Understanding deep brain stimulation in obsessive compulsive disorder: A preclinical study into the mechanism of action and behaviour
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Chapter 2

The serotonergic system in obsessive compulsive disorder

Addy van Dijk, Andre Klompmakers, Damiaan Denys

Handbook of the behavioral neurobiology of serotonin (2010)
Amsterdam: Academic Press
Abstract

Obsessive compulsive disorder (OCD) is a psychiatric disorder consisting of obsessions and compulsions. Over the past two decades, it has been suggested that OCD might be related to the functioning of brain serotonin systems, mainly because of the anti-obsessional efficacy of selective serotonin reuptake inhibitors (SSRIs). Though the efficacy of SSRIs suggests a role of the serotonergic system in OCD, the exact function of serotonin is still unclear. Is the serotonergic system implicated in the pathophysiology of OCD, or is it implicated in the treatment effect in OCD? Do SSRIs compensate for a fundamental abnormality of the serotonergic system, or do SSRIs modulate an intact serotonergic system to compensate for another neurotransmitter mechanism? This chapter reviews five lines of evidence that have been cited in support of the serotonin hypothesis: (1) pharmacotherapy, (2) pharmacologic challenge studies, (3) receptor binding studies, (4) genetic association studies, and (5) animal models.
2.1 Introduction

Obsessive compulsive disorder (OCD) is a psychiatric disorder which consists of obsessions and compulsions. Obsessions are unwanted ideas or impulses that repeatedly well up in the mind, such as persistent fears to harm a loved one, an unreasonable concern with becoming contaminated or an excessive need to do things correctly or perfectly. Compulsions are repetitive behaviours or rituals such as washing and checking, counting, mentally repeating phrases, list making, or endlessly rearranging objects.

Over the past two decades, it has been suggested that OCD might be related to the functioning of brain serotonin systems, mainly because of the anti-obsessional efficacy of SSRIs. The serotonin hypothesis originated from the observed efficacy of SSRIs in OCD, compared to inefficacy of selective noradrenergic and dopaminergic reuptake inhibitors, suggesting a specific abnormality of the serotonergic system in OCD (Baumgarten and Grozdanovic 1998). However, the exact function of serotonin in OCD is still unclear. This chapter provides an overview of the evidence supporting a role for the serotonergic system in OCD. It reviews five lines of evidence that have been cited in support of the serotonin hypothesis: (1) pharmacotherapeutic studies, (2) pharmacotherapy, (3) receptor binding studies, (4) genetic association studies, and (5) animal models.

2.2 Pharmacotherapy

A common method to unravel the pathophysiology of a disorder in psychiatry is to study the mechanism of action of effective drug therapy. The cornerstone of pharmacotherapy for OCD is serotonin reuptake inhibition, either with clomipramine or with selective serotonin reuptake inhibitors. Over the past 25 years, a number of double blind, randomized, placebo controlled studies in OCD have confirmed the efficacy of clomipramine and the selective serotonin reuptake inhibitors: fluvoxamine, paroxetine, sertraline, fluoxetine and citalopram. Efficacy of drug trials in OCD is commonly expressed in absolute changes of Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores. The Y-BOCS is a clinician rated 10-item scale with a total range of 0 to 40 that measures severity of obsessions and compulsions (Goodman et al. 1989a; Goodman et al. 1989b). In many cases, patients are classified as responders when their scores on the Y-BOCS decrease by 25 to 35%.

The efficacy of clomipramine was established in more than 10 placebo-controlled trials. In a recent meta-analysis, clomipramine shows a net improvement (difference) compared with placebo of 8.20 points on the Y-BOCS (Ackerman and Greenland 2002). Responder rates to clomipramine vary between 40-50% of patients. Though in some cases low doses of clomipramine over a short period of time may result in significant improvement of symptoms,
Clomipramine treatment should last at least 10 to 12 weeks in a dose of 250-300 mg/day to demonstrate a full effect. Clomipramine has never been tested in a controlled fixed-dose study to assess optimal doses. Fluvoxamine is superior to placebo in 4 placebo-controlled trials and equipotent to clomipramine in 5 comparison trials (Dell’osso et al. 2005). The pooled difference of fluvoxamine compared with placebo in these trials was 4.8 points on the Y-BOCS. Fluvoxamine has never been examined in a fixed dose trial, but appears to be efficacious from 150-300 mg/day. Fluoxetine is effective in 3 placebo-controlled trials and equipotent to clomipramine in 2 comparison trials. The pooled difference on the Y-BOCS of fluoxetine compared with placebo was 1.6 points (Ackerman and Greenland 2002). Responder rates to fluoxetine vary between 25-30% of patients. Sertraline was effective in 4 placebo-controlled trials and equipotent to clomipramine in 1 comparison trial. The pooled difference of sertraline compared with placebo in these trials was 2.5 points on the Y-BOCS (Ackerman and Greenland 2002). Although no correlation was found of sertraline plasma levels with treatment outcome, in a large multicenter trial, sertraline 50 mg/day and 200 mg/day were superior to placebo whereas 100 mg/day was not.

For a long time, paroxetine was shown to be effective in just one published placebo-controlled trial and equipotent to clomipramine in the same trial (Ackerman and Greenland 2002; Zohar and Judge 1996; Ninan 2003). The difference of paroxetine compared with placebo was 3.1 points on the Y-BOCS. Forty and 60 mg/day doses were significantly better than placebo whereas 20 mg was not. The efficacy of citalopram in OCD recently was established in a placebo-controlled study including 401 patients who were randomized to receive citalopram 20, 40 or 60 mg/day or placebo for 12 weeks (Montgomery et al. 2001). The difference of citalopram compared with placebo was 3.6 points on the Y-BOCS. The highest responder rate (65%), defined as 25% improvement in Y-BOCS entry score, was observed in the 60 mg group compared with 52% and 57.4% in the 40 mg and 20 mg groups, respectively. Surprisingly, the responder rate on placebo was 36.6% with a mean decrease on the Y-BOCS of 5.6 points. This high improvement rate on placebo, uncommon in OCD, has been explained as a result of inclusion of milder, atypical cases, in which spontaneous remission is more frequent. Patients with longer duration of OCD, more severe OCD symptoms or previous SSRI use were less likely to be responders to citalopram, whereas patients who received adequate medication doses for sufficient periods of time were more likely to be responders (Stein et al. 2001). In a small study, clinical response does not appear to be related to citalopram plasma concentrations (Bareggi et al. 2004).

The efficacy of clomipramine and five SSRIs has been established with placebo-controlled trials, but are clomipramine, fluvoxamine, paroxetine, sertraline, citalopram and fluoxetine equally effective (Soomro et al. 2008)? Meta-analyses using statistical methods to pool
samples from different studies may answer this question offering a precise estimate of the treatment effect from separate drug trials. Consistent with previous meta-analyses, Ackerman et al recently confirmed that clomipramine is more effective than SSRIs in placebo-controlled trials (Ackerman and Greenland 2002). For 7 clomipramine trials, the net Y-BOCS decrease compared with placebo was 8.19, whereas for 4 fluvoxamine trials the net Y-BOCS decrease was 4.84, for 3 fluoxetine trials 1.61, and for 4 sertraline trials 2.47. It is worth noting, however, that the largest effect sizes for clomipramine were found in early studies and have not been as clearly replicated in more recent studies comparing it with SSRIs. Moreover, on the long term, drop-out rates in clomipramine-treated patients are higher than SSRI-treated patients. In another meta-analysis which included 32 studies covering a total number of 3588 OCD patients, again, clomipramine had the largest effect size (1.55) versus 0.81 for fluoxetine to 1.36 for sertraline (Eddy et al. 2004). This meta-analysis also demonstrated that two-thirds of the patients who completed a medication trial improved. Across all active treatments, the mean Y-BOCS decrease was 7.1 resulting in a mean post-treatment Y-BOCS score of 17.9 whereas for placebo conditions the Y-BOCS decrease was 1.8.

Clearly, in effectiveness, clomipramine is superior to all the SSRIs. In practice, however, the choice of a drug also depends on side effect profile and potential for drug interactions. Clomipramine has the most anticholinergic side effect profile, potential cardiotoxicity, and is the most noxious in an overdose. In contrast, SSRIs may be associated with more complaints of headaches, nausea, insomnia, or agitation, but are safer and less prone to drug interactions. Considering side effects, toxicity, and potential drug interactions, SSRIs usually are the first treatment of choice.

The serotonin hypothesis of OCD has emerged from the observation that only antidepressants that preferentially block the serotonin transporter (5-HTT) are efficacious in OCD. A comparison of the clinical efficacy of clomipramine, fluvoxamine and sertraline with that of desipramine, an antidepressant that selectively blocks the uptake of norepinephrine, supports the notion that inhibition of the 5-HTT is required for antidepressants to be efficacious in OCD (Goodman et al. 1990; Zohar and Insel 1987; Leonard et al. 1989; Hoehn-Saric et al. 2000). Denys (Denys et al. 2003) and colleagues have shown that venlafaxine and paroxetine are equally efficacious in OCD, suggesting that inhibition of the norepinephrine uptake does not contribute to the effect of antidepressants as well. As mentioned previously, this finding does not necessarily point to an abnormal serotonergic system in OCD. On the contrary, several observations lend support to the idea that inhibition of the 5-HTT, although required for antidepressants to work in OCD, is not causally related to the genesis of the disorder. First, nearly half of OCD-patients do not respond to SSRI treatment (Denys 2006). Even with adequate treatment, the mean symptom decrease is 30-50% at the most (Denys et al. 2002). Second, the doses of SSRIs
required for treatment of OCD are substantially higher than necessary to completely block the 5-HTT (Kent et al. 2002; Meyer 2007; Voineskos et al. 2007). Third, depletion studies of tryptophan, necessary for the synthesis of serotonin, did not show a worsening of symptoms in OCD-patients (Berney et al. 2006). Fourth, the therapeutic effects in OCD are usually not seen within 8 weeks of treatment, which is much later than in patients with depression. Fifth, there is no relation between the selectivity and binding potential of the different SSRIs and clinical effect size (Baumgarten and Grozdanovic 1998).

In conclusion, the serotonin hypothesis was initially motivated by the observed differential efficacy of SSRIs in alleviating OCD symptoms. However, these findings, although attesting to the therapeutic versatility of serotonin transporter inhibition in OCD, do not necessarily reflect the existence of a neurobiological abnormality in the central serotonergic system in OCD. SSRIs may modulate serotonin via an intact serotonergic system to compensate for the underlying pathogenesis.

2.3 Pharmacologic challenge studies

Another approach assessing the function of the serotonergic system in OCD is by administration of indirect or direct serotonin receptor agonists or antagonists. Pharmacological challenges with meta-chlorophenylpiperazine (mCPP) have shown to exacerbate obsessive compulsive (OC) symptoms. mCPP is a non-selective serotonin receptor agonist acting mainly at the 5-HT2c receptors but with affinity also for the 5-HT1B/1D and 5-HT1A receptors (Westenberg et al. 2007). Administration of psilocybin, a psychedelic agent with potent 5-HT2A/2C and 5-HT1A agonist properties, in 9 subjects resulted in acute reductions of the YBOCS score in a controlled clinical environment (Moreno et al. 2006). A challenge with the selective 5-HT1A agonist ipsapirone did not induce exacerbation of OC symptoms in OCD patients (Lesch et al. 1991a; Lesch et al. 1991b). Pindolol, on the other hand, a β blocker and 5-HT1A receptor antagonist, was shown to augment the therapeutic effect of paroxetine by increasing serotonergic transmission (Dannon et al. 2000). Pharmacological challenge studies with 5-HT1D receptor agonists in OCD are inconsistent. Some studies show an exacerbation of OC-symptoms with sumatriptan, though zolmitriptan with a better penetration of the blood-brain barrier than sumatriptan, failed to increase OC-symptoms (Koran et al. 2001; Gross-Isseroff et al. 2004; Pian et al. 1998; Stein et al. 1999; Boshuisen and den Boer 2000). Atypical antipsychotics with potent 5-HT2A and D2 antagonistic properties have antiobsessional qualities in addition to SSRI treatment. Risperidone, an atypical antipsychotic, is the most potent and selective 5-HT2A antagonist available to clinicians (Marek et al. 2003). Multiple double-blind studies have found risperidone augmentation of ongoing SRI treatment in OCD to be effective (McDougle et al. 2000; Hollander et al. 2003; Erzegovesi et al. 2005). Hewlett et al initiated a pilot study with the 5-HT3A receptor
antagonist Ondansetron. They found that of the 8 OCD-patients, of which six completed the trail, three subjects achieved a clinically significant response of ≥ 35% reduction in YBOCS score (Hewlett et al.2003). On the contrary Broocks et al found that pre-treatment with ondansetron did not affect any of the self-rated behavioural symptoms induced by a m-CPP challenge with 11 OCD-patients (Broocks et al.1998).

In conclusion, pharmacological challenges implicate a role for the 5-HT$_{2A}$ receptor and/ or 5-HT$_{2C}$ receptor and possibly the SHT$_{1B/1D}$ receptor in the pathophysiology of OCD.

2.4 Receptor binding studies

Neuroimaging with positron emission tomography (PET) or single photon emission computer tomography (SPECT) offers a unique tool to probe in vivo the serotonergic system. For a summary of the different receptor binding studies discussed in this review see table 1.

2.4.1 5-HTT binding studies at baseline

Pogarell et al reported a 25% higher 5-HTT availability in the midbrain region of nine unmedicated OCD patients using the radiotracer [$^{123}$I]-2β-carbomethoxy-3β-(4-iodophenyl) tropane ([$^{123}$I]β-CIT) and SPECT imaging (Pogarell et al.2003). Stratification of the patients according to onset of the disorder revealed that the significant difference was only present in patients with an early age of onset compared to control. Patients and controls in this study were not matched by age and gender. (Pogarell et al.2003).

In contrast to this finding Stengler-Wenzke et al. described a significant reduction of 5-HTT availability in the midbrain and upper brainstem in 10 drug-free OCD patients compared to age matched controls. However, they did not report the age of onset of OCD symptoms (Stengler-Wenzke et al.2004).

In agreement with this, Hesse et al. reported a significant reduced 5-HTT density in the midbrain and the thalamus in 15 drug-naïve OCD patients compared to controls. (Hesse et al.2005). Comparing 24 drug-free OC checkers to controls, Zitterl et al. found an 18% reduction in 5-HTT availability in the thalamus and hypothalamus. Reduced 5-HTT availability correlated with increased severity of OC symptomatology and short duration of illness, however not with age and age at onset (Zitterl et al.2007). Hasselbach et al found a 13% reduced midbrain-pons 5-HTT binding in 9 drug-free OCD patients. No correlation between 5-HTT binding and any clinical variables (age at onset, disease duration, and YBOCS score) was shown (Hasselbalch et al.2007). A [$^{11}$C]DASB PET study reported a significantly reduced 5-HTT availability in the thalamus and in the midbrain in 9 drug free OCD patients (Reimold et al.2007).
<table>
<thead>
<tr>
<th>Research group</th>
<th>Transporter, Receptor of interest</th>
<th>Patients in study</th>
<th>Results</th>
<th>YBOCS (mean)</th>
<th>Co-morbidity</th>
<th>Control groups</th>
<th>Co-morbidity</th>
<th>Control groups</th>
<th>Aquisition time (hours)</th>
<th>Radiotracer</th>
<th>Imaging technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pogarell et al. 2003</td>
<td>5-HTT</td>
<td>9, heterogeneous, drug-free (7 drug-naive)</td>
<td>25% higher 5-HTT availability in the midbrain region</td>
<td>23.0 ± 8.2</td>
<td>Depression</td>
<td>-</td>
<td>24</td>
<td>-</td>
<td>[123I]B-CIT</td>
<td>SPECT</td>
<td></td>
</tr>
<tr>
<td>Stengler-Wenzke et al. 2004</td>
<td>5-HTT</td>
<td>10, heterogeneous, drug-free</td>
<td>Significant reduction of 5-HTT availability in the midbrain and upper brainstem</td>
<td>30 ± 2.5</td>
<td>-</td>
<td>Age matched</td>
<td>24</td>
<td>-</td>
<td>[123I]B-CIT</td>
<td>SPECT</td>
<td></td>
</tr>
<tr>
<td>Hesse et al. 2005</td>
<td>5-HTT/DAT</td>
<td>15 heterogeneous, drug-naive</td>
<td>Reduced availability of striatal DAT and of thalamic/hypothalamic, midbrain and brainstem 5-HTT</td>
<td>25.3 ± 8.8</td>
<td>-</td>
<td>-</td>
<td>24</td>
<td>-</td>
<td>[123I]B-CIT</td>
<td>SPECT</td>
<td></td>
</tr>
<tr>
<td>Zittler et al. 2007</td>
<td>5-HTT</td>
<td>24, homogeneous OC-checkers drug-free</td>
<td>18% reduction in 5-HTT availability in the thalamus and hypothalamus</td>
<td>25.1 ± 5.0</td>
<td>-</td>
<td>Age and gender matched</td>
<td>4</td>
<td>-</td>
<td>[123I]B-CIT</td>
<td>SPECT</td>
<td></td>
</tr>
<tr>
<td>Hasselbach et al. 2005</td>
<td>5-HTT</td>
<td>9, heterogeneous, drug-free</td>
<td>13% reduction in midbrain-pons 5-HTT binding</td>
<td>22</td>
<td>Anxiety, Depression</td>
<td>-</td>
<td>10 min-7 hours</td>
<td>-</td>
<td>[123I]B-CIT</td>
<td>SPECT</td>
<td></td>
</tr>
<tr>
<td>Reimold et al. 2007</td>
<td>5-HTT</td>
<td>9, heterogeneous, drug-free</td>
<td>Significant reduction in 5-HTT availability in thalamus and midbrain</td>
<td>21.4 ± 7.7</td>
<td>-</td>
<td>Age matched</td>
<td>4</td>
<td>-</td>
<td>[123I]B-CIT</td>
<td>SPECT</td>
<td></td>
</tr>
<tr>
<td>van der Wee et al. 2004</td>
<td>5-HTT</td>
<td>15, heterogeneous, psychotropia-naive</td>
<td>No difference in 5-HTT binding density in the thalamus, thalamic and pons of OCD patients compared to controls</td>
<td>23.4 ± 4.2 (cut off score of 16)</td>
<td>-</td>
<td>Age and gender matched</td>
<td>4</td>
<td>-</td>
<td>[123I]B-CIT</td>
<td>SPECT</td>
<td></td>
</tr>
<tr>
<td>Simpson et al. 2003</td>
<td>5-HTT</td>
<td>11, heterogeneous, drug-free</td>
<td>No significant difference was found between OCD patients and control subjects</td>
<td>20 ± 4</td>
<td>-</td>
<td>Age and gender matched</td>
<td>130 min</td>
<td>-</td>
<td>[11C]DASB</td>
<td>PET</td>
<td></td>
</tr>
<tr>
<td>Stengler-Wenzke et al. 2006</td>
<td>5-HTT</td>
<td>10, heterogeneous, drug-free at baseline; 5, after 1 year 60 mg citalopram treatment</td>
<td>The availability of 5-HTT in the thalamus, midbrain and brainstem decreased significantly after treatment with 60 mg citalopram for 1 year</td>
<td>32.0 ± 2.5 (pre-treatment)</td>
<td>-</td>
<td>Age matched</td>
<td>24</td>
<td>-</td>
<td>[123I]B-CIT</td>
<td>SPECT</td>
<td></td>
</tr>
<tr>
<td>Zitterl et al. 2008</td>
<td>5-HTT</td>
<td>24, OC-checkers, drug-free at baseline; 12 week clomipramine treatment Patients on stable 150 mg treatment during 2e scan</td>
<td>A 48% reduced brain SERT availability in the thalamus–hypothalamus after 12-week treatment. Significantly negative associations between SERT availability and Y-BOCS both at baseline and after treatment</td>
<td>26.2 ± 4.9 (pre-treatment)</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>-</td>
<td>[123I]B-CIT</td>
<td>SPECT</td>
<td></td>
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</tbody>
</table>

**Notes:**
- 5-HTT: Serotonin transporter;
- DAT: Dopamine transporter;
- OCD: Obsessive-compulsive disorder;
- PET: Positron emission tomography;
- SERT: Serotoninergic transporter (SERT);

**Table 1 Receptor Binding Studies**

- Co-variation and reversal in brain 5-HTT density were also observed in patients with anxiety, drug-free at baseline, normalized to controls.
- The availability of 5-HTT in the thalamus, midbrain and brainstem decreased significantly after treatment with 60 mg citalopram for 1 year.
- A 48% reduced brain SERT availability in the thalamus–hypothalamus after 12-week treatment. Significantly negative associations between SERT availability and Y-BOCS both at baseline and after treatment.
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</tr>
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<tbody>
<tr>
<td>Pogarell et al. 2005</td>
<td>5-HTT/ DAT</td>
<td>2, heterogeneous, drug-naïve; 12 weeks 40 mg citalopram treatment. Patients on stable treatment during 2e scan</td>
<td>A 36.5% decrease in 5-HTT availability after 12 week therapy with 40 mg citalopram. An increase of 40% in the availability of DAT</td>
<td>7</td>
<td>-</td>
<td>No control group</td>
<td>20-24</td>
<td>$^{[123]}$I$^-$β-CIT</td>
<td>SPECT</td>
</tr>
<tr>
<td>Kim et al. 2007</td>
<td>DAT</td>
<td>10, heterogeneous, drug-free; 16-week treatment 73.3 mg fluoxetine (n = 6), 53.3 mg paroxetine (n = 3), 250 mg clomipramine (n = 1). Patients on stable treatment during 2e scan</td>
<td>Decreased DAT binding ratio in the right basal ganglia after treatment with SRIs</td>
<td>33.10 ± 6.38</td>
<td>Depression, tic disorder</td>
<td>No control group</td>
<td>2</td>
<td>$^{[123]}$I$^-$JPT</td>
<td>SPECT</td>
</tr>
<tr>
<td>Moresco et al. 2007</td>
<td>D$_2$</td>
<td>9, heterogeneous, drug-naïve; 12 week treatment 150-300 mg fluvoxamine. Patients on stable treatment during 2e scan</td>
<td>Significant increase between 6.9 and 9.7% in striatal $[^{11}$C]$^-$Rac binding potential after chronic treatment with fluvoxamine. The mean values after treatment were closer to those observed in normal subjects</td>
<td>29 ± 5</td>
<td>-</td>
<td>-</td>
<td>0-60 min</td>
<td>$[^{11}$C]$^-$Rac</td>
<td>PET</td>
</tr>
<tr>
<td>Adams et al. 2005</td>
<td>5-HT$_{3A}$</td>
<td>15, heterogeneous, drug-free 12 week treatment 60-80 mg paroxetine, 50-150 mg sertraline, 60-80 mg fluoxetine, 60-80 mg citalopram. Patients on stable treatment during 2e scan</td>
<td>9% higher 5-HT$_{3A}$ receptor binding potential in the caudate nucleus before treatment. No significant change after SSRI treatment</td>
<td>30 ± 6.8</td>
<td>Depression, Anorexia, Anxiety, Single phobia</td>
<td>Age and gender matched</td>
<td>90 min</td>
<td>$[^{18}$F]$^-$altanserin</td>
<td>PET</td>
</tr>
<tr>
<td>Perani et al. 2008</td>
<td>5-HT$_{3A}$</td>
<td>9, heterogeneous, drug-naïve</td>
<td>Significant reduction of 5-HT$<em>{3A}$ receptor availability in frontal cortex, cingulated cortex, parietal and temporal associative cortices. Significant inverse correlation between 5-HT$</em>{3A}$ availability and YBOCS</td>
<td>29.44 ± 4.42</td>
<td>Age matched</td>
<td>0 min</td>
<td>$[^{11}$C]$^-$MDL-BP</td>
<td>PET</td>
<td></td>
</tr>
</tbody>
</table>

$^{[123]}$I$^-$β-CIT | $^{[123]}$Iodine-123-labeled N-[(3iodopropen-2-yl)-2 beta-carbomethoxy-3beta-(4-iodophenyl) tropane]; SPECT (single photon emission computer tomography); DAT (dopamine transporter); 5-HTT (serotonin transporter); OCD (obsessive compulsive disorder); PET (positron emission tomography); $^{[11}$C]$^-$Raclopride | $[^{11}$C]$^-$Rac
Finally, van der Wee et al found no difference in 5-HTT binding density in the midbrain, thalamus and pons of drug-naïve OCD patients compared to controls using $^{[123]}I\beta$-CIT and SPECT (van der Wee et al. 2004). Simpson and colleagues, using $^{[11]}C$McN 5652 as radioligand in combination with PET, found no significant difference between OCD patients and control subjects (Simpson et al. 2003).

### 2.4.2 5-HTT binding studies after SSRI treatment.

Treatment with 60 mg citalopram for a year in 5 patients resulted in a decrease of 5-HTT availability in the thalamus, midbrain and brainstem (Stengler-Wenzke et al. 2006). In a group of 24 OC checkers a 12 week treatment with clomipramine resulted in a 48% decrease in brain SERT availability in the thalamus–hypothalamus. A significantly negative association between SERT availability and Y-BOCS both at baseline and after treatment was also found in this group of 24 OC-checkers (Zitterl et al. 2008). A 12 week treatment period with 40 mg citalopram in 2 patients lead to a 36.5% decrease in 5-HTT availability and an increase of 40% in the availability of dopamine transporter (DAT) in the midbrain-pons region (Pogarell et al. 2005). A SPECT study with iodine-123-labeled N-(3-iodopropen-2-yl)-2 beta-carbomethoxy-3beta-(4-chlorophenyl) tropane ($^{[123]}I$PT) as radiotracer found a significantly decreased DAT binding ratio in the right basal ganglia after a 16 week treatment with SSRIs in 10 drug free patients (Kim et al. 2007). Moresco et al found, in a PET study with $^{[11]}C$raclopride ($^{[11]}C$Rac) as radiotracer, a slight but significant increase in striatal $^{[11]}C$Rac binding potential, varying from 6.9% to 9.7%, after a 12 week treatment with 150-300 mg fluvoxamine (Moresco et al. 2007).

### 2.4.2 5-HT$_{2A}$ receptor binding studies

A PET study with $^{[18}F$altanserin in naïve OCD-patients showed a significant higher 5-HT$_{2A}$ receptor binding potential in the caudate nucleus compared to age and gender matched healthy controls. This increase in 5-HT$_{2A}$ receptor binding was not influenced by subsequent treatment with SSRIs (Adams et al. 2005). The increased 5-HT$_{2A}$ binding density might result from a lack of serotonin in the basal ganglia. However, a PET study with the radioligand $^{[11]}C$MDL-BP found a significant reduction of 5-HT$_{2A}$ receptor availability in frontal cortex, cingulated cortex as well as in parietal and temporal associative cortices in drug-naïve OCD patients compared to age-matched controls. The reduced 5-HT$_{2A}$ receptor availability in the orbitofrontal and dorsolateral frontal cortex correlated with clinical severity (Perani et al. 2008).

In summary, though some of the neuroimaging studies suggest that an impaired 5-HTT function might play a role in the pathogenesis of OCD, others indicate that successful SSRI treatment is associated with normalization of the dopamine function. There are mixed results on the possible role of the 5-HT$_{2A}$ receptor in the neuroimaging studies.
2.5 Genetic association studies

Genetic studies investigating the possible role for polymorphism in the promoter region of the 5-HT gene (5-HTPPR) have generated conflicting results (table 2). Some studies reported an association between the S allele of the 5-HTPPR and OCD (Grados et al.2007; Lin2007; Perez et al.2006; Denys et al.2006). The S allele reduces 5-HTT mRNA expression and a higher frequency of this allele would suggest a lower density of 5-HTT in OCD patients. Others found an association between the 2 copies of the long allele (L) in the 5-HTTLPR region and OCD (Bengel et al.1999; McDougle et al.1998). Kim et al investigated the 5-HTPPR polymorphism in association with the phenotypic characteristics of OCD and found that patients with the L-genotype had higher scores for the religious and somatic obsessions (Kim et al.2005). A principal component analysis on the YBOCS checklist performed by Cavallini et al. demonstrated that patients who were homozygote for the L-allele more often could be classified as symmetry/ordering subtype OCD patients (Cavallini et al.2002). The S/L genotype of the 5-HTTLPR polymorphism was reported among the majority of OCD-patients who were responders to a 12-week treatment period with 300 mg venlafaxine (Denys et al.2007). However 8 studies reported no association between 5-HTPPR and OCD at all (Camarena et al.2001; Chabane et al.2004; Di Bella et al.2002b; Dickel et al.2007; Frisch et al.2000; Meira-Lima et al.2004; Wendland et al.2006; Saiz et al.2008).

Polymorphisms of the 5-HT1B receptor were studied by Mundo et al in a large Canadian family-based sample. They found a significant association between OCD and the G861 polymorphism of this gene. The G- allele was associated with OCD and predicted OC severity (Mundo et al.2002). Two subsequent studies also reported an association between OC severity and the G861 variant, although they did not find a significant association between G861 polymorphism and OCD (Camarena et al.2004; Levitan et al.2006). In an Italian family based study no preferential transmission of either allele of the 5-HT1B/1D was observed (Di Bella et al.2002a). The -1438G/A polymorphism of the 5-HT2A receptor gene has also been linked to OCD. Enoch et al reported a higher frequency of the -1438G/A allele in female OCD patients compared to healthy women (Enoch et al.2001). A statistically significant difference in the frequency of the A-allel was also reported in a study with 55 children and adolescent with OCD compared to control subjects (Walitza et al.2002). Denys et al found an association between the 5-HT2A G-allele in 156 OCD patients and a positive family history and an early onset of the disease compared to 134 control individuals (Denys et al.2006).

The G/G genotype of the 5-HT2A polymorphism was also reported amongst the majority of OCD-patients who responded with an YBOCS decrease of more than 25% to a 12-week treatment period with 60 mg paroxetine (Denys et al.2007). Difference in OCD phenotype may
explain these discrepant findings. However 2 studies found no association between 5-HT$_{2A}$ polymorphism and OCD (Dickel et al. 2007; Saiz et al. 2008).

A genetic study in 7 early-onset OCD probands found no evidence for functional mutations in the sequenced regions of 5-HTR$_{2B}$ (Kim et al. 2000). Cavallini et al found no association between OCD and the CYS23Ser mutation of the 5-HT$_{2C}$ receptor gene in a genetic study comparing 109 OCD patients with 107 healthy control subjects (Cavallini et al. 1998).

The C178T variant of the 5-HT$_{3A}$ receptor influences among others the 5-HT$_{3}$ receptor expression. In a family-based approach of 75 children and adolescents with OCD as well as their biological parents no evidence for a preferential transmission of either allele of the 5-HT$_{3A}$ receptor was found. This is contrary to the involvement of the 5-HT$_{3A}$ receptor in OCD (Mossner et al. 2007).

The results of genetic association studies are, as of yet, inconsistent and except for the 5-HT$_{2A}$ receptor mainly negative.
The serotonergic system in obsessive compulsive disorder

Table 2 Genetic association studies

<table>
<thead>
<tr>
<th>Research group</th>
<th>Transporter, Receptor of interest</th>
<th>Patients in study</th>
<th>Origin</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grados et al. 2007</td>
<td>5-HTTPR</td>
<td>149 OCD patients, 397 controls</td>
<td>Caucasians (&gt;90%)</td>
<td>A trend for both the s/s genotype and the s allele frequency was found.</td>
</tr>
<tr>
<td>Lin et al. 2007</td>
<td>5-HTTPR</td>
<td>Meta- analyse of 13 independent case-control association studies, 3000 subjects</td>
<td>-</td>
<td>An association between OCD and the SS homozygous genotype was found. It is inversely associated with the LS heterozygous genotype and no association with the LL homozygous genotype or the allelic distribution was found.</td>
</tr>
<tr>
<td>Perez et al. 2006</td>
<td>5-HTTPR</td>
<td>26 OCD patients, 87 controls</td>
<td>Caucasians</td>
<td>A significant association between the s/s genotype and OCD.</td>
</tr>
<tr>
<td>Denys et al. 2006</td>
<td>5-HTTPR/5-HT2A</td>
<td>156 OCD patients, 134 controls</td>
<td>Caucasians</td>
<td>No significant differences in genotype distribution and allele frequency for polymorphisms investigated relative to controls. However an indication towards an association of the 5-HTTLPR S allele with female OCD patients, and the 5-HT2A G-allele and GG genotype with patients with a positive family history of OCD and an early onset of disease.</td>
</tr>
<tr>
<td>Bengel et al. 1999</td>
<td>5-HTTPR</td>
<td>75 OCD patients, 397 ethnically matched controls</td>
<td>Caucasians</td>
<td>A statistically significant association between the l/l genotype and OCD.</td>
</tr>
<tr>
<td>McDougle et al. 1998</td>
<td>5-HTTPR</td>
<td>34 family trios</td>
<td>European-Americans</td>
<td>An association between the I allele in the 5-HTTPR region and OCD was found.</td>
</tr>
<tr>
<td>Kim et al. 2005</td>
<td>5-HTTPR</td>
<td>124 OCD patients, 171 controls</td>
<td>Koreans</td>
<td>No significant association between OCD and 5-HTTPR. However patients with the L-genotype had higher scores for the religious and somatic obsessions.</td>
</tr>
<tr>
<td>Cavallini et al. 2002</td>
<td>5-HTTPR</td>
<td>180 OCD patients, 112 controls</td>
<td>Italians</td>
<td>Patients who were homozygote for the I-allele could more often be classified as symmetry/ordering subtype OCD patients.</td>
</tr>
<tr>
<td>Denys et al. 2007</td>
<td>5-HTT, 5-HT2A</td>
<td>91 OCD patients</td>
<td>Dutch</td>
<td>The S/L genotype of the 5-HTTLPR polymorphism was amongst the majority of OCD-patients who responded with an YBOCS decrease of more than 25% to a 12-week treatment period with 300 mg venlafaxine. The G/G genotype of the 5-HT2A polymorphism was amongst the majority of OCD-patients who were responders to a 12-week treatment period with 60 mg paroxetine. The G/G genotype of the 5-HT2A polymorphism was amongst the majority of OCD-patients who were responders to a 12-week treatment period with 60 mg paroxetine.</td>
</tr>
<tr>
<td>Camarena et al. 2001</td>
<td>5-HTTPR</td>
<td>115 OCD patients, 136 controls Family based design: 43 trios</td>
<td>Mexicans</td>
<td>No significant association between I allele and OCD. No preferential transmission of I allele to OCD probands.</td>
</tr>
<tr>
<td>Chabane et al. 2004</td>
<td>5-HTTPR</td>
<td>Case-control study: 106 OCD patients, 171 controls. Family association study: 116 trios including an OCD patient</td>
<td>French Caucasians</td>
<td>There was no association between the 5-HTTLPR polymorphism and OCD in either the case control study or the family study.</td>
</tr>
<tr>
<td>Di Bella et al. 2002</td>
<td>5-HTTPR</td>
<td>181 OCD patients, 191 controls</td>
<td>Italians</td>
<td>No significant differences in allele/ genotype distribution of the 5-HTTLPR was found.</td>
</tr>
</tbody>
</table>
### Table 2 (Continued)

<table>
<thead>
<tr>
<th>Research group</th>
<th>Transporter, receptor of interest</th>
<th>Patients in study</th>
<th>Origin</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ockel et al. 2007</td>
<td>5-HT1B/ 5-HT2A</td>
<td>21 parent–child trios from singleplex families, 7 parent–child trios from multiplex families, 26 Proband with Early-onset OCD</td>
<td>Americans</td>
<td>There was no evidence for association detected at any of the polymorphisms in the entire set of subjects.</td>
</tr>
<tr>
<td>Frisch et al. 2000</td>
<td>5-HTTPR/ 5-HT2A/ 5-HT2C</td>
<td>75 patients, 172 ethnically matched controls</td>
<td>Jews</td>
<td>There were no statistically significant differences between patients and control for the genotypic and allelic distribution of all polymorphisms tested.</td>
</tr>
<tr>
<td>Meira-Lima et al. 2004</td>
<td>5-HTTPR/ 5-HT1A</td>
<td>79 OCD patients, 202 controls</td>
<td>Brazilians, Caucasians (90.5%)</td>
<td>A statistically significant difference in the genotypic distribution and in the allelic frequencies for the C516T 5HT1A gene polymorphism. However no significant difference for the SHTTLPR and the T102C 5HT1A gene polymorphisms.</td>
</tr>
<tr>
<td>Wendland et al. 2006</td>
<td>5-HTTPR</td>
<td>279 OCD-probands, 390 controls</td>
<td>Caucasians</td>
<td>Allelic frequencies for GS6A did not differ significantly between probands and controls.</td>
</tr>
<tr>
<td>Saiz et al. 2008</td>
<td>5-HTTPR/ 5-HT1A</td>
<td>99 OCD patients, 56 non OCD psychiatric patients, 420 controls</td>
<td>Spanish, Caucasians</td>
<td>No significant differences were found with respect to 5-HTTLPR and 5-HT1A polymorphisms.</td>
</tr>
<tr>
<td>Mundo et al. 2002</td>
<td>5-HT1B/1D</td>
<td>Family-based design: 121 families, 157 OCD-patients, 72 trios</td>
<td>Canadians, Caucasians (96.7%)</td>
<td>A significant association between OCD and the G861 polymorphism of the 5-HT1B gene. The G- allele was associated with OCD and predicted OC severity.</td>
</tr>
<tr>
<td>Camarena et al. 2004</td>
<td>5-HT1B/1D</td>
<td>Family based design: 79 trios</td>
<td>Mexicans</td>
<td>No significant association between the G-allele and OCD. However subjects with a preferential transmission of the G861 variant showed higher YBOCS Obsession scores compared to patients carrying the C861 allele.</td>
</tr>
<tr>
<td>Levitan et al. 2006</td>
<td>5-HT1B/1D</td>
<td>165 female probands with bulimia nervosa</td>
<td>Canadians</td>
<td>There was no significant association between the G-allele and OCD. The G861C polymorphism did strongly differentiate between full syndrome vs. partial syndrome OCD.</td>
</tr>
<tr>
<td>Di Bella et al. 2002</td>
<td>5-HT1B/1D</td>
<td>Family based design: 101 OCD patients, 138 controls</td>
<td>Italians</td>
<td>No preferential transmission of either allele of the 5-HT1B gene was observed.</td>
</tr>
<tr>
<td>Enoch et al. 2001</td>
<td>5-HT1A</td>
<td>55 OCD patients, 223 controls</td>
<td>Caucasians</td>
<td>A statistically significant association between the A-allele of the 5-HT1A receptor gene with OCD.</td>
</tr>
<tr>
<td>Waltza et al. 2002</td>
<td>5-HT2A</td>
<td>7 early onset probands, 10 autism probands, 10 controls</td>
<td>Germans</td>
<td>No evidence for functional mutation was found in the sequenced regions of HTR2A.</td>
</tr>
<tr>
<td>Kim et al. 2000</td>
<td>5-HT2A</td>
<td>109 OCD patients, 107 controls</td>
<td>Italians</td>
<td>No allelic or genotypic association of OCD with the SHT2C receptor gene mutation was found.</td>
</tr>
<tr>
<td>Cavalline et al. 1998</td>
<td>5-HT2C</td>
<td>Family based design: ± 75 trios</td>
<td>Germans, Caucasians</td>
<td>No evidence for a preferential transmission of either allele of the 5-HT2C.</td>
</tr>
</tbody>
</table>
2.6 Animal models

In the past decades OCD-like animal models were developed using chemical, genetic and behavioural induction. Table 3 gives a summary of the different animal models for OCD available.

Suppression of spontaneous burying in the marble burying behaviour model was originally used as a measure of anxiolytic drug action. Analysis of the marble burying behaviour later led to the suggestion that it was more related to compulsive behaviour (Joel2006).

The 5-HT\textsubscript{1A} agonists, perospirone, MKC-242 and aripiprazole, were tested in the marble burying behaviour model. All three inhibited marble-burying behaviour. The inhibition of the behaviour may be antagonized with WAY100135, a selective 5-HT\textsubscript{1A} antagonist (Abe et al.1998; Egashira et al.2008; Matsushita et al.2005). Ichumaru et al demonstrated that the suppressive effect of fluvoxamine on marble-burying behaviour may be inhibited by the 5-HT\textsubscript{1A} antagonist NAN-190 (Ichimaru et al.1995). Ketanserin, a 5-HT\textsubscript{2A} antagonist, had no effect on the marble-burying behaviour (Egashira et al.2008). However YM992, a compound with selective serotonin reuptake inhibition and 5-HT\textsubscript{2A} receptor antagonistic activity, significantly inhibited marble-burying behaviour (Takeuchi et al.2002).

An extensive study examined the effects of 36 compounds, including typical, atypical and novel antipsychotics, on marble burying behaviour in mice. They concluded that the inhibition of marble burying behaviour may result from the interplay of several receptor systems such as 5-HT\textsubscript{2} receptor blockade, 5-HT\textsubscript{1A} agonism and dopamine D\textsubscript{2} partial agonism (Bruins Slot et al.2008).

The adjunctive drinking in the scheduled-induced polydipsia (SIP) model decreased after acute administration of WAY-181187, a novel and selective 5-HT\textsubscript{6} receptor agonist and several 5-HT\textsubscript{2C} receptor agonists (Schechter et al.2007; Dunlop et al.2006; Bos et al.1997; Martin et al.1998; Rosenzweig-Lipson et al.2007).

In the signal attenuation rat model, the 5-HT\textsubscript{2A} antagonist MDL as well as the 5-HT\textsubscript{2A/2C} agonist DOI had no effect on the compulsive lever pressing (Flaisher-Grinberg et al.2008).

However, the 5-HT\textsubscript{2C} antagonist RS 102221 decreased the compulsive lever-pressing after systemic administration and after administration directly into the orbital frontal cortex (Flaisher-Grinberg et al.2008). Naratriptan, a selective 5-HT\textsubscript{1D} receptor agonist, did not exacerbate compulsive behaviour in the reinforced spatial alternation animal model. The fact that mCPP, a non-selective serotonin receptor agonist acting at the 5-HT\textsubscript{2C}, 5-HT\textsubscript{1A} receptors, did increase compulsive behaviour in this animal model speaks against the involvement of the 5-HT\textsubscript{1B/1D} receptor in the OCD pathophysiology (Tsaltas et al.2005).
The m-CPP induced self-grooming in rats was reversed by a subtype-selective 5-HT\textsubscript{2C} antagonist SB-242084 but not by the the subtype-selective 5-HT\textsubscript{2B} receptor antagonist SB-215505 (Graf et al.2003).

Several animal models for OCD originated from genetic modification of the serotonergic system. The 5-HT\textsubscript{2C} receptor knockout mouse exhibited compulsive behaviour. It chewed more clay, produced a distinct pattern of ‘neat’ chewing of plastic screens and exhibited reduced habituation of head dipping activity. This suggests that the 5-HT\textsubscript{2C} receptor knockout mouse could be a promising model of compulsive behaviour (Chou-Green et al.2003). Hedlund et al investigated mice lacking the 5-HT\textsubscript{7} receptor compared to wild-type mice in three behavioural models for OCD. The 5-HT\textsubscript{7}\textsuperscript{−/−} mice buried fewer marbles than 5-HT\textsubscript{7}\textsuperscript{+/+} mice in the marble burying behavioural model. Furthermore when the 5-HT\textsubscript{7}\textsuperscript{+/+} mice were treated with SB-269970, a selective 5-HT\textsubscript{7} receptor antagonist, they also buried fewer marbles than the 5-HT\textsubscript{7}\textsuperscript{−/−} mice treated with vehicle. In other words, inactivation as well as blockade of the 5-HT\textsubscript{7} receptor had a positive effect on OCD activity. However in the two other behavioural models, head dipping and plastic mesh screen chewing, no difference was found between the 5-HT\textsubscript{7}\textsuperscript{−/−} mice and the wild-type mice (Hedlund and Sutcliffe2007).

Currently, preclinical research into the 5-HTT function has progressed rapidly since 5-HTT knockout animal models became available. However, as of yet, research in the 5-HTT knockout rat or mouse behaviour paradigms have not directly linked any behavioural deviations to OCD (Homberg et al.2007; Mathews et al.2004; Olivier et al.2008)

In summary, preclinical research gives conflicting results. It suggests involvement of the 5-HT\textsubscript{2C} receptor and provides interesting preliminary results in animal models for the 5-HT\textsubscript{6} and the 5-HT\textsubscript{7} receptors.
### Table 3: Summary of the animal models available for OCD

<table>
<thead>
<tr>
<th>Inductor</th>
<th>Face validity</th>
<th>Symptoms</th>
<th>Predictive validity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacological models</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous alternation behavior</td>
<td>8-OHDPAT 5-HT$_{1A}$ agonist</td>
<td>Indecision (T-maze)</td>
<td>-</td>
<td>Seibell et al.2003</td>
</tr>
<tr>
<td>Spontaneous alternation behavior</td>
<td>8-OHDPAT 5-HT$_{1A}$ agonist</td>
<td>Perseveration (T-maze)</td>
<td>SSRI</td>
<td>Yadin et al.1991</td>
</tr>
<tr>
<td>Spontaneous alternation behavior</td>
<td>Quinpirole D$_2$ agonist</td>
<td>Perseveration (T-maze)</td>
<td>SSRI</td>
<td>Einat and Szechtman1995</td>
</tr>
<tr>
<td>Reinforced spatial alternation</td>
<td>m-CPP 5-HT$_{1A/1B/2C}$ agonist</td>
<td>Persistence (T-maze)</td>
<td>SSRI</td>
<td>Tsaltas et al.2005</td>
</tr>
<tr>
<td>Singular behavior</td>
<td>DOI 5-HT$_{1B/2C}$ agonist</td>
<td>Head twitch</td>
<td>SSRI</td>
<td>Rojas-Corrales et al.2007</td>
</tr>
<tr>
<td>Singular behavior</td>
<td>m-CPP 5-HT$_{1B/2C}$ agonist</td>
<td>Self-grooming</td>
<td>S-HT depletion caused more grooming</td>
<td>Graf2006</td>
</tr>
<tr>
<td>Motor behavior</td>
<td>Oxytocin</td>
<td>Hyper-grooming</td>
<td>-</td>
<td>Marroni et al.2007</td>
</tr>
<tr>
<td>Motor behavior</td>
<td>Quinpirole D$_2$ agonist</td>
<td>Compulsive checking</td>
<td>SSRI</td>
<td>Szechtman et al.1998</td>
</tr>
<tr>
<td><strong>Behavioural models</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marble burying</td>
<td></td>
<td>Compulsive burying</td>
<td>SSRI</td>
<td>Njung'e and Handley1991</td>
</tr>
<tr>
<td>Scheduled induced polydipsia</td>
<td>Food deprived/ fixed time feeding</td>
<td>Excessive drinking</td>
<td>SSRI</td>
<td>Woods et al.1993</td>
</tr>
<tr>
<td>Signal attenuation</td>
<td>Food deprivation</td>
<td>Compulsive lever pressing</td>
<td>SSRI</td>
<td>Joel2006</td>
</tr>
<tr>
<td>Head dipping</td>
<td>-</td>
<td>Head dipping</td>
<td>-</td>
<td>Chou-Green et al.2003</td>
</tr>
<tr>
<td>Plastic-mesh screen chewing</td>
<td>-</td>
<td>Plastic-mesh screen chewing</td>
<td>-</td>
<td>Chou-Green et al.2003</td>
</tr>
<tr>
<td><strong>Genetic models</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sapap3 mutant mice</td>
<td>Compulsive grooming behaviour</td>
<td>-</td>
<td>SSRI</td>
<td>Welch et al.2007</td>
</tr>
<tr>
<td>5-HT$_{7}$ receptor knockout mice</td>
<td>None</td>
<td>-</td>
<td></td>
<td>Hedlund and Sutcliffe2007</td>
</tr>
<tr>
<td>5-HT$_{2C}$ receptor knockout mice</td>
<td>Compulsive like behaviour: Chewing of non-nutritive clay, chewing patterns on plastic-mesh screens, head dipping</td>
<td>-</td>
<td></td>
<td>Chou-Green et al.2003</td>
</tr>
<tr>
<td>Hoxb8 mutant mice</td>
<td>Excessive grooming</td>
<td>-</td>
<td></td>
<td>Greer and Capecci2002</td>
</tr>
<tr>
<td>DAT KD mice</td>
<td>Rigid syntactic grooming chain patterns</td>
<td>-</td>
<td></td>
<td>Berridge et al.2005</td>
</tr>
<tr>
<td>DICT-7 mice</td>
<td>Compulsive behaviour</td>
<td>-</td>
<td></td>
<td>Campbell et al.1999</td>
</tr>
</tbody>
</table>
2.7 Discussion

There is compelling evidence that the serotonergic system plays a major role in the treatment of OCD. Pharmacotherapeutic studies have shown that SSRIs are more effective in achieving clinical response compared to placebo, and that atypical antipsychotics, which have a high affinity for 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors, may augment the effect of SSRIs. However, these findings do not necessarily reflect the existence of a neurobiological abnormality in the central serotonergic system in OCD. SSRIs may modulate serotonin via an intact serotonergic system to compensate for the underlying pathogenesis that is related to another neurotransmitter system.

A general survey of the specific role of serotonin transporters and serotonin receptors in OCD arrives at inconsistent conclusions. Though an impaired 5-HTT function is suggested by some neuroimaging studies, others indicate that successful SSRI treatment is associated with normalization of the dopamine function. Genetic and animal studies give insufficient evidence to implicate a fundamental role for 5-HTT in the pathophysiology of OCD. As of yet, the role of 5-HT$_{1A}$ receptor in OCD is unclear since 5-HT$_{1A}$ agonists as well as 5-HT$_{1A}$ antagonist improve OC symptoms in pharmacologic challenge studies. Assuming that chronic SSRI treatment leads to a desensitisation of the terminal 5HT$_{1B/1D}$ receptor, some authors have hypothesised that 5HT$_{1B/1D}$ receptors are supersensitive in OCD resulting in chronic reductions in synaptic levels of serotonin (Moret and Briley2000). There is circumstantial evidence that the 5-HT$_{2A}$ receptor may be of particular relevance to OCD. Genetic studies linked the -1438G/A polymorphism of the 5-HT$_{2A}$ receptor gene to OCD, but non-selective 5-HT$_{2A}$ agonists as well as antagonist have a positive effect on OC symptoms. Reports on involvement of the 5-HT$_{2A}$ receptor in neuroimaging and animal research are inconsistent. Though pharmacological challenges with mCPP suggest a role for the 5-HT$_{2C}$ receptor, animal models report conflicting results since 5-HT$_{2C}$ agonists as well as antagonists reduce or induce obsessive compulsive behaviour. At this moment there is no evidence to underscore a role for the 5-HT$_{2B}$, 5-HT$_{3}$, 5-HT$_{6}$ or 5-HT$_{7}$ receptor in OCD.

In summary, direct evidence for an abnormality in the serotonergic system in the pathophysiology of OCD is still scarce. Hence, it is open to discussion whether the serotonergic system plays a primary role in the pathophysiology OCD or is secondarily involved due to the efficacy of SSRIs. Reasonably, SSRIs modulate an intact serotonergic system to compensate for another neurotransmitter mechanism. Several observations lend support to the assumption that inhibition of 5-HTT is not causally related to the genesis of the disorder (Baumgarten and Grozdanovic1998).
First, the mean response rate in OCD is 50% or less (Denys et al. 2002), indicating that for a substantial number of patients 5-HTT inhibition is insufficient to alleviate OC symptoms. Phenotypic heterogeneity may partly explain this phenomenon as e.g. patients with contamination fear respond more favorably to SSRIs than patients from the subtype symmetry/perfectionism/hoarding (Denys et al. 2004a). Second, the doses of antidepressants necessary for OCD are substantially higher than those for depression or anxiety disorders and also substantially higher than necessary to completely block the 5-HTT (Kent et al. 2002). Third, the synthesis of serotonin depends on the availability of tryptophan in the brain. Depletion studies in depression have shown deterioration in patients on antidepressants in remission (Neumeister 2003), but no worsening of symptoms was seen in patients with OCD who underwent a tryptophan depletion paradigm (Berney et al. 2006). Fourth, the therapeutic effects in OCD are usually not seen within 8 weeks of treatment, which is much later than in patients with depression. El Mansari (El Mansari and Blier 2006) and colleagues have argued on the basis of their electrophysiological work that this difference in onset of action between depression and OCD can be accounted for by a greater delay in effect of SSRIs on serotonin release in the orbital frontal cortex (OFC), a brain region supposedly implicated in OCD, as compared to other brain regions. According to these investigators, this delay in effect in the OFC might be explained by a slower desensitization of the 5-HT_{1A} autoreceptors in the OFC. They also used this finding as an argument to explain why in OCD larger doses of SSRIs are needed. In line with this finding, Dannon (Dannon et al. 2000) and colleagues have reported pindolol, a non-selective 5-HT_{1A} receptor antagonist, to hasten the effect of SSRIs in OCD patients. They also suggest that the effect of SSRIs in OCD might be explained by the delayed stimulation of the postsynaptic 5-HT_{2A} receptors in the OFC. If this were to be true, one would expect mirtazapine, which among others is a 5-HT_{2A} receptor antagonist, and atypical antipsychotics that also have antagonistic effects at this receptor, to attenuate the effect of SSRIs. Clinical studies with these drugs, however, have shown the opposite. Mirtazapine, although not effective by itself, has shown to hasten the effect of paroxetine (Pallanti et al. 2004) and several studies have shown that atypical antipsychotics augment the effects of SSRIs in refractory OCD patients (Bloch et al. 2006). Moreover, mCPP, a nonselective 5-HT_{2A} receptor agonist is either not effective or causes a worsening of OC symptoms after acute administration (Charney et al. 1988; Goodman et al. 1995; Gross-Isseroff et al. 2004; Ho Pian et al. 1998; Hollander et al. 1992).

In conclusion, future research should focus much more on the interaction of the serotonergic system with other neurochemical systems, such as dopamine and glutamate. There is some evidence that dopamine might be involved in OCD. Atypical antipsychotics with potent 5-HT_{2A}, 5-HT_{2C} and D_{2} antagonistic properties have antiobsessional properties as additional therapy to SSRIs. Denys et al. found that the combination of quetiapine and fluvoxamine may cause a synergistic dopamine increase in the prefrontal cortex and thalamus (Denys et al. 2004b).
Moreover, SPECT and PET studies hint to decreased $D_2$ receptor binding in the ventral striatum (Denys et al. 2004c), and indicate that successful SSRI treatment in OCD is associated with normalization of the dopamine function. Additionally more selective agents need to be developed to investigate the specific role of the different receptors of the serotonergic system. In the pipeline are a series of $5\text{-HT}_{2c}$ agonists which are investigated by Hoffman-La Roche, while Janssen Pharmaceutical is studying an azeprine derivative with mixed $5\text{-HT}_{2A/2C}$ antagonism for use in OCD. Furthermore a $5\text{-HT}_{1B/1D}$ antagonist is investigated by GlaxoSmithKline and Vanderbilt University is looking at a selective $5\text{-HT}_3$ antagonist (Davidson and Bjorgvinsson, 2003). The development of better animal models will be a tool to further enrich our understanding of OCD. OCD is a complex psychiatric disorder affecting cognition, affect and volition. It is therefore unlikely that one single neurotransmitter is involved in its pathophysiology.
References


Chapter 2


The serotonergic system in obsessive compulsive disorder


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