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ORIGINAL PAPER

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# Reduced serotonin transporter-availability in obsessive-compulsive disorder (OCD)

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**Abstract** We investigated the availability of brain serotonin transporters in 10 drug-free patients with obsessive-compulsive disorder (OCD) and age-matched healthy controls *in vivo* using single-photon emission computed tomography (SPECT) and the radioligand [$^{123}$I]-2β-carbomethoxy-3β-(4-idiophenyl)-tropane ([$^{123}$I]β-CIT). For quantification of regional serotonin transporter a ratio of specific to non-specific [$^{123}$I]β-CIT-binding was used. The availability of serotonin transporter was calculated using regions of interests (ROI) for thalamus/hypothalamus, midbrain, brainstem (highest density of serotonin transporter) and cerebellum as a reference. The mean specific to non-specific [$^{123}$I]β-CIT binding ratios in the thalamic/hypothalamic ROI were 4.95 ± 0.57 (OCD patients), and 5.48 ± 0.87 (control group). The mean ratios in the midbrain ROI were 3.51 ± 0.45 (OCD patients) and 4.89 ± 1.23 (controls) and in the brainstem ROI the ratios were 2.38 ± 0.76 (OCD patients) and 3.53 ± 1.01 (controls). This *in vivo* finding of significant reduced serotonin transporter availability in midbrain/brainstem using [$^{123}$I] β-CIT SPECT further supports the serotonin deficit hypothesis of OCD.

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## Introduction

There is strong evidence for neurobiological as well as psychological factors playing an important role in the pathogenesis of obsessive-compulsive disorder (OCD) (Stein 2002; Hollander et al. 2002). Functional neuroimaging studies have provided strong evidence that the pathophysiology of OCD involves abnormal functioning along specific frontal-subcortical circuits (Rauch 2000). Most SPECT (Stein et al. 1999) and PET studies (Baxter et al. 1996; Saxena et al. 1998) indicate that OCD symptoms are associated with increased activity in orbitofrontal cortex, caudate nucleus, thalamus, and/or anterior cingulate gyrus. Therapeutic response to selective serotonin reuptake inhibitors (SSRIs) and the absence of improvement with norepinephrine reuptake inhibitors and dopamine agonists argue strongly for a role of serotonin in the pathophysiology and treatment of OCD (Baumgarten and Grozdanovic 1998). A recent PET study showed that improvement of OCD symptoms was significantly correlated with higher pretreatment glucose metabolism in the right caudate nucleus, whereas improvement of depressive symptoms was associated with metabolic changes in other brain areas (amygdala, thalamus, medial prefrontal cortex and anterior cingulate gyrus) (Saxena et al. 2003).

For measurement of SERT availability SPECT was used in healthy humans and various neuropsychiatric disorders, mostly using the cocaine congener [$^{123}$I]–2β-carbomethoxy-3β-(iodophenyl)tropaneiodophenyl) tropane ([$^{123}$I]β-CIT) as a sensitive SERT (and dopamine transporter) marker (Brücke et al. 1993; Pirker et al. 2000; Murai et al. 2001). With this method reduced SERT availabilities in the upper brainstem and midbrain were observed in patients with major depression (Malison et al. 1998) and affective disorders accompanying Parkinson's disease (Murai et al. 2001) and

stroke (Murai et al. 2003). In order to test the hypothesis that patients with OCD and supposed synaptic serotonin deficits show a significant reduction of SERT density in the midbrain, brainstem and thalamus/hypothalamus regions we measured SERT density using [$^{123}$I]β-CIT SPECT and a MRI based region of interest (ROI) analysis of data obtained with a brain dedicated SPECT camera system.

## Methods and materials

The study was approved by the ethics committee of the University of Leipzig. Informed consent for the [$^{123}$I]β-CIT SPECT imaging was obtained from all subjects.

### Patients and control subjects

In this pilot study we investigated 10 drug-free female (n = 6) and male (n = 4) patients with OCD (ICD 10, F42.0-F42.2, age 19–42 years, mean 29 ± 9). The average duration of illness was 14.2 years (range 2–28). All patients were recruited from the specialized outpatient clinic for patients with OCD and anxiety disorders at the Department of Psychiatry of the University of Leipzig. The patients were diagnosed by experienced psychiatrists using the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) (APA 1994). Severity of OC symptoms of the patients were measured by the Yale Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al. 1989a, b) and yielded a mean score of 30 (± 2.5 SD, range 26–31). Patients were excluded on the basis of evidence of psychiatric co-morbidity and therapy with drugs which affect the serotonin system within 6 months before participation. Especially (comorbid) depressive symptoms were assessed with the Beck Depression Inventory (BDI) (Beck et al. 1961) and yielded a mean score of 6.7, range 2–14. Seven age-matched (30.0 ± 9.8 years) healthy female and male subjects, who did not receive psychotropic medication and were without past or present neurologic or psychiatric disorder served as the control group. Our controls have been described elsewhere (Müller et al. 2000; Hesse et al. 2003).

### SPECT imaging

SPECT was performed 24 hours after i. v. application of 185 MBq [$^{123}$I]β-CIT with a high-resolution (7.5 mm FWHM) camera system (Ceraspect, DSI, Waltham, USA) as previously described (Murai et al. 2001). For SPECT data analysis, SERT-rich areas in thalamus–hypothalamus, midbrain and brainstem were determined by co-registration of SPECT data with a standard MRI data set which was paralleled to canthomeatal line (Murai et al. 2001). By applying a region of interest (ROI) technique (HERMES workstation, MultiModality software Nuclear Diagnostics AB, Stockholm, Sweden), specific to nondisplaceable [$^{123}$I]β-CIT binding ratios in the target region were calculated representing a simplified reference tissue model ($V3''$, cerebellum = reference ROI; Pirker et al. 2000).

### Statistical analysis

All data were tested for normal distribution using the Shapiro Wilks test. For group comparison of values Student's two-tailed t-test was applied (significance levels at $p < 0.005$ and $p < 0.05$, SPSS 10.0, Chicago, USA).

## Results

The mean specific to nondisplaceable [$^{123}$I]β-CIT binding in the thalamic-hypothalamic areas were 4.95 ± 0.57 (OCD patients), and 5.48 ± 0.87 (control group), respectively. The mean specific to nondisplaceable [$^{123}$I]β-CIT binding in midbrain ROI were 3.51 ± 0.45 (OCD patients) and 4.89 ± 1.23 (controls) (Fig. 1), and the mean specific to nondisplaceable [$^{123}$I]β-CIT binding in the brainstem area were 2.38 ± 0.76 (OCD patients) and 3.53 ± 1.01 (control group). Whereas the binding difference was significant in both the midbrain and the brainstem ROI ($p < 0.005$, and $p < 0.05$, respectively), there was a trend towards lower [$^{123}$I]β-CIT binding ratios in the OCD group in the thalamic-hypothalamic area ($p = 0.15$). No significant correlation was found between the clinical scores and the specific [$^{123}$I]β-CIT binding in all investigated SERT-rich brain regions.

## Discussion

The main finding was a significant reduction of SERT availability in the midbrain and upper brainstem in 10 OCD patients compared with healthy controls. The reduced SERT availability in OCD may reflect a reduced number of serotonergic (raphe) neurons that may result in low serotonin levels. SSRIs enhance synaptic serotonin levels and are a well-established clinical treatment for OCD. Reduced numbers of SERTs may reflect a genetic predisposition or result from degeneration of serotonergic neurons.

For delineation of the SERT-rich brain areas we used a magnetic resonance imaging (MRI) based co-registration technique to overcome the lack of anatomical information of SPECT data which has always been a methodological limitation in previous SPECT studies

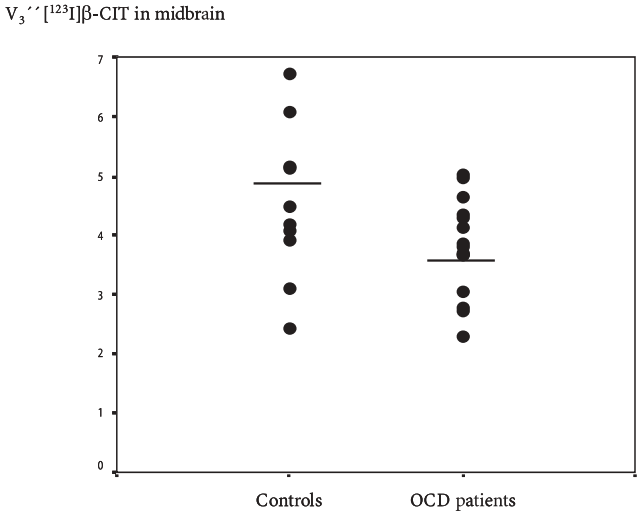


**Fig. 1** Availability of serotonin transporters in midbrain of patients with obsessive compulsive disorder (OCD) and healthy controls (controls)

investigating the central SERT (Malison et al. 1998; Willeit et al. 2000; Tauscher et al. 2001). Using this co-registration technique differential measurement of central monoaminergic transporters, i. e. SERT, dopamine, and norepinephrine, to which the used radioligand [$^{123}$I]β-CIT binds with different affinities (Okada et al. 1998), is possible due to variation of distribution of these transporter types within the brain (Olivier et al. 2000).

Up to now, in vivo imaging studies of serotonergic neurotransmission, which is believed to be involved in the pathogenesis of OCD are limited in this disorder (Staley et al. 2001). Our results differ from two recently published studies in OCD with similar sample sizes that found either increased SERT availability using [$^{123}$I]β-CIT (Pogarell et al. 2003) or unchanged SERT availability using [$^{11}$C](+)McN5652 PET (Simpson et al. 2003). The finding of higher SERT availabilities in early onset (mean age 26.4) as compared to late onset (mean age 43.8 years) patients in the first study seem to be confounded by age effects, because SERT densities are generally higher in young adults (Hesse et al. 2003). The inverse correlation of SERT ratios and BDI depression scores in the Pogarell et al. (2003) study is in line with reports of reduced SERT density in patients with depression and other affective disorders (Malison et al. 1998). In our study there were no correlations with depression scores. The [$^{11}$C]McN 5652 PET study found no differences of SERT densities in OCD patients without depression as compared to healthy controls (Simpson et al. 2003).

Further SERT neuroimaging studies with larger numbers of patients are necessary to understand the role of the serotonergic system in OCD and the relationships of SERT availability with clinical subtypes (form of obsessions and compulsion, age at onset, treatment response, depressive comorbidity) and other parameters like age, gender and genetic predisposition.

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