hamilton Depression Rating Scale; MDD, major depressive disorder; PET, positron emission tomography.

\( p > 0.05 \) in all between-group comparisons unless otherwise apparent.
The mean effect size across brain regions was 0.85
with these results, patients in the PSY group had a
greater increase in BPND following treatment com-
pared to patients in the FLU group in 7/15 ROIs, as
well as in the average of post-synaptic ROIs (Table 2).
The change in the mean post-synaptic 5-HT1A
density was not associated with the change in symptom
scores in either group (not shown). Neither did base-
line 5-HT1A density predict symptom reduction, re-
response to treatment, or remission status (not shown).
However, in patients who had reached remission in
the PSY group (n=4), increase in the mean post-syn-
aptic 5-HT1A density was tightly correlated with the
reduction in HAMD (R = −0.99, p = 0.009) and BDI
total scores (R = −0.99, p = 0.013).
There were no group differences in the changes in
the input function, estimated by AUCs for the refer-
ence region time–activity curves (cerebellar white
matter) (p = 0.904). In the healthy control group, the
measurement of neocortical 5-HT1A density was found
to be very stable in the long term, with low within-
subject variability (6–10%) and good reliability (ICC
0.67–0.87).

**Discussion**

We found increased serotonin 5-HT1A receptor bind-
ing in multiple cortical regions following psycho-
therapy in patients with MDD. No change was
observed in patients receiving fluoxetine medication,
although the clinical outcome in terms of symptom
ratings was similar in both groups. This is the first
direct demonstration of a specific neurotransmitter
mechanism involved in the neurobiology of psycho-
therapy.

The small sample size in the present study sets in-
herent limitations to the interpretation of the observed
results that should be considered preliminary. How-
ever, they serve as a starting point for applying
other molecular imaging probes in the research for
neurobiological underpinnings of psychotherapy in
larger study samples. This line of research has thus far
received little attention, and the few studies on this
topic have documented focal changes in cerebral
metabolism or blood flow (Beauregard, 2009). The
mechanisms involved in the change in the serotonin
system following psychotherapy remain unknown.

Given the importance of serotonin in cognitive and
emotional processes, and the fact that psychotherapy
is a form of emotional learning, the increase in 5-HT1A
BPND following psychotherapy could reflect a top-
down modulation of the serotonin system based on
increased emotion regulation and decreased stress.
Our findings would then be consistent with the hy-
pothesis that psychotherapy could lead to changes in
gene expression through learning, by altering the

![Fig. 1. Visualization of the results from the SPM analysis. The analysis of parametric [carbonyl]-11C]WAY-10625 binding potential (BPND) maps at the voxel level showed two large clusters [kE=9515, Tmax=5.82 at (−26, 0, −36) and kE=18231 voxels, Tmax=4.10 at (−46, −20, 42)] located mainly in frontal, temporal and parietal cortex. These clusters represent significantly increased BPND in the psychotherapy group as compared with the fluoxetine group. The results are visualized on a T1-weighted MRI template in stereotactic standard space; the colour bar represents the T statistic at voxel level.](image-url)
Table 2. Regional [carbon-11C]WAY-100635 (binding potential) BPND values before and after treatment for fluoxetine (FLU) and psychotherapy (PSY) groups, and for test and retest conditions for the control group.

<table>
<thead>
<tr>
<th>ROI</th>
<th>Fluoxetine (n = 15)</th>
<th>Psychotherapy (n = 8)</th>
<th>Control (n = 4)</th>
<th>ΔBPND FLU v. PSY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BPND</td>
<td>Change</td>
<td>BPND</td>
<td>Change</td>
</tr>
<tr>
<td></td>
<td>PET1</td>
<td>PET2</td>
<td>%</td>
<td>p</td>
</tr>
<tr>
<td>AMY</td>
<td>6.24 ± 1.5</td>
<td>6.11 ± 1.6</td>
<td>−1.4</td>
<td>0.650</td>
</tr>
<tr>
<td>ANG</td>
<td>3.99 ± 0.7</td>
<td>3.84 ± 0.7</td>
<td>−3.6</td>
<td>0.178</td>
</tr>
<tr>
<td>DAC</td>
<td>5.07 ± 0.8</td>
<td>5.00 ± 1.0</td>
<td>−1.3</td>
<td>0.702</td>
</tr>
<tr>
<td>DLP</td>
<td>4.11 ± 0.7</td>
<td>3.95 ± 0.8</td>
<td>−3.7</td>
<td>0.227</td>
</tr>
<tr>
<td>HIP</td>
<td>6.39 ± 1.6</td>
<td>6.39 ± 1.7</td>
<td>+1.1</td>
<td>0.990</td>
</tr>
<tr>
<td>INS</td>
<td>5.83 ± 1.0</td>
<td>5.73 ± 1.2</td>
<td>−2.2</td>
<td>0.468</td>
</tr>
<tr>
<td>ITG</td>
<td>3.79 ± 0.7</td>
<td>3.61 ± 0.7</td>
<td>−4.5</td>
<td>0.065</td>
</tr>
<tr>
<td>MFC</td>
<td>4.91 ± 0.9</td>
<td>4.82 ± 0.9</td>
<td>−1.7</td>
<td>0.466</td>
</tr>
<tr>
<td>MTG</td>
<td>4.76 ± 0.8</td>
<td>4.62 ± 0.9</td>
<td>−2.9</td>
<td>0.257</td>
</tr>
<tr>
<td>ORB</td>
<td>5.50 ± 0.9</td>
<td>5.27 ± 0.9</td>
<td>−3.9</td>
<td>0.174</td>
</tr>
<tr>
<td>PC</td>
<td>4.23 ± 1.0</td>
<td>3.89 ± 0.8</td>
<td>−6.7</td>
<td>0.112</td>
</tr>
<tr>
<td>SMAR</td>
<td>4.18 ± 0.7</td>
<td>4.04 ± 0.7</td>
<td>−3.2</td>
<td>0.252</td>
</tr>
<tr>
<td>STG</td>
<td>4.57 ± 0.8</td>
<td>4.36 ± 0.8</td>
<td>−4.2</td>
<td>0.192</td>
</tr>
<tr>
<td>VAC</td>
<td>5.43 ± 0.9</td>
<td>5.31 ± 1.0</td>
<td>−2.0</td>
<td>0.481</td>
</tr>
<tr>
<td>VLP</td>
<td>3.99 ± 0.7</td>
<td>3.84 ± 0.8</td>
<td>−3.7</td>
<td>0.230</td>
</tr>
<tr>
<td>Average</td>
<td>4.87 ± 0.8</td>
<td>4.72 ± 0.9</td>
<td>−1.3</td>
<td>0.207</td>
</tr>
</tbody>
</table>

AMY, Amygdala; ANG, angular gyrus; DAC, dorsal anterior cingulate cortex; DLP, dorsolateral prefrontal cortex; HIP, hippocampus; INS, insular cortex; ITG, inferior temporal gyrus; MFC, medial prefrontal cortex; MTG, middle temporal gyrus; ORB, orbitofrontal cortex; PC, posterior cingulated cortex; PET, positron emission tomography; ROI, region of interest; SMAR, supramarginal gyrus; STG, superior temporal gyrus; VAC, ventral anterior cingulate cortex; VLP, ventrolateral prefrontal cortex.

*p values are from paired t tests except for the last column, which gives the p value of the group comparison of BPND changes (ΔBPND) between fluoxetine and psychotherapy groups. p values denoting statistical significance (p < 0.05) appear in boldface and are indicated by an asterisk.
strength of synaptic connections between nerve cells and inducing morphological changes in neurons (Kandel, 1998).

Previous studies have found reduced 5-HT\textsubscript{1A} receptor binding in MDD (Drevets et al. 1999; Sargent et al. 2000; Bhagwagar et al. 2004; Meltzer et al. 2004, but see Parsley et al. 2006), that is not reversed by SSRI treatment (Sargent et al. 2000; Bhagwagar et al. 2004; Moses-Kolko et al. 2007). Our observations are consistent with these findings, since fluoxetine did not alter 5-HT\textsubscript{1A} receptor binding despite clinical efficacy. Some authors have suggested that reduced 5-HT\textsubscript{1A} receptor binding could be a trait marker of depression that increases the risk of future depression. Our results would then suggest that psychotherapy may lead to a change in this trait, although BP\textsubscript{ND} was not decreased specifically in this sample (Hirvonen et al. 2008). This is supported by the finding that the relapse rate in MDD patients may be lower in those treated with psychotherapy compared to those treated with antidepressant medication (Hollon et al. 2005).

Acknowledgements

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Declaration of Interest

Dr Karlsson has received lecture fees from AstraZeneca, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck and Wyeth, Dr Hirvonen has received lecture fees from AstraZeneca, Bristol–Myers Squibb, Janssen-Cilag, Lundbeck and Novartis, congress travel grants from AstraZeneca and Lundbeck, and research funding from Orion Pharma and Lundbeck. Dr Markkula has received lecture fees from Eli Lilly, GlaxoSmithKline, and Janss-Cilag. Dr Hietala has received lecture fees from AstraZeneca, Bristol–Myers Squibb, Eli Lilly, Janssen-Cilag, and Lundbeck, congress travel grants from AstraZeneca, Bristol–Myers Squibb, and Eli Lilly, and has acted as consultant for Orion Pharma.

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