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The comparison of pre- and post-treatment ^{99m}Tc HMPAO brain SPECT images in patients with obsessive-compulsive disorder

Filiz Karadağ [a], Nalan Kalkan Oğuzhanoğlu [a,*], Doğangün Yüksel [b], Suna Kıraç [b], Çiğdem Cura [a], Osman Özdel [a], Figen Ateşci [a]

[a] Pamukkale University, Medical Faculty, Department of Psychiatry, Denizli 20100, Turkey
[b] Pamukkale University, Medical Faculty, Department of Nuclear Medicine, Denizli 20100, Turkey

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ABSTRACT

The objective of the present study was to compare brain activation in patients with obsessive-compulsive disorder (OCD) who received pharmacotherapy (selective serotonin reuptake inhibitor (SSRI) or a SSRI–risperidone combination) with that in healthy controls using ^{99m}Tc-hexamethyl propyleneamine oxime (HMPAO) brain single photon emission tomography (SPECT). Twelve OCD patients achieving clinical response (seven SSRI responders, five patients responded to SSRI plus risperidone) underwent post-treatment SPECT scan. The baseline regional cerebral blood flow (rCBF) was significantly reduced in a large part of the cerebral cortex and the left cingulate gyrus in OCD patients compared with controls. After a 50% reduction of the OCD symptoms, bilaterally increased rCBF in the thalamus showed a significant effect of time in both of the patient groups. In the remitted state, although rCBF in the cingulate gyrus did not differ in SSRI responders compared with controls, patients who responded to the combination of SSRI+ risperidone showed significant hypoperfusion in the left anterior cingulate gyrus. SSRI responders had normalized rCBF in the frontal region relative to the control group. Consequently, based on our results, we attribute the observed thalamic rCBF alteration to SSRI treatment. Our results also suggested that brain perfusion changes associated with clinical remission may differ across patient subgroups.

1. Introduction

Functional brain imaging studies have consistently shown a dysfunction of cortico-thalamo-striatal circuits in the pathophysiology of obsessive-compulsive disorder (Saxena and Rauch, 2000). Findings have suggested functional abnormalities in the orbitofrontal cortex (OFC), thalamus, caudate nucleus and cingulate gyrus of patients with obsessive-compulsive disorder (OCD) (Friedlander and Desrocher, 2006). These findings seem to be state-dependent, as successful treatment with a serotonin reuptake inhibitor (SRI) or behavioral therapy decreases the cerebral metabolism in these regions (Benkelfat et al., 1990; Swedo et al., 1992; Baxter et al., 1992; Perani et al., 1995; Rubin et al., 1995; Schwartz et al., 1996; Saxena et al., 1999, 2002).

Although selective serotonin reuptake inhibitors (SSRIs) are the treatment of choice in OCD patients, as many as 40–60% of patients may not respond or may have only a partial response to these medications (Bloch et al., 2006; Pallanti and Quercioli, 2006). In such cases, the addition of a low dose atypical antipsychotic, such as risperidone or olanzapine, to ongoing SSRI treatment has been shown to be effective (McDougle et al., 2000; Bystritsky et al., 2004). Only one-third of treatment-refractory OCD patients show a meaningful treatment response to antipsychotic augmentation (Bloch et al., 2006). These differences suggest that OCD is a highly heterogeneous condition, and it is possible that there are biological differences among subgroups of OCD as defined by pharmacological response or symptom clusters (Gilbert et al., 2008; van den Heuvel et al., 2009; Sumitani et al., 2007; Buchsbaum et al., 2006). Two recent brain-imaging studies have suggested the presence of psychopharmacological subtypes within OCD. Sumitani et al. (2007) reported that OCD patients who responded to augmentation of SSRI treatment with an atypical antipsychotic (risperidone) had distinct biological abnormalities in the anterior cingulate. Buchsbaum et al. (2006) found that a successful treatment with an SSRI plus risperidone was associated with low relative metabolic rates in the striatum and high relative metabolic rates in the anterior cingulate gyrus in OCD patients who were nonrespondent to serotonin reuptake inhibitors.

In order to understand the underlying pathophysiology and to investigate trait characteristics rather than state-dependent alterations, the comparison of brain activity between remitted OCD patients and healthy controls may be more valuable than only

* Correspondence to: Pamukkale University, Medical Faculty, Department of Psychiatry, Doktorlar Cad. No: 42/613, Denizli 20100, Turkey.
Tel.: +90 542 6309600; fax: +90 258 2410040.
E-mail addresses: n_oguzhan@yahoo.com, noguzhan@pau.edu.tr (N. Kalkan Oğuzhanoğlu).

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comparing the pre- and post-treatment differences. We were able to carry out a limited number of neuroimaging studies comparing remitted OCD patient with health individuals. Two of them have been reported by Nabeyama et al. (2008) and Lázaro et al. (2009).

The objective of the present study was to compare the brain activity in OCD patients who responded to an SSRI trial and an SSRI plus an atypical antipsychotic drug (risperidone), using ^{99m}Tc-hexamethyl propyleneamine oxime (HMPAO) brain SPECT (single photon emission computed tomography) imaging. According to our first hypothesis consistent with the pathophysiological models of OCD, at the beginning OCD, patients would initially be expected to show abnormal brain perfusion in frontostriatal circuits as compared with the healthy subjects as well as in other central and posterior brain regions in which abnormalities are reported less frequently. Secondly, OCD patients who respond to different pharmacotherapeutic regimens would be expected to show differential brain perfusion changes in the particular brain regions under treatment. And finally, besides the pre- and post-treatment changes, we also planned to compare brain perfusion in two remitted patient groups with that in healthy subjects to examine whether brain perfusion in remitted patients normalized after positive treatment response.

2. Methods

2.1. Participants

Participants comprised 23 OCD patients and 10 healthy controls. All participants gave written informed consent to take part in the study after the procedures were explained and all recommendations of the local ethical committee were met. OCD patients were consecutively recruited from psychiatric outpatient clinics, and control subjects were chosen among hospital staff. OCD and comorbid diagnoses were established using the Structured Clinical Interview for DSM-IV (SCID-I) (First et al., 1997; Özkürkçügil et al., 1999). The patients had been drug-free for at least 2 weeks before the study; the patients included in the study had either never been treated for OCD or had needed to be switched over from an ongoing SSRI therapy to other medications due to intolerable side effects or ineffectiveness.

Patients completed the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al., 1989) and Hamilton Depression Rating Scale (HDRS-17) (Hamilton, 1960). Exclusion criteria for the patients were as follows: current medical illness, lifetime history of alcohol or substance abuse or dependence, history of head injury, epilepsy or any other neurological disease, or exposure to any medication known to have a significant effect upon the central nervous system in the 2 weeks preceding the study. Comorbid depression or any other psychiatric diagnoses, e.g., panic disorder or generalized anxiety disorder, were also considered as exclusion criteria for OCD patients. Exclusion criteria for the control subjects were lifetime history of head injury or any DSM-IV Axis I diagnosis, current medical problems, and current or prior neurological disease. All subjects were right-handed.

2.2. ^{99m}Tc-HMPAO SPECT study

The participants rested in a supine position with closed eyes in a silent and darkened room for approximately 20 min before radiopharmaceutical administration. ^{99m}Tc-HMPAO was prepared according to the manufacturer's instructions. The SPECT study was performed 30 min after the injection of ^{99m}Tc-HMPAO (550 MBq) through an IV cannula.

A single-head 360° rotating CamStar AC/T gamma camera (GE, Milwaukee, WI, USA) equipped with a LEAP collimator was used for SPECT acquisition. A head holder was used in order to minimize motion artifacts. Data were obtained in a matrix of 128 × 128 pixels with a 1.6 zoom and at 3-degree intervals, at a rate of 20 s per frame. Filtered back-projection was applied to raw SPECT data, and then the Ordered Subset Expectation Maximization (OSEM) method in five subsets and ten times was applied for reconstruction before the segmental analysis. Attenuation correction was not performed.

The segmental analysis was performed on eight selected sequential transverse slices (thickness: 9.51 mm) parallel to the orbitomeatal line (OM) (Fig. 1). Sixteen regions of interest (ROIs) were automatically placed to the brain cortex on each slice. Eleven cortical areas on each cerebral hemisphere were evaluated according to the illustrations in a morpho-functional atlas (Guerra, 1998) showing the relevant slice levels depicting the cross-sections of the normal brain by the consensus of two experienced nuclear medicine physicians. The basal ganglia and the cingulate gyrus were semi-quantitatively analyzed in a 22.82-mm thickness of frame using the segmental analysis program. Additionally, coronal slices of 2-pixel thickness were used to select the best slices for thalamic evaluation, and ROIs over the bilateral thalamus were drawn manually. The mean count value per pixel for each ROI was calculated.

Cerebral regional perfusion was measured by using the cerebral to cerebellar ratio method. Cerebellum ROIs only covered the hemispheres without lying on the vermis. An average count in each of the cerebellar hemisphere ROIs was used for calculating the ratio of each cerebral segment to cerebellum. Additionally, the perfusion ratio of the basal ganglia, the cingulate gyrus, and the thalamus was semi-quantitatively calculated using the same method depending on the average count of the ROI..

2.3. Choice of treatment and groups

The choice of SSRI was based on individual responses to the previous medication and the side effect history of each patient, and the patients were scheduled to received fluvoxamine ($n=8$), sertraline ($n=2$), citalopram ($n=1$) and fluoxetine ($n=1$) accordingly. Immediately after the pre-treatment (HMPAO) SPECT scans were obtained, patients were started on a low dose SSRI (50 mg/day for fluvoxamine and sertraline, 20 mg/day for fluoxetine and citalopram). SSRI dosage, if tolerated, was slowly increased to the maximum dosage recommended for OCD. Y-BOCS and HDRS assessments were performed at weeks 0, 2, and 4, and the later follow-up assessments were performed at an interval of 4 weeks over 52 weeks. SSRI responders were the patients who showed a $>25\%$ decrease in the Y-BOCS scores at the end of 12–16 weeks of treatment with a high dose SSRI. These patients were monitored for a period of 24–52 weeks, and post-treatment scans were performed when a reduction of $\geq 50\%$ was achieved in the Y-BOCS total scores, on an individual basis. A low dose of risperidone (1–3 mg/day) was added to the treatment in patients who had incomplete responses to SSRI treatment (a $<25\%$ decrease in Y-BOCS total scores) at the end of 12–16 weeks of treatment with the maximum tolerated doses. When these patients achieved a $\geq 50\%$ decrease in Y-BOCS total scores at any point in the follow-up (min 24–max 52 weeks), they were considered responders to an SSRI plus risperidone treatment, and post-treatment ^{99m}Tc-HMPAO SPECT scans were performed.

An improvement in the global Y-BOCS score of $\geq 40\%$ was considered to represent a clinical response in a recent study suggesting that patients with Y-BOCS scores decreased by 39% or less were still rated as moderately ill at post-treatment (Tolin et al., 2005). Furthermore, they suggested that treatment responders, as defined by a Y-BOCS reduction cut-off of 40–50%, were in remission. Therefore, we adopted a more stringent criterion, a reduction of

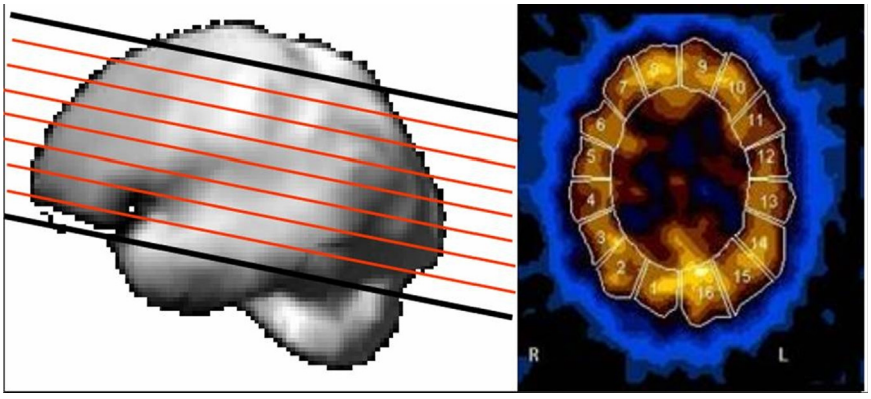

Fig. 1. Segmental analysis was performed on 8 selected sequential transverse slices (thickness: 9.51 mm) parallel to orbitomeatal line (OM).