Chapter 5

Decreased Thalamic Blood Flow in Obsessive-compulsive Disorder Patients Responding to Fluvoxamine

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submitted
Abstract

Functional imaging studies have pointed to a role of the orbitofrontal cortex (OFC), striatum and thalamus in the pathophysiology of obsessive-compulsive disorder (OCD). Effective treatment has been found to change brain activity within this circuitry. The aim of the present study was to explore possible differential effects of OCD responders and non-responders to drug treatment on the regional cerebral blood flow (rCBF). rCBF was measured in 15 out of 22 patients with OCD who completed an open-label trial with fluvoxamine. Patients were studied with $^{99}$mTc-HMPAO single photon emission computed tomography (SPECT) before and after 12 weeks of treatment. In addition, a structural MRI was obtained on all patients. Regions of interest were OFC, caudate nucleus, putamen and thalamus. Seven patients responded to treatment. rCBF was significantly decreased in the left caudate nucleus and left and right putamen in both responders and non-responders to treatment. In responders, but not in non-responders, a significant decrease in rCBF was found in the right thalamus. Pre-treatment cerebellar- and whole brain HMPAO uptake was significantly higher in responders to treatment compared to non-responders. We suggest that the thalamus plays a central role in the response to drug treatment.
Introduction

Obsessive-compulsive disorder (OCD) is a severe, chronically disabling illness characterized by intrusive ritualistic thoughts and behaviors, over which patients have often little control. Treatment with serotonin reuptake inhibitors (SRIs) is currently the mainstay for drug treatment of patients with OCD. Although a substantial number of OCD patients benefit from this treatment, a sizable minority is refractory and in those who do respond residual symptoms usually persist, despite a meaningful clinical response. Generally, improvement is attained in about 40-60% of the patients on monotherapy with SRIs. These findings underline the necessity of getting a better understanding of the mechanisms underlying the effects of SRIs in this disorder.

Brain imaging research in OCD has indicated involvement of specific brain structures, which led to an assumed dysfunction in the fronto-striatal-thalamic-frontal circuit. Structural imaging studies have found alterations in frontal grey and white matter, caudate nucleus and ventrical volumes in OCD patients. Functional imaging studies have shown metabolic changes in frontal cortex, anterior cingulate, caudate nucleus and thalamus, which were increased during symptom provocation. These findings seem state-dependent as successful treatment with SRIs or behavioral therapy decreased metabolism in aforementioned regions. Various neuroimaging studies found predictors for treatment response. A beneficial treatment response to SRIs was predicted by higher pre-treatment metabolism in the prefrontal cortex, lower metabolism in the caudate nucleus and lower metabolism in the orbitofrontal cortex (OFC). Higher values in the OFC were associated with good response following behavioral therapy. In the posterior cingulate cortex, pre-treatment values were higher following response to SRIs and cingulotomy.

The thalamus is of particular interest in OCD, because it is thought to play a pivotal role in integrating intero- and exteroceptive information relayed to cortical areas. In pediatric OCD patients, pre-treatment increased thalamic volumes were decreased following paroxetine treatment, but not after cognitive behavioral therapy. Using proton magnetic resonance spectroscopy, decreased thalamic N-acetyl aspartate (NAA) levels, a marker for neuronal number and activity, were found in drug-naive OCD patients when compared with controls.

The aim of this study was to get more insight in the effects of SRI treatment on brain metabolism by measuring the effect of fluvoxamine on the regional cerebral blood flow (rCBF) in the fronto-striatal-thalamic-frontal circuit of patients responding and non-responding to this treatment. We used single photon emission computed
tomography (SPECT) in combination with structural magnetic resonance imaging (MRI) to ensure a more accurate assessment of the brain regions of interest.

Patients and Methods

Patients

Patients aged 18-55 years, referred to the outpatient clinic of the University Medical Center Utrecht and suffering from OCD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) were recruited for this study. Patients with concomitant anxiety disorders, major depressive disorder, a score of more than 15 on the 17-item Hamilton Depression Rating Scale (HDRS) and alcohol or drug abuse were excluded. Subjects were in good physical health as determined by physical examination and routine laboratory tests. Female patients who were pregnant, lactating women and women not using reliable methods for contraception were excluded.

Twenty-two patients were included in the study. Two patients dropped out during week 8 and 12, because of lack of response to treatment. Four patients refused to perform the MRI scan and due to technical problems the SPECT data of one patient was lost. The results of this study are based on the data set of the remaining fifteen patients (4 men, 11 women). Six patients were drug-naive. The washout period for patients using antidepressants was 2 weeks (8 weeks for fluoxetine). The mean ± SD age was 34.5 ± 11.8 years. The mean duration of symptoms was 13.6 ± 10.2 (range 3-30) years. Mean length and weight were 172.6 ± 8.3 cm and 69.4 ± 12.6 kg, respectively. All patients suffered from obsessive-compulsive symptoms of at least moderate severity as determined by the Yale-Brown Obsessive-compulsive Scale (YBOCS) score of 28.2 ± 5.2. The subscores “obsessions” and “compulsions” derived from the YBOCS were 14.0 ± 2.9 and 14.2 ± 2.7, respectively. Patients suffered from checking and cleaning compulsions, but also from ordering- and repeating rituals, list making and obsessions only. Two patients suffered from motor tics. The mean score on the Hamilton Anxiety Rating Scale (HAS) was 10.4 ± 5.3 and the score on the HDRS was 7.1 ± 3.5. Seven out of 15 patients were responders to treatment by a pre-established criterion (see statistical analysis). The patient characteristics stratified into responders and non-responders are summarized in Table 1. There were no significant differences between the responder groups on any of the demographic variables. The study was approved by the Ethics Committee of the University Medical Center Utrecht. Written informed consent was obtained from all patients.
Treatment and assessments

Fluvoxamine treatment started with 50 mg/day, immediately after performance of the pre-treatment $^{99m}$Tc-hexamethyl-propyleneamineoxime (HMPAO) SPECT scan. The fluvoxamine dosage was increased to a maximum of 300 mg/day, if tolerated. Neither use of other psychotropic drugs, nor behavioral and/or cognitive therapy was allowed during the study. Assessments of blood pressure, pulse rate, weight, YBOCS, Clinical Global Impression Scale (CGI) and HAS were performed at week 0, 2, 4, 8, and 12. The HDRS was assessed at week 0 and 12. After 12 weeks of fluvoxamine treatment the post-treatment $^{99m}$Tc-HMPAO SPECT scan was performed. On a separate occasion after treatment a MRI scan was performed.

SPECT and MRI methods

From 15 minutes before up to 10 minutes after intravenous administration of $^{99m}$Tc-HMPAO, subjects were instructed to remain silent. $^{99m}$Tc-HMPAO dose was 800 MBq (±5%) for all subjects. They were lying supine in a low ambient noise environment with their eyes and ears open. SPECT acquisition was performed with subjects head immobilized with velcro bands. Imaging data were acquired using a triple-headed, rotating gamma camera system (PRISM 3000, Picker, Ohio, USA) with UHRFAN beam collimators. A routine protocol of step and shoot mode (6 degree angles with a total of 60 projections), duration of 60 seconds per projection and 140 KeV photon peak with a 10% window was followed. Images were reconstructed in a $64 \times 64$ pixel matrix, with a reconstruction diameter of 25 cm. The acquired data were pre-filtered using
Metz filters (over a distance of 10 cm), followed by ramp-filtered back projection and reconstructed as transaxial slices of 7.1 mm.

For segmentation of the SPECT data, a MRI scan was acquired from each patient, with the following parameters; scanner Philips ACS NT 1.5 Tesla, scan 3D-FFE, TE = 4.6 ms, TR = 30 ms, matrix 128 by 128, FOV 256 by 256 mm, flip angle 30, slice thickness 1.2 mm, 150 slices. This volume was re-sliced to isotropic voxels of 1 mm, and was brought into spatial correspondence with the MNI standard brain using a rigid body transformation (i.e. translations and rotations only), that was computed with the MNI AutoReg software.

Images were re-sliced to isotropic voxels of 2 mm³, and were further treated as 3D volumes. Next, the two rigid body transformations that co-register the two SPECT volumes to the MRI volume were computed using the linear version of the ANIMAL registration software. Mutual information was selected as objective function because it yields good results for cross-modality registration.

Regions of interests (ROIs) were manually created for each individual subject on the MRI volume, using Analyze software. The ROIs were the caudate nucleus, putamen, thalamus, OFC and cerebellum bilaterally, and were identified and outlined on the basis of a standard MRI-based neuroanatomical atlas. The ROI masks were then overlaid on the co-registered SPECT volumes, and ROI mean HMPAO uptake (total counts/number of voxels) was calculated automatically for each ROI and for each SPECT volume. Finally, mean HMPAO uptake values for the ROIs were normalized to the mean uptake value of the cerebellum and to the mean uptake value of the whole brain, yielding a double set of rCBF data for each patients (see section on statistical analysis).

**Statistical Analysis**

Statistical analyses were performed by means of the Statistical Package for the Social Sciences (SPSS for WINDOWS software), version 11.5 (SPSS inc., Chicago, 2002). Patients were defined as responders to fluvoxamine treatment when the YBOCS total score showed a decrease of 25%, after 12 weeks of treatment. Patient characteristics, baseline behavioral- and physical measurements and fluvoxamine dosage were compared between response-groups using t-tests for independent groups.

Behavioral (YBOCS, HAS, HDRS and CGI) and physiological measurements were analyzed using multivariate analysis of variance (MANOVA) with ‘time’ as within factor and baseline measurement as a covariate. Pre-treatment (normalized) rCBF data of both response groups were compared using Student’s t-tests for independent groups.
Pre- and post-treatment absolute HMPAO uptake in the reference regions cerebellum and whole brain were also analyzed with Student’s t-tests.

The effect of treatment on the rCBF values for the ROIs was analyzed using MANOVA with treatment and ROI as within factors and response as between factor. Student’s t-test was used post hoc to evaluate response and treatment effects. All results are presented as mean ± SD and are reported as significant when \( p < 0.05 \).

**Table 2. Clinical assessments in OCD responders and non-responders before and after treatment with fluvoxamine (mean ± SD).**

<table>
<thead>
<tr>
<th></th>
<th>Responders (n = 7)</th>
<th>Non-responders (n = 8)</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-</td>
<td>Post-</td>
<td>Pre-</td>
<td>Post-</td>
</tr>
<tr>
<td>YBOCS total score</td>
<td>27.9 ± 7.2</td>
<td>17.4 ± 4.4</td>
<td>28.5 ± 3.0</td>
<td>25.5 ± 3.7</td>
</tr>
<tr>
<td>YBOCS obsessions</td>
<td>13.7 ± 4.1</td>
<td>8.7 ± 2.8</td>
<td>14.3 ± 1.5</td>
<td>11.8 ± 1.8</td>
</tr>
<tr>
<td>YBOCS compulsions</td>
<td>14.1 ± 3.2</td>
<td>8.7 ± 2.1</td>
<td>14.3 ± 2.3</td>
<td>13.6 ± 2.9</td>
</tr>
<tr>
<td>HAS</td>
<td>11.4 ± 5.8</td>
<td>5.1 ± 2.6</td>
<td>9.5 ± 5.0</td>
<td>9.3 ± 6.1</td>
</tr>
<tr>
<td>CGI</td>
<td>5.6 ± 1.0</td>
<td>4.3 ± 0.5</td>
<td>5.4 ± 0.7</td>
<td>5.3 ± 0.7</td>
</tr>
<tr>
<td>HDRS</td>
<td>8.0 ± 3.8</td>
<td>4.1 ± 1.8</td>
<td>6.4 ± 3.3</td>
<td>5.9 ± 5.5</td>
</tr>
</tbody>
</table>

OCD = obsessive-compulsive disorder; YBOCS = Yale-Brown Obsessive-compulsive Scale; HAS = Hamilton Anxiety Rating Scale; CGI = Clinical Global Impression Scale; HDRS = Hamilton Depression Rating Scale, ^a multivariate tests, ^b Huynh-Feldt correction

**Results**

**Clinical variables**

Obsessive-compulsive symptoms were significantly reduced in 7 out of 15 OCD patients after fluvoxamine treatment, as measured by the total score of the YBOCS (see Table 2).

There was a statistically significant interaction between response to treatment and behavioral assessments. Responders showed a statistically significant greater decrease on the YBOCS subscales obsessions and compulsions, HAS and CGI, as compared to
non-responders (Table 2). Baseline measurements were not significantly different for both groups for any of the ratings scales. Of the seven (3 men, 4 women) patients excluded from the study, 4 were non-responders (including the 2 drop-outs) and 3 responders to treatment.

**Brain SPECT imaging results**

In the reference regions cerebellum and whole brain pre-treatment HMPAO uptake was significantly different between responders and non-responders to treatment with responders showing a higher uptake in both regions as compared to non-responders (cerebellum $t = -2.557$, df = 13, $p = 0.024$; whole brain $t = -2.555$, df = 13, $p = 0.024$). After fluvoxamine treatment, HMPAO uptake was significantly decreased in both reference regions in responders (cerebellum $t = 3.362$, df = 6, $p = 0.015$; whole brain $t = 3.327$, df = 6, $p = 0.016$), but not in non-responders (Figure 1). Post-treatment HMPAO uptake was no longer statistically different between responders and non-responders for both reference regions.

Fluvoxamine treatment was associated with a statistically significant decrease in rCBF in a number of ROIs. Multivariate analysis showed a statistically significant mean treatment effect for both normalization methods (cerebellum $F = 15.888$, df = 5.9, $p = 0.004$; whole brain $F = 10.436$, df = 4.1, $p = 0.019$). In addition, a statistically significant ROI $\times$ treatment $\times$ response interaction was found for normalization to the cerebellum ($F = 7.558$, df = 5.9, $p = 0.019$) and a statistical trend was seen for normalization to whole brain ($F = 5.591$, df = 4.1, $p = 0.056$). Post hoc analysis on the difference scores in rCBF (before and after treatment) in both responder groups separately, found a significantly decreased rCBF for the right thalamus in responders to treatment (cerebellum $t = 2.987$, df = 6, $p = 0.024$; whole brain $t = 2.427$, df = 6, $p = 0.051$) (Figure 1). In non-responders, a non-significant increase in right thalamic rCBF was seen. In the right caudate nucleus, a non-significant trend for a differential effect between responders and non-responders was found.

With all patients entered in the analysis, fluvoxamine treatment was associated with a significant decrease in rCBF in the left caudate nucleus for both normalization methods (whole brain $t = 3.341$, df = 14, $p = 0.005$; cerebellum $t = 3.296$, df = 14, $p = 0.005$) and bilaterally in the putamen (left putamen: whole brain $t = 4.527$, df = 14, $p < 0.001$ and cerebellum $t = 3.900$, df = 14, $p = 0.002$; right putamen: whole brain $t = 4.022$, df = 14, $p = 0.001$ and cerebellum $t = 4.766$, df = 14, $p < 0.001$). The OFC was not significantly affected by fluvoxamine treatment (Table 3). Pre-treatment rCBF data of the ROIs in responders versus non-responders were not statistically different.
Table 3. ROI/whole brain rCBF ratios (mean ± SD) for various ROIs in OCD patients responding and non-responding to fluvoxamine treatment.

<table>
<thead>
<tr>
<th>ROI</th>
<th>Responders (n = 7)</th>
<th>Non-responders (n = 8)</th>
<th>ROI/cerebellum</th>
<th>ROI/whole brain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-treatment</td>
<td>Post-treatment</td>
<td>Pre-treatment</td>
<td>Post-treatment</td>
</tr>
<tr>
<td>left caudate nucleus</td>
<td>0.806 ± 0.080</td>
<td>0.768 ± 0.078</td>
<td>0.826 ± 0.114</td>
<td>0.777 ± 0.104</td>
</tr>
<tr>
<td>right caudate nucleus</td>
<td>0.803 ± 0.097</td>
<td>0.773 ± 0.121</td>
<td>0.826 ± 0.123</td>
<td>0.828 ± 0.108</td>
</tr>
<tr>
<td>left putamen</td>
<td>1.082 ± 0.074</td>
<td>1.041 ± 0.050</td>
<td>1.146 ± 0.052</td>
<td>1.086 ± 0.072</td>
</tr>
<tr>
<td>right putamen</td>
<td>1.104 ± 0.072</td>
<td>1.069 ± 0.050</td>
<td>1.157 ± 0.066</td>
<td>1.108 ± 0.056</td>
</tr>
<tr>
<td>left thalamus</td>
<td>0.956 ± 0.053</td>
<td>0.947 ± 0.074</td>
<td>1.041 ± 0.077</td>
<td>1.028 ± 0.077</td>
</tr>
<tr>
<td>right thalamus</td>
<td>0.996 ± 0.066</td>
<td>0.963 ± 0.069</td>
<td>1.025 ± 0.077</td>
<td>1.034 ± 0.082</td>
</tr>
<tr>
<td>left OFC</td>
<td>1.653 ± 0.036</td>
<td>1.669 ± 0.046</td>
<td>1.644 ± 0.054</td>
<td>1.643 ± 0.045</td>
</tr>
<tr>
<td>right OFC</td>
<td>1.663 ± 0.049</td>
<td>1.675 ± 0.050</td>
<td>1.660 ± 0.111</td>
<td>1.671 ± 0.093</td>
</tr>
</tbody>
</table>

ROI = region of interest; rCBF = regional cerebral blood flow; OFC = orbitofrontal cortex

*a* MANOVA ROI by treatment

*b* significant decrease in responders (normalized to whole brain: *P* = 0.051; normalized to cerebellum: *P* = 0.024)
Figure 1. Difference scores ± SEM (before and after treatment) for ROI/whole brain rCBF ratios in OCD-responders and non-responders to fluvoxamine treatment.

Fluvoxamine dosage and physical measurements
The mean fluvoxamine dosage at 12 weeks of treatment was 268.3 ± 46.7 mg/day; the dosage for responders and non-responders were not significantly different.

Systolic blood pressure decreased significantly in all patients during treatment, but this effect was not clinically relevant (week 0: 128 mm Hg, week 12: 120 mm Hg). Diastolic blood pressure, pulse rate and weight did not change during treatment.


Discussion

In this SPECT study, using co-registered MRI scans to ensure exact neuroanatomical localization of the ROIs, a treatment-response related change in rCBF was found in the right thalamus of OCD patients after fluvoxamine therapy. Twelve weeks of treatment caused a significant decrease in rCBF in the right thalamus of patients who responded to treatment, but not in treatment-non-responders. In addition, a treatment-related, but not response-related, decrease in rCBF was found in the caudate nucleus and putamen. The data suggest that the “pharmacological” effect of fluvoxamine is reflected in both the caudate nucleus and putamen, but that the “anti-obsessive-compulsive” effect is revealed predominantly in the thalamus, suggesting that this region might play a central role in the generation of obsessive-compulsive symptoms.

The thalamus is thought to play a key role in the fronto-striatal-thalamic-frontal circuit, which is composed of a direct and indirect system. These two pathways are purported to operate in parallel, with opposing effects at the level of the thalamus. Earlier investigations have already pointed to the role of the thalamus in OCD. Differences in brain activity between patients and controls were seen in the thalamus under baseline conditions\textsuperscript{12,19}. In a challenge paradigm a positive association between symptom intensity and rCBF in the thalamus was found\textsuperscript{14}. Saxena and co-workers\textsuperscript{22} have reported a decrease in metabolic activity in the thalamus of both OCD responders and non-responders to paroxetine treatment. In another study by the same investigators paroxetine treatment effects were compared between OCD and major depression patients. In OCD responders decreased metabolic activity in the thalamus was found\textsuperscript{23}. Baxter et al.\textsuperscript{18} have reported decreased thalamic metabolism in responders to fluoxetine treatment, but information on non-responders was not presented. Recently, Lacerda et al.\textsuperscript{43} found an inverse correlation between the right thalamic rCBF and compulsive behavior.

Additional evidence for involvement of the thalamus in OCD comes from a structural MRI study in children with OCD, showing increased pre-treatment thalamic volumes which decreased following paroxetine treatment\textsuperscript{29}. On the other hand, in a cognitive behavioral treatment study no changes were found in thalamic volume\textsuperscript{30}. It is difficult, however, to compare findings of the various imaging techniques, as volumetric data, rCBF and metabolic findings are different modalities.

Findings from neuroimaging data in OCD suggest that the fronto-striatal-thalamic-frontal circuit is involved in the pathogenesis of OCD. Moreover, symptoms such as difficulty in planning, learning new information, perseveration, or shifting behavioral
sets, are associated with dysfunctions in this brain circuit\textsuperscript{28, 44}. The fronto-striatal-thalamic-frontal circuit is a functional pathway in which input from multiple cortical areas are funneled through subcortical nuclei to the thalamus and subsequently projected back to specific cortical areas. Five known fronto-subcortical circuits (motor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal, and anterior cingulate circuit) have been defined, each with its specific functions, e.g. motor functions, executive functions, social behavior and motivational states. Each circuit has both a direct and an indirect pathway with opposing effects on the thalamus. The direct loop connects the striatum, via the globus pallidus interna - substantia nigra complex directly with the thalamus. The indirect loop runs from the striatum via the globus pallidus externa and the subthalamic nucleus to the globus pallidus interna - substantia nigra complex and then to the thalamus. Functionally, the direct pathway has a net excitatory effect on the thalamus, whereas the indirect pathway has a net inhibitory influence on the thalamus.

Drawing on the fronto-striatal-thalamic-frontal model of OCD, Baxter et al.\textsuperscript{18} have hypothesized an augmented resting neuronal activity in this circuit of OCD patients, which normalizes after successful treatment. This notion suggests state-dependent, “anti-obsessional” mechanisms within this circuit. The response-related changes in thalamic rCBF observed in this treatment study, point towards a central role for the thalamus in the anti-obsessional effects of SRIs. It may be hypothesized that the thalamus represents the final common pathway in the mechanism underlying symptom reduction following SRI treatment in OCD and that perhaps an imbalance between the direct and indirect pathway to the thalamus is crucial in this respect.

A confounding factor in this study was the higher HMPAO uptake in the reference regions cerebellum and whole brain in responders compared to non-responders at baseline. Moreover, cerebellar and whole brain HMPAO uptake decreased following treatment in responders, but not in non-responders, yielding no post-treatment significant differences between both groups. This posed a methodological problem in the normalization procedure. Statistical analyses were therefore performed using both normalization methods and effects were considered statistically significant only if both methods yielded significant results.

The increased HMPAO uptake in the cerebellum and whole brain at baseline and the subsequent decrease in activity after successful treatment is an interesting finding in itself. It may suggest a role for the cerebellum in the pathophysiology of OCD. Some data on the cerebellum in OCD have been presented. In a PET study\textsuperscript{8} an increased absolute cerebral glucose metabolic rate (CMRglc) was found in the cerebellar region.
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in OCD patients and a MRI study showed a decrease in cerebellar white matter volume. There is also circumstantial evidence for the cerebellum to be involved in other psychiatric disorders such as schizophrenia, autism and dementia, suggesting a role beyond its motor effects. It may be hypothesized that higher pre-treatment HMPAO uptake in the cerebellum and whole brain is a predictor for response to SRI treatment.

Other confounding factors are the small sample size, which increases risk for a type II error and the heterogeneous symptom profile of the patients included in this study.

In conclusion, fluvoxamine treatment in OCD patients significantly decreased rCBF in the left caudate nucleus, putamen and right thalamus. The rCBF decrease in the right thalamus was associated with a decrease in obsessive-compulsive symptoms.

Acknowledgements

This study was supported in part by an unrestricted grant from Solvay-Duphar.
References


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