# Windows on the brain

## Functional neuroimaging studies in obsessive-compulsive disorder

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**Functional neuroimaging studies in obsessive-compulsive disorder**

*Met een samenvatting in het Nederlands*

Proefschrift

Ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de Rector Magnificus, Prof. dr. W.H. Gispen, ingevolge van het besluit van het College van Promoties in het openbaar te verdedigen op vrijdag 13 mei 2005 des middags om 14.30 uur.

Door

Nicolaas Johannes Adam van der Wee

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Promotoren

Prof. dr. R.S. Kahn

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# Chapter I

# Introduction

" *I worked in a pizza store and was put in charge of closing the place down at night. I found myself checking the ovens, the locks, the safe and ALL appliances (even the refrigerator doors) several times over. This was very aggravating for the person closing w/me but VERY embarrassing for me, but I just couldn't help it. I would often get home and then drive back to the restaurant to check the door to make sure that I locked it, get in my car, sit there for a few minutes and get out and check the door again. I would do this over and over a few more times before I could finally go home. At home the rituals continued, I had to check the curling iron, all the knobs on the stove, the front and back door locks and my daughters breathing several times before going to bed".*

*'Hillary' on in the OCD community at* www.healthyplace.com/communities/

Obsessive-compulsive disorder (OCD) is an intriguing psychiatric disorder characterized by recurrent, persistent and intrusive thoughts or images that cause anxiety or distress (obsessions), and repetitive behaviors or mental acts aimed at reducing this distress or anxiety (compulsions). Patients recognize that these obsessions and compulsions are unreasonable and products of their own mind. Examples of obsessions are the thought that one is contaminated or will harm others, but also bizarre sexual or aggressive images. Compulsions may vary from washing, checking and counting, to complex mental acts like repeating conversations in one's head with all the words, sounds and movements included. The Diagnostic and Statistic Manual of Mental Disorders (DSM-IV), the prevailing psychiatric classification instrument, states that in order to be classified as a disorder, the obsessions and compulsions have to cause marked distress, are time-consuming or significantly interfere with usual psychosocial functioning.

Once considered extremely rare, epidemiological data from the last two decades suggest lifetime prevalence rates of OCD from around 3%, making OCD the fourth most prevalent psychiatric disorder.[1;2] Obsessive-compulsive symptoms occur in an even larger percentage subclinically, probably in more than 10% of the general population.[3] Transient obsessive-compulsive symptoms also occur during normal maturation of the human brain.[4]

Prevalences of OCD are roughly the same across cultures and women appear to develop OCD slightly more frequently than do man. Age of onset in OCD has a bimodal distribution, with a juvenile onset and an onset in adulthood. The juvenile onset OCD is more common in males, has a greater genetic component and a worse prognosis than the adult onset OCD.[5]

OCD not only happens to be a frequent disorder, but it is also one of the most disabling medical conditions, with substantial direct and indirect socio-economical costs.[6] In 1990 the total costs of OCD in the United States were estimated to be $8.4 billion, 5.7% of the estimated $147.8 billion cost of all mental illness, and 18.0% of the costs of all anxiety disorders, estimated to be $46.6 billion. The indirect costs of OCD, reflecting lost productivity of individuals suffering from or dying from the disorder, were estimated at $6.2 billion.[7]

Typically, it takes several years from symptom onset to correct diagnosis of OCD because patients feel too embarrassed to visit a doctor for their complaints.[8] Furthermore, OCD is often underdiagnosed and despite the existence of clinical guidelines, a large percentage of patients receive an inappropriate treatment. In the majority of patients the natural course of OCD is a chronic one, with some fluctuation of symptoms over time.[9]

## Past and current concepts of OCD

Descriptions from persons suffering from obsessions and compulsions can be found in clerical, medical and fictional literature as early as the fifteenth and the sixteenth century, a famous example being William Shakespeare's description of Lady Macbeth. In these and earlier centuries obsessions and compulsions were predominantly placed in the religious domain. Inflicted persons were considered to be possessed by the devil and a ritual of exorcism was the preferred treatment.[10] The first formal medical descriptions and definitions of OCD were composed in the nineteenth century by some well known French, German and English psychiatrists, like Esquirol and Westphal.[11;12] At that time OCD was thought to be the result of an organic (brain) abnormality with a genetic component. However, especially with the rise of Freud's psychoanalytical approach in the beginning of the twentieth century, this view of OCD fell into the background. Freud conceptualized OCD as a typical example of a neurosis, i.e. the result of a putative inadequately suppressed unconscious intrapsychic conflict.[13] This became the predominant concept of OCD in mainstream psychiatry and for many decades obsessive-compulsive neurosis was seen as a disorder that provided an important window on the functioning of the unconscious mind. Eventually OCD became known as a rare disorder that was poorly responding to (psychoanalytic) therapy.
In the second half of the twentieth century several lines of research and the reappraisal of some older data led to the development of more effective treatments and finally to a reconceptualization of OCD as a neurobiological disorder, paralleling the paradigm shift for many other major psychiatric disorders. Several findings that have led to the paradigm shift for OCD are summarized below.

## Neurochemical findings

In the late 1960s the earliest reports were published that OCD symptoms responded not only to specific forms of psychotherapy based on learning theory (i.e. behavioral therapy), but also to pharmacotherapy with clomipramine, an antidepressant.[14;15] Subsequent clinical studies showed that OCD only responded to treatments with antidepressants that predominantly block the reuptake of the neurotransmitter serotonin. Indirect evidence for abnormalities of the serotonergic system was also found in several biochemical studies of OCD.[16;17] To date the selective serotonin reuptake inhibitors (SSRI's) are the standard pharmacotherapy for OCD.[18;19] In patients who have no effect of an SSRI, the addition of low doses of a dopaminergic blocking agent often leads to improvement of symptoms.[20;21]

## Neuroanatomical findings

In several studies and case reports, some already published in the 1920's, OCD was found to be associated with neurological disorders like Parkinson's disease, Huntington's disease, encephalitis lethargica and Tourette's syndrome.[22-24] These disorders are all known to afflict a group of nuclei called the basal ganglia, originally believed to be primarily involved in the control of movement. There were also several reports of subjects developing OCD after lesions to the basal ganglia or the orbitofrontal cortex.[25;26] Forms of neurosurgery in which

specific connections between the basal ganglia and the frontal cortex are lesioned, have been proven to be an effective treatment for severe OCD.[27] Studies examining neuropsychological and neurological functioning in OCD found abnormalities that were also consistent with dysfunctions of specific neuronal circuits between the frontal cortex and deeper brain structures.[28;29]

More recently, neuroimaging studies techniques (i.e. techniques that enable the visualization of the structure and functioning of the living brain) have been very influential in shaping the neuroanatomical models of OCD. Neuroimaging studies examining the blood flow in brain regions have consistently shown an increased flow in the orbitofrontal cortex and parts of the basal ganglia at rest, and during exposure to feared stimuli. Interestingly, both pharmacotherapy and behavioral therapy lead to a normalization of the blood flow in these brain regions. It is now widely appreciated that brain regions like the basal ganglia, the orbitofrontal cortex, the thalamus and the amygdala are parts of brain circuits that mediate cognitive (especially procedural strategies) as well as motor processes and emotional behavior, and are involved in OCD.[30;31]

## Neuroimmunological findings

OCD was found to be associated with Sydenham's chorea, an autoimmune disease afflicting the basal ganglia as a result of an infection with the streptococcus strain responsible for acute rheumatic fever.[32] More recently cohorts of children were described who had an acute onset of OCD after an infection with this streptococcus. The OCD abated after effective treatment of the infection and antibiotic prophylaxis prevented its recurrence.[33] Currently studies are underway to determine the relative contribution of this post-streptococcal autoimmune dysfunction to the pathogenesis of OCD in children en adults.

## Data from comparative animal research

It has been long appreciated that the stereotypies (i.e. repetitive non-functional behaviors like excessive grooming or specific territorial maintenance behavior) occurring in a range of non-human species seem to resemble obsessions in humans. Stereotypies are known to be mediated by circuitry responsible for species-specific motor and cognitive procedural strategies, involving the basal ganglia.[34;35] In many species stereotypies can be elicited by dopamine agonists or specific environmental cues.[36] Interestingly, in veterinary medicine a condition analogue to OCD is diagnosed in dogs and cats, responding in a similar way as in humans to pharmacotherapy with a selective serotonin reuptake inhibitor as well as to behavioral therapy, and showing a clear genetic component.[37]

## Epidemiological and genetic findings

Finally, epidemiological data show similar cross-cultural male and female ratios and prevalences of OCD, as well as a remarkable consistency of the themes of obsessions and compulsions. A familial component in OCD was already postulated in the nineteenth century, and twin studies and well-defined family studies have indeed yielded evidence for a heritable

component in OCD.[38;39] More recent lines of research focus on polymorphisms of components of several neurotransmitter systems such as receptors and transporters.

## Outline of the thesis

In this thesis specific aspects of the neuropsychology and neurochemistry of OCD are investigated in carefully selected patients, mainly with two functional neuroimaging techniques: functional Magnetic Resonance Imaging and Single Photon Emission Computer Tomography. Functional neuroimaging is used to refer to imaging methods or modalities that provide information on the activity, metabolism or neurochemistry of the brain. Magnetic Resonance Imaging (MRI) is based on the observation that certain atomic nuclei, the most abundant being hydrogen nuclei or protons, behave like little magnets which will resonate when they receive energy at a certain radiofrequency. In the process of returning to their equilibrium state they will lose energy and emit a radiofrequency signal. The characteristics of this signal depend on the properties of the specific brain tissue or structure and are used to construct images. In functional MRI this principle is used in combination with the paramagnetic properties of deoxyhemoglobin (one of the two states of the oxygen carrier in the blood) to assess blood flow related to brain activity. Because functional MRI has a very good spatial and temporal resolution (i.e. a good ability to separate activity in time and space) and does not use radioactivity, it allows for the use of more complex research designs with multiple scan sessions.
Single Photon Emission Tomography uses a radioactive nuclide incorporated into a carrier, which is injected intravenously. When the carrier does not pass the blood-brain barrier, this permits the assessment of cerebral blood flow by measuring the radioactivity in brain areas. SPECT can also be used to examine aspects of the neurochemistry of the brain. Radioactive nuclei can be incorporated into ligands, carriers that are transported to the brain, pass the blood-brain barrier and bind to specific neurochemical elements like transporters or receptors. SPECT is easy to use, but has a limited spatial and temporal resolution and patients are exposed to radioactivity.

### *Section 1*
### *Cognitive functioning*

As illustrated earlier, converging evidence suggests dysfunctions of complex frontal-thalamo-basal ganglia circuitry in OCD. Dysfunctions in this circuitry may also result in disturbances of executive functioning (i.e. higher-order processes necessary for effective and contextually appropriate goal directed behavior) that may underlie parts of the symptomatology of OCD.[31;40-42] Studies examining cognitive function in OCD have been performed since the late 70's and have shown rather specific deficits in several domains of executive functioning such as cognitive set-shifting, trial-and-error learning and inhibition capacities.[43-46] The distinctive phenomenology of OCD has led to the hypothesis that a general deficit in inhibition capacities is a common denominator of the cognitive disturbances in OCD. Strong support for this hypothesis comes from oculomotor studies finding a reduced performance in OCD on

antisaccade tasks. In antisaccade tasks subjects have to suppress the reflex to look towards a novel presented peripheral stimulus, in order to make a volitional eye movement in the opposite direction. Chapter II describes the first study to examine whether saccadic abnormalities in OCD represent a stable biomeasure of the disorder or a feature that normalizes with treatment, i.e. are a state dependent phenomenon. Stable biomeasures (biomarkers) are important for research into the vulnerability for obsessive-compulsive symptoms. Because previous oculomotor studies in OCD included patients with comorbidity or on psychotropic medication, we first compared carefully selected adult psychotropic-naïve patients with OCD with no comorbid diagnoses and matched healthy controls on different oculomotor tasks. Subsequently, we investigated the effects of response on aspects of these oculomotor tasks in a group of psychotropic-free or naïve patients with no comorbid diagnoses.

Other recent neuropsychological studies examining executive functioning in OCD have shown that OCD is consistently associated with a specific deficit in spatial working memory, i.e. the system that regulates manipulation and short-term storage of information on the location or position of items in space. The nature of this spatial working memory deficit in OCD has not been elucidated yet. The spatial working memory system in OCD has never been investigated before with functional neuroimaging techniques. Chapter III presents a functional MRI study of the spatial working memory system in psychotropic naïve patients with no comorbid diagnoses and matched healthy controls, using a working memory task with increasing levels of difficulty. The subsequent study described in chapter IV investigates the state or trait dependent nature of the spatial working memory deficit in OCD in a group of psychotropic free patients with no comorbid diagnoses. We examined the effect of response to treatment on the functioning of the working memory system as assessed with the spatial working memory task and functional MRI.

*Section 2*
*Neurochemistry*

The selective response of OCD patients to serotonin reuptake inhibitors has led to the hypothesis that changes in the central serotonergic systems may be the mechanism by which these compounds exert their effect.[17] However, direct evidence that serotonergic perturbations are implicated in the neurobiology of OCD is sparse. Studies with serotonergic pharmacological challenges and metabolite studies have yielded data that are too inconsistent, or too open to different interpretations, to serve as a valid basis for dissecting out the neurobiology of OCD.[17;47;48] Recent data suggests that other neurotransmitter systems, especially the dopamine system, may be involved as well. Growing evidence that atypical antipsychotics may augment the response to serotonin reuptake inhibitors in refractory OCD patients and in patients with comorbid tics, studies showing an exacerbation of symptoms after administration of a dopamine agonist and findings from preclinical studies would seem to point to an increased activity of dopaminergic systems in OCD.[20;49] However, despite the advent of several radiolabeled ligands, i.e. chemicals with a high affinity for dopaminergic or serotonergic binding sites suitable for neuroimaging techniques

like single photon emission computed tomography (SPECT) or positron emission tomography (PET), the functional neuroanatomy of these neurotransmitter systems in OCD has scarcely been investigated.

In chapter V we compared the binding patterns of radioactive labeled [$^{123}$I] beta-CIT ($^{123}$ I labeled 2ßcarbomethoxy3ß(4iodophenyl)tropane), a ligand for dopamine and serotonin transporters in the brain, in psychotropic-naive patients with OCD and carefully matched healthy controls. Serotonin transporter binding sites are the main target of the serotonin reuptake inhibitors, the standard pharmacotherapy for OCD. Chapter VI describes another SPECT study examining possible abnormalities of the dopaminergic system in OCD. [$^{123}$I] iodobenzamide ([$^{123}$I] IBZM) was used to visualize the dopamine $D_2$ receptor. D2 receptor antagonism is common to antipsychotics, which have been shown to be efficacious in the therapy of treatment resistant OCD.[20;49] Binding patterns of the radiolabeled IBZM were compared between psychotropic free patients with OCD and matched healthy controls.

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*Section 1*

# *Cognitive functioning*

# Chapter II

# Saccadic abnormalities in obsessive-compulsive disorder before and after treatment

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# Summary

Obsessive-compulsive disorder (OCD) is characterized by recurrent, persistent and intrusive thoughts or images that cause anxiety or distress (obsessions), and repetitive behaviors or mental acts aimed at reducing this distress or anxiety (compulsions). It is now considered a disorder with a heterogeneous neurobiological etiology, involving complex fronto-thalamo-basal ganglia circuitry. Oculomotor studies have found saccadic abnormalities in OCD, lending support for models postulating a central role for inhibition in OCD. Saccadic abnormalities in OCD may also be potential candidates for a biological marker, important for more endophenotype-oriented research. So far, reliable biological markers have not been identified in obsessive-compulsive disorder. We therefore assessed the state or trait dependent nature of saccadic abnormalities in OCD. Because previous oculomotor studies in OCD included patients with comorbidity or on psychotropic medication, we first compared the error rates and latencies of 14 carefully selected adult psychotropic-naïve patients with OCD with no comorbid diagnoses and 14 matched healthy controls on a fixation task (requiring only active inhibition), on a prosaccade task and on an antisaccade task (requiring both active inhibition and the initiation of a saccade to an imagined target). Subsequently, in our second study in a group of 17 psychotropic-free or naïve patients with OCD with no comorbid diagnoses, we investigated the effects of pharmacotherapy and response on error rate and latencies on the same oculomotor tasks. In the first study patients with OCD showed normal error rates on all tasks, but latencies on the antisaccade task were significantly increased. This seems to be a specific pattern for OCD, to our knowledge not described in other putative frontostriatal disorders. In the second study we found no effects of pharmacotherapy or response on error rate or latencies on the three oculomotor tasks. Our results indicate that patients with OCD have no gross impairment of oculomotor inhibitory capacities, but may have a disturbed capacity to deliberately initiate a saccade to an imagined target. This specific pattern of oculomotor performance in OCD seems to constitute a state-independent phenomenon.

# Introduction

Obsessive-compulsive disorder (OCD) is characterized by recurrent, persistent and intrusive thoughts or images that cause anxiety or distress (obsessions), and repetitive behaviors or mental acts aimed at reducing this distress or anxiety (compulsions). Patients recognize that these obsessions and compulsions are unreasonable and products of their own mind. OCD is now recognized as a severe, prevalent and incapacitating disorder with a heterogeneous neurobiological etiology.[1] The risk of developing OCD is in part inherited, but can also be the result of specific autoimmune processes, trauma or vascular lesions.[2] Obsessive-compulsive symptomatology is also found in patients suffering from Tourette's syndrome or Huntington's disease.[3] Converging evidence suggests dysfunctions of complex frontal-thalamo-basal ganglia circuitry in OCD, resulting in disturbances of executive functioning (i.e. higher-order processes necessary for effective and goal directed behavior) that may underlie parts of the symptomatology of OCD.[4;5] The distinctive phenomenology of OCD has led to the hypothesis that a general deficit in inhibitory capacities is a common denominator of the (cognitive) disturbances in OCD.

Strong support for this appealing hypothesis comes from oculomotor studies finding a reduced performance on antisaccade tasks in OCD. In antisaccade tasks subjects have to suppress the reflex to look towards a novel presented peripheral stimulus (the reflexive prosaccade) in order to make a volitional eye movement in the opposite direction towards an imagined target (the antisaccade).[6] Performance is usually expressed as the percentage of incorrect, i.e. not suppressed, reflexive prosaccades (error rate) and the time needed for the initiation of correct antisaccades (latency). Saccadic movements are known to be subserved by fronto-thalamo-striatal circuitry.[7] Oculomotor studies in OCD using an antisaccade paradigm almost all found an increased error rate with normal latencies, indicating reduced inhibitory capacities in OCD.[8-10] Only a recent study by Maruff et al. found normal error rates and an abnormal increase in latency[11].

In view of the findings in the literature and the dependence of saccadic capacities on fronto-thalamo-striatal circuitry, saccadic abnormalities may be potential candidates for a biological marker of OCD. So far, distinct biological markers, important for more endophenotype-oriented research, have not yet been identified in OCD. To our knowledge there are to date no studies that have examined whether saccadic abnormalities in OCD represent a stable biomeasure of the disorder or a feature that normalizes with treatment, i.e. a state dependent phenomenon. We therefore decided to examine the trait or state-like nature of the reported saccadic abnormalities in OCD.

Because previous oculomotor studies in OCD included patients with comorbidity or on psychotropic medication, we first compared the performance of carefully selected adult psychotropic-naïve, comorbidity-free patients with OCD and matched healthy controls on a prosaccade task and on an antisaccade task. To allow for a clear distinction between the two elements of an antisaccade, i.e. the inhibition of prosaccades and the deliberate initiation of movement to an imagined location, we also included an active fixation task in which subjects only had to suppress reflexive prosaccades.[12] Subsequently, we investigated in our second study the effects of pharmacotherapy and response on saccadic measures in a group of psychotropic-free or naïve patients with OCD with no comorbid diagnoses.

# Methods and materials

## Subjects

Psychotropic-naïve or psychotropic-free patients with OCD without significant psychiatric or somatic comorbidity were recruited from a cohort of 375 patients with OCD as primary diagnosis referred to the anxiety research unit of the Department of Psychiatry at the University Medical Center of Utrecht from 1997 to 2001. Most patients came from direct physician referrals. In the first part of the study 14 psychotropic medication-naïve right-handed patients with OCD according to the Diagnostic and Statistical Manual of Mental Disorders-4$^{th}$ edition (DSM-IV) criteria and with no comorbidity, and fourteen healthy controls matched pair-wise for age, gender and handedness participated. Healthy controls were recruited from an existing database or trough advertising.

All subjects had no lifetime history of illnesses with possible central nervous system or oculomotor sequelae and were in good physical health, as confirmed by physical and laboratory examinations. All subjects also had normal or corrected vision. Screening for psychopathology was done by administering the Mini International Neuropsychiatric Interview IV (MINI-IV) for patients and for controls.[13] Diagnoses were confirmed by an experienced clinician (H.M, N.W). Only subjects without a lifetime history of psychosis, substance abuse, recurrent major depression, bipolar disorder, eating disorders, other anxiety disorders, tic disorders and stuttering were included. Furthermore, all subjects had no first-degree history of a major DSM-IV axis I disorder (except for OCD in patients) or tics. Subjects used less than four cups of coffee, two units of alcohol and six cigarettes a day. Patients were included when they had a minimum score of 16 on the Yale Brown Obsessive Compulsive Scale (Y-BOCS) [14] and a maximum score of 13 on the Hamilton Depression Rating Scale (HAM-D).[15] We also administered the Hamilton Anxiety Scale (HAM-A).[16] Demographic and clinical characteristics of the subjects are presented in Table 1. Subjects underwent oculomotor testing within two weeks after inclusion. At the time of testing patients were not receiving any form of psychotherapy, and cognitive behavioral therapy had been terminated at least three months before the test day. The protocol was approved by the ethical committee of the University Medical Center of Utrecht. After complete description of the study to the subjects, written informed consent was obtained.

In the second study 19 psychotropic-free or psychotropic-naïve patients with OCD with no comorbid diagnoses who fulfilled the above inclusion criteria were enrolled. All patients also participated in a double blind comparison study of paroxetine and venlafaxine in OCD.[17] Psychotropic-free patients were al least 2 weeks without psychotropic medication. For patients who had used fluoxetine the medication washout period was extended to at least four weeks. Patients had not received any form of psychotherapy, especially cognitive behavioral therapy, within the three months preceding the study. Seventeen patients were tested immediately before and after the standardized 12-week pharmacotherapy with dosages titrated upward to paroxetine 60 mg or venlafaxine 300 mg daily in week seven, following a fixed dosing schedule. Amongst the ten psychotropic-naïve patients were seven patients who participated also in the first study. Two psychotropic-free patients were considered dropouts from the standardized treatment and were only tested once. In both studies patients with various OCD symptomatology were included.

## Procedure and tasks

We performed electro-oculography (EOG) during three oculomotor tasks (fixation, prosaccade and antisaccade), similar to the procedure used in our previous functional MRI study in schizophrenic patients.[12] For each task subjects were allowed to practice for a short period of time until they understood the tasks. Instructions were given verbally before the start of the experiments. For the fixation task patients were instructed to hold their gaze at the location of a central fixation cross and not to look at a peripheral square when it appeared. For the prosaccade task to look as quickly as possible to the square when it appeared, and for the antisaccade task to look as quickly as possible to the opposite direction of the square when it appeared. For the prosaccade and antisaccade task subjects were instructed to look back to the fixation cross when the square disappeared and the central fixation cross-reappeared. Tasks were presented in a prosaccade-antisaccade-fixation sequence. All 50 stimuli for each task were presented in 1 block. Stimuli were presented with a 0.8 degree visual angle size. The peripheral stimulus was presented at a visual distance of 7 degrees from the central fixation point. The interstimulus interval was 2.5 seconds, of which 1 second was used for central fixation, followed by a gap of 0.2 s with a blank screen, 0.8 seconds for peripheral square display and 0.5 seconds of blank screen. Subjects were seated in a near-dark room at one meter in front of a VGA monitor. EOG data for horizontal saccades were acquired using surface electrodes at a sampling rate of 500 Hz. Data were processed offline with the aid of a custom made nonautomated EOG analysis program. Latencies were calculated as the time from onset of the peripheral square till onset of the saccade. An initial movement of the eyes in the wrong direction (depending on the task) after the appearance of the peripheral square with a latency longer than 90 ms was counted as an error.[18] Initial eye movements with latencies less than 90 ms were considered anticipatory and excluded from further analysis. Any stimulus related saccades during the fixation task were counted as errors.

## Statistical analysis

For the first part of the study, age was compared using a Student *t*-test. Error rates on the three tasks were compared using a Student *t*-test. A repeated-measures analysis of variance (rANOVA) with group as between-subject factor and task as one within-subject factor was applied to compare the latencies on the anti and prosaccade tasks in psychotropic naïve patients and controls.

For the second part of the study we applied rANOVAs with response as between-subject factor and time and task (prosaccade, antisaccade) or error rate (fixation, prosaccade and antisaccade) as within-subject factors. Response was conservatively defined as a decrease in the Y-BOCS total score of at least 35%. Correlations with scores on the symptom scales were assessed using Spearman correlations coefficients. Demographical and clinical characteristics of responders and non-responders at baseline were compared using a Students *t*-test or Mann Whitney U test when applicable. Two-tailed significances (alpha = 0.05) are reported throughout. For all statistical evaluations SPSS (Version 9.0) software was used.

# Results

## First study (psychotropic-naïve patients with OCD versus pair wise matched controls)

From the 375 patients with OCD as primary diagnosis referred to our specialized unit between 1997 and 2001, 104 had never received treatment with an effective drug.[19]Unfamiliarity with OCD treatment guidelines, as well as several patient related factors may underlie this lack of adequate treatment. Fifty patients were psychotropic-naïve. Eighteen psychotropic-naïve patients fulfilled the inclusion criteria and finally 14 patients participated. Controls were mainly recruited from the existing database. Five potential controls refused participation. All subjects completed the study. Patients and controls were perfectly matched for sex. Age was not significantly different between the two groups. Although most patients had some aspects of depressive symptomatology, as reflected by the average Hamilton depression scores, none fulfilled criteria for a depressive episode or dysthymia or any other comorbid disorder at screening. Five patients had a prior single episode of a DSM-IV depressive episode NOS (in three patients with dysthymic and in two with more depressive features). One patient had a history of two DSM-IV depressive episodes NOS, one with dysthymic and one with more depressive features.

Student *t*-tests showed no significant differences between patients and controls in error rate on the fixation ($t = 0.891$, $df = 13$, $p = 0.650$), prosaccade ($t = 0.466$, $df = 13$, $p = 0.391$) and antisaccade ($t = 1.225$, $df = 13$, $p = 0.214$) tasks (see Figure1). The rANOVA for the latencies for prosaccades and antisaccades showed a significant effect for task ($F = 307.01$, $df = 1, 26$, $p < 0.001$) and a significant diagnosis by task interaction ($F = 28.51$, $df = 1, 26$, $p < 0.001$), and no significant effect for diagnosis ($F = 0.00$, $df = 1, 26$, $p = 0.99$). Post-hoc *t*-tests showed that patients had significantly increased latencies on the antisaccade task ($t = 2.685$, $df = 26$, $p = 0.012$) but not on the prosaccade task ($t = -1.174$, $df = 26$, $p = 0.251$). There were no significant correlations between the error rate, latencies on the two saccade tasks or the increase in latency, and scores on the Y-BOCS total and subscales, type of onset or duration of the illness.

## Second study (saccadic measures before and after pharmacotherapy)

Like in the first study, most patients had some aspects of depressive symptomatology, as reflected in the average Hamilton depression scores, but none fulfilled criteria for a depressive episode or dysthymia or any other comorbid disorder at screening. Seven patients had a prior single episode of a DSM-IV depressive episode NOS (in five patients with dysthymic and in two with more depressive features). Two patients had two prior DSM-IV depressive episodes NOS. After 12 weeks of treatment ten patients could be classified as a responder (mean change in Y-BOCS score 43.7 ± 11.4%) and seven patients as non-responder (mean change in Y-BOCS score 14.5 ± 12.1%) to treatment. There were no significant differences in clinical and demographic variables between responders and non-responders at baseline (Table 2).

rANOVA for the error rates showed a significant effect of task ($F = 14.945$, $df = 2, 14$, $p < 0.001$) but no effect of time. ($F = 0.031$, $df = 1, 15$, $p = 0.324$) or response ($F = 0.010$, $df = 1, 15$,

p = 0.922), and no significant interactions (time x response (F = 0.010, df = 1,15, p = 0.923), time x task (F = 2.499, df = 2,14, p = 0.118) response x task (F = 1.222, df = 2,14, p = 0.324, time x response x task (F = 0.065, df = 2, 14, p = 0.937).
rANOVA for the saccadic latencies showed a significant effect of task (F = 51.09, df = 1,15, p < 0.001), but no significant effect of time (pre-treatment versus post-treatment) (F = 0.126, df = 1, 15, p = 0.728) or response (F = 0.00, df = 1,15, p = 0.998), and no significant interactions (response x time (F = 0.024, df = 1,15, p = 0.878), time x task (F = 0.518, df = 1,15, p = 0.483), response x task (F = 0.345, df = 1,15, p = 0.566), time x response x task (F = 0.822, df = 1,15, p = 0.397). Absence of effects on the factor time indicates that treatment did not affect saccadic latencies. Absence of effects involving response indicates that clinical improvement is not reflected in changes in saccade latencies.
To examine if saccadic measures at baseline were potential predictors for response we calculated correlations between the latencies for the two tasks and the difference in latency for the two tasks at baseline on the one hand, and response and change in Y-BOCS scores on the other. There were no significant correlations. Because of the absence of a significant interaction we did not further explore possible correlations between oculomotor measures and Y-BOCS total and subscale scores.

# Discussion

In the first study we examined saccadic abnormalities in a carefully selected group of adult psychotropic-naïve and comorbidity-free patients with OCD. The patients with OCD were found to have normal error rates on the active fixation task and on the antisaccade task, as compared to healthy controls. This indicates that patients with OCD have no gross impairment of oculomotor inhibitory capacities. There was however an abnormal increase in latency for the antisaccade task in patients with OCD. In the second study we investigated whether this saccadic abnormality constitutes a trait or state dependent phenomenon. We found no effects of pharmacotherapy or response on saccadic measures (error rate and latency) in patients with OCD, suggesting that the specific pattern of antisaccadic performance in OCD constitutes a state independent phenomenon.
In contrast to our findings, in most previous studies examining performance on antisaccade tasks in patients with OCD and controls, higher error rates on antisaccade tasks and normal latencies in OCD were reported. However, several studies may have been hampered by the presentation of an inadequate number of stimuli, probably leading to incorrect estimations of the error rates and latencies. Furthermore, all previous studies included patients with comorbidity or on psychotropic medication.[8-11]
In line with our results, the recent study of Maruff et al., in which a carefully designed oculomotor paradigm with an adequate number of stimuli was used, reported normal error rates on an antisaccade task in patients with OCD and also found an abnormal increase in latency on the antisaccade task in OCD.[11] Like almost all previous studies of antisaccadic performance in OCD we found no correlations between oculomotor abnormalities and symptom variables.[9-11]

The normal error rates of patients with OCD on our fixation and antisaccade tasks indicate that patients with OCD can adequately suppress reflex saccades and thus have no gross disturbance of inhibitory oculomotor capacities. Neuropsychiatric disorders involving frontostriatal circuitry, like Tourette's syndrome or Parkinson's disease, are known to have overlapping yet distinct manifestations in terms of saccadic abnormalities.[20] The combination of an increased latency on the antisaccade task and normal error rates as found in OCD, has to our knowledge not been described in other putative frontostriatal disorders and suggests that this may be a specific pattern for OCD.

Our findings argue against the idea of inhibition as a common denominator of cognitive dysfunction in OCD. In line with the results of the study by Maruff et al., our data suggest that the abnormal increase in latency on the antisaccade task may be due to a disturbed capacity to initiate a saccade on the basis of an internally represented goal.[11] Interestingly, previous neuropsychological research by Purcell et al. suggests that an impaired ability to use an internal representation for the guidance of behavior may not be limited to saccadic movements, but may represent a more general cognitive deficit in OCD.[21] They found performance in OCD to be compromised during a specific working memory task when external validation of ongoing performance was not provided. A more general impairment in the ability to guide behavior on the basis of an internal representation may be relevant for aspects of the phenomenology of OCD, as patients may need to obtain external validation (checking) of inadequately used internal representations of (automated) behavior (e.g. locking the door). Some limited data regarding deficits in memory for actions and reduced confidence in memories in OCD supports this hypothesis.[22-24] However, a general impairment in the ability to guide behavior on the basis of an internal representation of the objective would not explain all symptoms of OCD, like for example aggressive obsessions or superstitious rituals.[25;26]

Saccadic movements are known to be subserved by fronto-thalamo-cortical circuitry and our data suggest a dysfunction in this particular circuitry in OCD. The exact nature of such a dysfunction still needs to be elucidated. Studies examining the functional neuroanatomical substrate of saccadic movements in healthy volunteers and psychiatric patients have indeed shown the involvement of a complex network of cortical and subcortical structures, but are inconclusive as to which areas are specifically involved in inhibition or initiation.[27-29]

In the second study we found no effects of pharmacotherapy or response on oculomotor performance, indicating that the specific pattern of saccadic performance in OCD may constitute a state independent phenomenon. This is also supported by the absence of correlations between saccadic measures and symptom scales before treatment. As a state-independent biological marker, the specific pattern of saccadic abnormalities in OCD may be a potential endophenotype for OCD. However, it is not known whether the saccadic abnormalities found in this study were already present before the onset of OCD (a vulnerability factor) or have resulted from the disease process (a so-called 'scar' phenomenon). There are also no data available yet on the presence of this specific oculomotor abnormality in subsyndromal populations or in relatives of OCD patients.

To our knowledge saccadic abnormalities have not been studied previously in a carefully selected sample of psychotropic-naïve and comorbidity-free patients with OCD. This is also the first report on the state or trait like nature of saccadic abnormalities in OCD. Patients and

controls were selected following rigorous criteria and carefully matched. We presented an adequate number of stimuli and included an active fixation task to investigate the ability to suppress reflexive saccades. There are also some potential limitations to this study. Although comparable to the sample sizes of other oculomotor studies in OCD and other psychiatric disorders, the sample sizes are relatively small compared to oculomotor studies in healthy volunteers.[7;30;31;18] Unfortunately, the design of our study did not allow for a direct comparison of our data with those from the study of Maruff et al.[11] Further, we only examined the effect of pharmacotherapy and not of cognitive behavioral therapy on saccadic measures in OCD. We included patients with various OCD symptomatology, which may have reduced the chance to find significant correlations. Finally, one may argue that the within-subject test-retest variability was too large to discover any effect of treatment on oculomotor functioning. However, saccadic measures have been found to have high test-retest reliability in both healthy volunteers and psychiatric patients.[30;32]

If the pattern of saccadic performance in OCD indeed would prove to constitute a state-independent biological marker for OCD, oculomotor research could be useful in genetic and vulnerability studies of OCD and OCD spectrum disorders, as is currently the case for schizophrenia and Huntington's disease.[33-36] Finally, with the advent of functional magnetic resonance imaging it is now possible to directly examine the neuroanatomical correlates of saccadic abnormalities in OCD.

**Acknowledgement**

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TABLE 1

Demographic and Clinical Characteristics of patients with OCD and Pair-Wise Matched Healthy Controls*

| Subject characteristics | OCD (n = 14) | Controls (n = 14) |
|---|---|---|
| Age, y | 29.1 (7.2) | 28.4 (6.28) |
| Gender (M/F) | 9/5 | 9/5 |
| Handedness (N right/left) | 14/0 | 14/0 |
| Y-BOCS total | 23.7 (3.8) | – |
| Y-BOCS obs. | 12.5 (2.0) | – |
| Y-BOCS comp. | 11.2 (2.3) | – |
| HAM-D | 8.0 (4.3) | – |
| HAM-A | 11.3 (5.6) | – |
| Onset | 8 juvenile, 6 adult | – |
| Years of illness | 11.3 (6.1) | – |

Abbreviations: OCD is obsessive-compulsive disorder, Y-BOCS is Yale Brown Obsessive Compulsive scale, HAM-D is Hamilton Depression scale, HAM-A is Hamilton Anxiety scale.

* Data are given as the mean (SD), unless otherwise indicated

TABLE 2

Demographic and Baseline characteristics of Responders and Non-Responders to Pharmacological Treatment*

| Subject characteristics | Responders (n = 10) | Non-Responders (n = 7) |
|---|---|---|
| Age (y) | 27.6 (3.2) | 29.0 (2.8) |
| Gender (M/F) | 7/3 | 4/3 |
| Y-BOCS total | 24.4 (3.8) | 24.7 (2.2) |
| Y-BOCS obs. | 11.7 (1.8) | 12.5 (1.6) |
| Y-BOCS comp. | 12.7 (2.3) | 12.1 (1.7) |
| HAM-D | 7.4 (3.8) | 8.1 (4.2) |
| HAM-A | 9.6 (4.0) | 10.3 (5.4) |
| psychotropic naïve/free | 6/4 | 4/3 |
| Onset | 5 juvenile, 5 adult | 4 juvenile, 3 adult |
| Years of illness | 14.0 (5.4) | 13.1 (4.5) |

Abbreviations: OCD is obsessive-compulsive disorder, Y-BOCS is Yale Brown Obsessive Compulsive scale, HAM-D is Hamilton Depression scale, HAM-A is Hamilton Anxiety scale.

* Data are given as the mean (SD), unless otherwise indicated

Figure 1

Performance on the three oculomotor tasks in patients with obsessive-compulsive disorder (n = 14) and healthy control subjects (n = 14). OCD is obsessive-compulsive disorder, HC is healthy controls. Error bars represent standard errors.

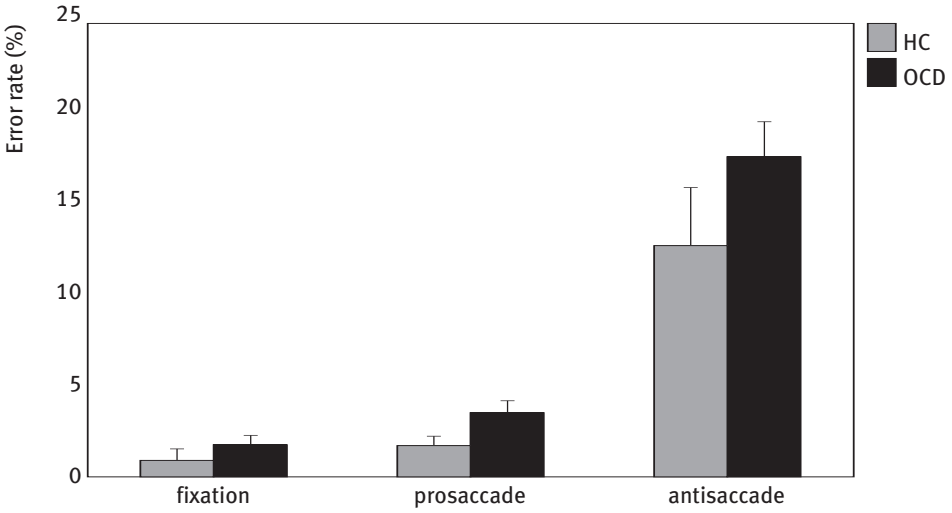
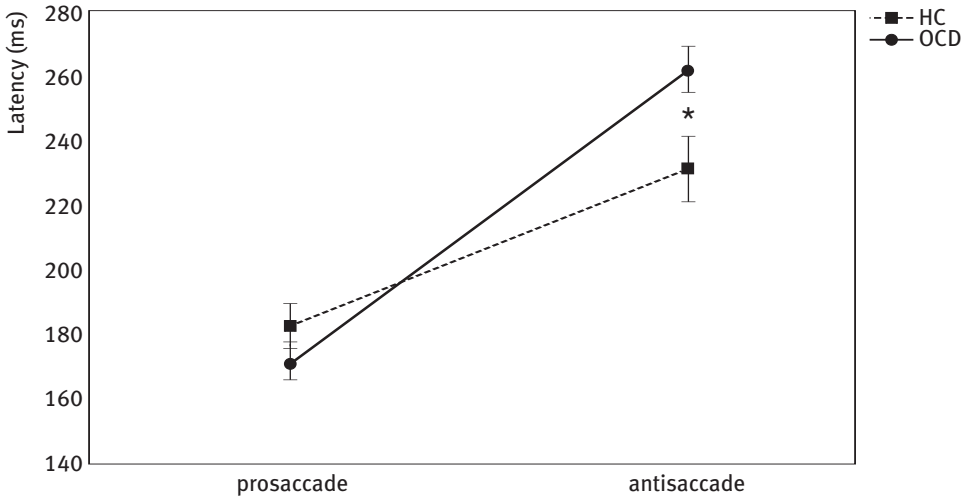



Figure 2

Mean latencies and standard errors for the prosaccade and antisacade task for patients with obsessive-compulsive disorder (n = 14) and healthy controls (n = 14). OCD is obsessive-compulsive disorder, HC is healthy controls. Asterisk indicates a significant difference (Post-hoc *t*-test, $p < 0.05$).



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# Chapter III

# Spatial working memory deficits in obsessive-compulsive disorder are associated with excessive engagement of the medial frontal cortex

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# Summary

Recent studies have shown that obsessive-compulsive disorder (OCD) is associated with a specific deficit in spatial working memory, especially when task difficulty (i.e. working memory load) is high. It is not clear whether this deficit is associated with dysfunction of the brain system that subserves spatial working memory, or whether it is associated with a more generalized effect on executive functions. In contrast to studies in healthy volunteers and schizophrenia, spatial working memory in OCD has not been investigated before using functional neuroimaging techniques. We conducted a functional MRI study in 11 treatment-free female patients with OCD and 11 for sex, age, education and handedness pair-wise matched healthy controls in order to assess performance on a parametric spatial *n*-back task as well as the underlying neuronal substrate and its dynamics.

Patients with OCD performed poorly at the highest level of task difficulty and engaged the same set of brain regions as the matched healthy controls. In this set, the effect of difficulty on magnitude of brain activity was the same in patients and in controls except for a region covering the anterior cingulate cortex. In this region activity was significantly elevated in patients with OCD at all levels of the parametric task. These findings do not provide evidence for a deficit of the spatial working memory system proper, but suggest that the abnormal performance pattern may be secondary to another aspect of executive dysfunctioning in OCD.

# Introduction

Obsessive-compulsive disorder (OCD) is characterized by recurrent, persistent and intrusive thoughts or images that cause anxiety or distress (obsessions), and repetitive behaviors or mental acts aimed at reducing this distress or anxiety (compulsions). Patients recognize that the obsessions and compulsions are unreasonable and are products of their own mind. Once considered rare, recent epidemiological data suggest prevalence rates of OCD from 1,5% to 3%.[1-3]

Convergent evidence from neurological, neurosurgical, neuroimaging, pharmacological, and neuropsychological studies suggests a neurobiological basis for OCD, resulting in the current fronto-thalamo-cortical model of OCD. According to this model obsessive compulsive symptoms result from dysfunction of complex frontal, cortical, and basal ganglia circuitry involved in executive functioning, i.e. higher-order processes necessary for effective and contextually appropriate goal directed behavior.[4;5]

Studies examining cognitive function in OCD have been performed since the late seventies and have shown deficits in several domains of executive functioning such as cognitive set-shifting, trial-and-error learning and inhibition capacities.[6-9] Subtle cognitive deficits have also been reported in sub-clinical populations.[10;11] Some recent studies, including one of the few functional imaging studies with a cognitive paradigm, have shown that OCD may be associated with rather specific cognitive deficits which are taken to reflect fronto-striatal dysfunction.[12;13] One of the cognitive domains addressed in these studies is working memory, i.e. a system that regulates manipulation and short-term storage of information.[14] OCD patients perform poorly on tasks that engage spatial working memory, when task difficulty is high (i.e. a high workload).[12;13] From the neuropsychological findings it is not clear whether at higher load levels the working memory system is physiologically dysfunctional (i.e. has a physical basis), or whether working memory is intact, but somehow disrupted by other processes (i.e. is intact but is utilized inefficiently). Surprisingly, this deficit has not been studied in detail in OCD, in spite of recent advances in the design of working memory tasks that followed developments in neuroimaging techniques. These developments have identified many of the brain regions involved in working memory, offering an opportunity to examine this system in OCD.[15]

To further investigate the deficit in working memory in OCD patients, we conducted a functional MRI study to assess performance on a task as well as the underlying neuronal substrate. The task involves multiple levels of difficulty, and enables visualization of the way in which the working memory system responds to increasing load. The advantage of this parametric design is that it allows for determination of the relationship between load, regional brain activity and performance.[16-18] To exclude the confound of treatment effects, we included only patients who were medication-free for at least two weeks and had not received cognitive behavioral therapy for at least three months. Furthermore, all patients were free of comorbidity, and were compared to closely- matched controls.

We used a parametric spatial variant of the *n*-back working memory task that has been used in healthy volunteers and patients with schizophrenia.[16-18] This variant of the *n*-back task consistently elicits activity bilaterally in dorsolateral prefrontal and parietal cortices, and in the anterior cingulate in patients with schizophrenia and in healthy controls. The

involvement of these brain areas has also been demonstrated in other functional imaging studies of working memory.[19-22]

Based on reported cognitive deficits, we expected that patients with OCD would perform worse than the matched controls on the spatial *n*-back task, but only when the workload is high.[12;13] Furthermore, we postulated that the performance deficit would be accompanied by a different response to increasing workload in brain regions known to be involved in spatial working memory.

# Methods and materials

## Subjects

Fifteen patients with OCD according to DSM-IV criteria and no other Axis I or major Axis II pathology, and 15 healthy controls matched pair-wise for age, gender and level of education participated. Patients were recruited from the outpatient department of the University Medical Center of Utrecht, healthy controls from an existing database or through advertising. The protocol was approved by the ethical committee of the University Medical Center of Utrecht. All subjects were right handed as assessed with the Edinburgh Handedness Score (EHS), had no history of illnesses with possible central nervous system sequelae and were in good physical health as confirmed by physical and laboratory examinations.[23] Screening for psychopathology was done by administering the Mini International Neuropsychiatric Interview IV (MINI-IV) for patients and for controls.[24] Diagnoses were confirmed by an experienced clinician (H.M, N.W). There were no subjects with a lifetime history of psychosis, substance abuse, recurrent major depression, bipolar disorder, eating disorders, other anxiety disorders or tic disorders. Patients were included when they had a minimum score of 16 on the Yale Brown Obsessive Compulsive Scale (Y-BOCS [25] and a maximum score of 13 on the Hamilton Depression Rating Scale (HAM-D).[26] We also administered the Hamilton Anxiety Scale (HAM-A). Subjects were scanned within two weeks after inclusion. Immediately before the functional imaging we administered a Visual Analogue of Mood Scale to asses nervousness and anxiety. At the time of functional imaging patients were at least two weeks free of psychotropic medication and the severity of obsessive compulsive and depressive symptoms was assessed again. For patients who had used fluoxetine the medication washout period was extended to at least four weeks. Patients were not taken off medication especially for our study, but participated in a medication trial with a medication free period of at least two weeks before start of the treatment. At the time of functional imaging patients were not receiving any form of psychotherapy and cognitive behavioral therapy had been terminated at least three months before the scan day. After complete description of the study to the subjects, written informed consent was obtained. After the experiment three patients with OCD were excluded from further analysis due to loss of performance data (one subject), not following the task instructions during the experiment (one subject) and several cough attacks during the experiment (one subject). One healthy control was excluded due to loss of performance data. The final analysis included 11 female patients and 11 pair-wise matched healthy female controls. Age, gender, handedness, level of education and VAS scores did not

differ significantly between these two groups. Seven of the patients with OCD had predominantly obsessions of contamination and compulsions of washing, four predominantly obsessions of doubt and compulsions of checking. Most patients had also other obsessive-compulsive symptomatology like aggressive or sexual obsessions or compulsions of counting. Clinical and demographic characteristics for the two groups are shown in table I.

## Working memory task

Subjects were trained on the task for one hour before the start of the experiment. A video-projector was placed in the scanner control room to project stimuli from outside the control-room to a screen in front of the volunteer. A mirror enabled the subjects to see the screen. Subjects had to perform a spatial variant of the *n*-back working memory task with four increasing levels of difficulty (load levels). The task was designed after Gevins and has been used by our group and others in healthy volunteers and patients with schizophrenia.[27;16-18] Subjects looked at a screen, which showed four large dots in a diamond-shaped diagram indicating the four possible places where a stimulus could appear (see figure 1). The stimulus consisted of one dot changing color at a time. Subjects were instructed to respond to the stimulus by pushing one of four buttons on a pneumatic response button box with the right thumb. Layout of the four buttons corresponded spatially to the four possible positions in which the stimulus appeared. Responses had to be made either directly following the stimulus ('0-back'), or with a delay of one ('1-back'), two ('2-back') or three ('3-back') stimuli, hereafter referred to as 0B-1B-2B-3B. The load-level was shown above the stimuli during the whole task. The different load levels were run in blocks of 21 stimuli, with an interstimulus interval of 2.8 s, in total 59 s per block. The sequence of load levels, including a baseline resting condition, was semi-randomized. In total each load level was presented four times. During the rest condition no stimuli were presented and subjects simply looked at the background image of the task.

The design of the *n*-back task is such that in all levels, subjects have to respond to all stimuli, so the task requires a continuous monitoring and updating of information in working memory. The information that is presented during each trial is the same within all levels, as are the demands made on response selection and execution.

## Imaging procedure

After training subjects were allowed to familiarize with the scan setting. Extra care was taken to avoid provocation of OCS symptoms in patients with contamination obsessions, by changing sheets and by extensively cleaning the head support in the presence of patients. A total of 84 functional scans was acquired for each load level. fMRI scans were obtained with a Philips ACS-NT 1.5 T clinical scanner with PT6000 gradients, and a navigated BOLD 3D-PRESTO pulse sequence (parameters: TE/TR 37/24 ms, flip angle 10°, EPI factor 17, matrix 64*52*30, FOV 225*175*105, voxels 3.5mm isotropic, scantime 2.8 s).[28] To compensate for the delay of the vascular response to neuronal activity, execution of the task started six seconds before the first functional scan. FMRI data were acquired in five blocks of 84 scans

(with 21 scans per load level or rest condition), lasting a total of approximately 20 minutes. The session was concluded with an anatomical scan (3D-FFE; TE/TR 4.6/30 ms; flip angle 30º; FOV 256 by 256 mm.; matrix 128 by 128 by 130 mm; slice thickness 1.2 mm; scan time seven minutes).

# Data Analysis

## Performance

The performance on the *n*-back task was expressed as the average percentage incorrect or omitted responses for each subject on each different load level. Performance was analyzed with an analysis of variance procedure (ANOVA) for repeated measurements with group as between-subject factor and load level as within-subject factor.

## fMRI data

The fMRI data were analyzed in three steps, similar to the procedure used by Jansma et al. and the methodology based on the random effects model as described by Ramsey et al.[29-31] The first step consisted of the generation of individual t-maps, analogous to a standard subtraction method. The second step was the creation of group-t-maps based on the data from step one and the identification of clusters of active voxels based on these group-t-maps. The third and final step was the analysis of activity in these clusters and the comparison between patients and controls. Identification of the clusters was done for each group separately, rather than for all subjects taken together. This was done to enable comparison of the locations of clusters between the two groups, and to account for the possibility that locations were different.

Individual fMRI data were processed off-line on a HP™ workstation using PV-Wave™ processing software. All scans were registered to one high contrast functional scan to correct for rotation and translation between scans.[32] Scans were normalized for mean volume signal-intensity and a 3D gaussian filter (10,5 mm full width at half maximum) was applied to the functional scans. A voxel-wise multiple regression algorithm with four experimental factors (modeling the load levels) and several signal drift factors was used to obtain individual activation t-maps for each of the four task levels vs. rest.[33]. Three additional contrast maps were generated, for the contrast of the load levels 1B-, 2B-, and 3B vs. 0B to identify regions specifically associated with working memory, and exclude non-specific functions such as visual and motor processing.

In the next (second) step all individual activation maps were spatially normalized into stereotactic space by a linear registration to the Montreal Neuroimaging Institute (MNI) 305 average brain.[34] Group-wise-t-maps were calculated using all individual contrast maps from each group by testing the values in each voxel against zero using the pooled variance calculated over all voxels. The resulting group-activation maps, one for patients and one for controls, were thresholded at a t-value of 4.4. This value corresponds to a one-sided corrected p-value of 0.05, Bonferroni corrected for the total number of voxels.[35] Voxels with a

t-value above 4.4 in any of the 'working memory' contrasts (1B-, 2B-, and 3B vs. 0B) were selected. Selected voxels that were neighbors at any point were clustered. A cluster minimum of five voxels was applied. In the third and final step, the mean activity for every load level was determined for each subject in each of the identified clusters. The mean activities were analyzed with an ANOVA for repeated measures with diagnosis as between-subject factor and load level and cluster as within-subject factors.

### Correlations

Correlations between the activity in the clusters and the performance at each load level were examined in patients and controls. In patients correlations with activity and with performance at each load level were examined for the Y-BOCS total score, the Y-BOCS obsessions and compulsions subscales, the HRDS-score, the HAS score, the VAS scores and medication history (naïve or not). Correlations were assessed using Pearson and when applicable Spearman correlations coefficients. Results were corrected for multiple comparisons. For all statistical evaluations SPSS (Version 9.0) software was used.

## Results

### Performance

An ANOVA for repeated measures showed a significant interaction between load level and diagnosis ($F = 6.285$, $df = 3, 24$, $p < 0.01$). All subjects made more errors with higher working memory load, but performance deteriorated disproportionally in patients (fig 2). Bonferroni-corrected post-hoc *t*-tests revealed a significant difference in performance between patients and controls at the 3B load level ($t(26) = 3.420$, $p = 0.002$). The average percentage of incorrect responses at this load level was 48 ± 17 for patients and 25 ±18 for controls. At debriefing, patients with OCD were asked if they had experienced obsessions or compulsions while performing the *n*-back task. Only one patient reported to have been aware of obsessions during a short interval. An ANOVA for repeated measures for the performance of patients with OCD showed no interaction between medication history and load level ($F = 0.128$, $df = 3,7$; $p = 0.941$).

### Regions specifically involved in spatial working memory

As described above the identification of regions that were specifically involved in spatial working memory was based on clusters of at least 5 voxels with a t-value above 4.4 in one or more of the group 'working memory' contrast maps (1B-, 2B-, and 3B vs. 0B). In both groups several bilateral clusters in the frontal and in the parietal cortex were identified (see figure 3). The group-activity maps were highly similar, in that the same regions in frontal and parietal cortex were active (see table 2). In both groups the clusters in the frontal cortex consisted of a region containing the anterior cingulate cortex, extending to the supplementary motor area in OCD, and a bilateral prefrontal region containing clusters in the dorsolateral prefrontal and

premotor cortex. In the parietal cortex a bilateral cluster was identified in patients and controls. In total six common clusters were identified. Two prefrontal clusters were identified in patients but not in controls, i.e. in Brodmann areas 47 and 9/46 in the left hemisphere. Noteworthy, in all regions the clusters in the group-activation maps contained more voxels in patients than in controls.

## Signal analysis in brain regions associated with working memory

To compare the activity levels between patients and controls in the same regions, the t-values of individual subjects, averaged across voxels within each of the six common clusters, i.e. in the anterior cingulate, in the left and right prefrontal cortex, and in left and right parietal cortex, were entered into the ANOVA. The ANOVA for repeated measures of the activity in each cluster and load level revealed a main effect of load level ($F = 58.559$, $df = 3, 18$; $p < 0.001$), but not of diagnosis ($F = 1.063$, $df = 1, 20$; $p = 0.315$) or cluster ($F = 1.347$, $df = 5, 16$; $p = 0.251$). There was a significant interaction between cluster and diagnosis ($F = 3.566$, $df = 5, 16$; $p = 0.019$) but no interaction between load level and diagnosis ($F = 1.038$, $df = 3, 18$; $p = 0.399$) or between load level, diagnosis, and cluster ($F = 1.428$, $df = 15, 6$; $p = 0.346$). Following up on the cluster by diagnosis interaction, ANOVA's for repeated measures performed separately for each cluster revealed a significant between-group effect in the cluster containing the anterior cingulate ($F = 5.735$, $df = 1, 20$, $p = 0.008$), but not in any of the other clusters. The load-activity patterns for each cluster are shown in figure 4.
For the two clusters identified only in patients, i.e. in the left BA 9/46 and BA 47, we performed an exploratory analysis. In controls the same clusters could be identified at a lower threshold ($t>3.0$). ANOVA's for repeated measures for the activity levels in each cluster revealed an effect of load level (left BA 9/46: $F = 10.361$, $df = 3,17$ ;$p < 0.001$; left BA 47: $F = 20.944$, $d f = 3,17$; $p < 0.001$), but not of diagnosis (left BA 9/46: $F = 0.018$, $df = 1, 20$; $p = 0.894$; left BA 47: $F = 1.621$, $df = 1,20$; $p = 0.218$). There were also no interactions between load level and diagnosis (left BA 9/46: $F = 0.508$, $df = 3,18$; $p = 0.682$; left BA 47: $F = 1.449$, $df = 3,18$; $p = 0.264$).
As patients differed in medication history, this was entered as a between-subjects factor for the patients with OCD in an ANOVA for repeated measures for the activity in each cluster and load level. This revealed no effect of medication history ($F = 1.068$, $df = 1, 9$; $p = 0.328$) and also no interactions between load level and medication history ($F = 0.715$, $df = 3,7$; $p = 0.573$) or load level and cluster ($F = 3.890$, $df = 6,4$; $p = 0.205$).

## Correlations

In patients and controls none of the clusters, including the cluster containing the anterior cingulate/supplementary motor area, showed a significant correlation between activity and the performance at any load level. In patients there were also no significant correlations between activity in any of the clusters or performance at each load level, and the total Y-BOCS score, the scores on the Y-BOCS subscales, the HRDS score, the HAS scores, the VAS scores and medication history. When correlations were examined uncorrected for multiple comparisons, there were correlations between the activity and performance at the highest

load level in the right BA6 ($p = 0.03$) and left BA 7 ($p = 0.045$). Given the large number of comparisons, however, these results should be regarded with caution.

# Discussion

Treatment-free patients with OCD were tested on a parametrically controlled spatial *n*-back working memory task, and were found to perform poorly at the highest level of task difficulty ('load level'). The fMRI data showed that the patients engaged the same set of brain regions during the working memory task as the matched healthy controls. However, the activity in the anterior cingulate was significantly elevated in patients with OCD at all load levels, but showed no significant correlations with performance or clinical scales.

The brain circuit subserving spatial working memory was the same in patients and controls and involved the anterior cingulate, and the dorsolateral prefrontal and parietal cortex bilaterally. This set of areas is typical for this task, as has been reported in previous functional imaging studies of non verbal working memory that used the same spatial variant of the *n*-back task.[16-18] The load-activity patterns of the healthy controls in these areas and their performance on the working memory task were also comparable to the findings in these previous studies.[16-18] This confirms that the design of the task is such that the load on the working memory system is manipulated effectively.

In the present study we focused on areas that are generally regarded as critical for working memory, and particularly on the relationship between load level and brain activity. The patients with OCD exhibited an enhanced activity in the anterior cingulate and normal activity in the other working memory areas at all load levels, even when performance deteriorated at the highest load level. This indicates that the working memory system did not disengage with excessive demand. We argue that this finding does not support the notion that the capacity of the working memory system is affected in OCD. If capacity would be reduced, then one would expect disengagement, i.e. a significant failure to activate at the highest load level, compared to controls, which was clearly not the case. This is in contrast to the results of studies in schizophrenia using the same parametric *n*-back to study the dynamics of the non-verbal working memory system. Patients with schizophrenia also perform poorly on this task, where activity is elevated in the dorsolateral prefrontal cortex at intermediate load level, but drops at the highest load level. The observed difference in load-response curve in dorsolateral prefrontal cortex is regarded as an indication that this region is dysfunctional in schizophrenia, resulting in a diminished information processing capacity.[30;36]

It has been suggested that a deficit in specific aspects of non-verbal memory may give rise to the checking and doubt found in many patients with OCD. Several neuropsychological studies have indeed reported deficits like a reduced memory for actions or reduced confidence in memory in patients with OCD, that could explain the frequent checking in many forms of OCD.[37] On the other hand, a deficit in non-verbal memory would not explain many other symptoms of OCD, like for example aggressive obsessions or superstitious rituals.[38] Furthermore, like in our study, most neuropsychological studies investigating memory in OCD found no or only very weak correlations between test measures and symptomatology,

indicating that a non-verbal or spatial memory deficit should not be considered causal for OCD. As for the spatial working memory system, our data suggest that the deficit in spatial working memory may be secondary to another disturbed aspect of executive functioning in OCD.

We found evidence for a regionally selective excess of physiological activity in the anterior cingulate, which was present at all load levels but showed no interaction with load level. The fact that the lateral prefrontal and parietal regions of the spatial working memory system were not affected suggests that the capacity for maintenance and manipulation of information may not be affected in OCD. This is in line with studies of working memory in healthy subjects showing that the anterior cingulate is probably not involved in storing and manipulating information in the working memory process. Thus, Barch et al. have shown a dissociation between working memory load and task difficulty in areas involved in working memory, with the anterior cingulate showing greater activity only on more difficult task conditions, but not necessarily with higher working memory demands.[39] This correlation of activity in the anterior cingulate with task difficulty was also found in the extensive review of 107 blood flow activation studies with positron emission tomography by Paus et al.[40]

Previous functional neuroimaging and neurosurgical studies in OCD have consistently implicated the anterior cingulate as part of an abnormally functioning fronto-thalamo-basal ganglia circuitry. Several functional neuroimaging studies that examined brain metabolism in resting state or after symptom provocation found hyperactivity in the anterior cingulate.[41-45] The neurosurgical procedure of cingulotomy is known to reduce severe OCD symptomatology, with a concomitant reduction of hyperactivity in the fronto-thalamo-basal ganglia circuitry.[46;47]

Studies examining the role of the anterior cingulate in executive functioning in healthy volunteers and non-human primates have led to two main hypotheses regarding its function.[48] One hypothesis postulates that the anterior cingulate plays a key role in the implementation of a strategy, the other that its function is crucial in evaluating the effects of a strategy through the monitoring of performance.[48;49] Monitoring of performance may be based on processes like error checking or the detection of conflicting responses.[50;51]

Interestingly, recent neuropsychological studies in OCD have found deficits in organizational strategy in verbal and non verbal (working) memory domains. Savage et al found that organizational strategy scores in patients with OCD during the encoding phase of complex visual spatial information is correlated strongly with non verbal memory performance as measured with the Rey-Osterrieth Complex Figure Test.[52] In a study examining encoding problems of verbal information, Cabrera et al. found that patients with OCD exhibited less reliance on organizational strategies than did healthy controls.[53] Purcell et al. examined spatial working memory in patients with OCD and matched healthy controls using a paradigm with an increasing working memory load and employed measures for organizational strategy.[12;13] Like in our study, the performance of the patients with OCD dropped significantly at higher load levels, compared to the controls. The patients with OCD also showed a lack of organizational strategy for the higher load levels of the task.

Other recent studies examining event-related brain potentials associated with monitoring of actions and error detecting, known to originate from the anterior cingulate, found enhanced activity in patients with OCD and in subjects with OCD symptoms relative to controls.[54;55]

In this light, the hyperactivity we have found in the anterior cingulate area of patients with OCD when they perform the *n*-back working memory task, might reflect an effort to develop or maintain an efficient strategy to perform this task, or is representing an increased error monitoring. On the other hand it may also be the result of compensatory mechanisms necessary to perform certain cognitive tasks in the presence of OCD. The latter may involve processes like the automatic suppression of obsessions or compulsions or a form of parallel processing of both the stimuli presented in the working memory task and obsessions that come into awareness. The latter seems less likely because only one patient in the present study reported to have been aware of obsessions during a short interval while performing the working memory task.

The clusters activated during the task appeared to be larger in patients than in controls, although this could not be tested statistically. One could argue that this introduces a bias in the final comparisons, and that it would be more appropriate to select volumes of interest (VOIs) on the activity maps of all subjects taken together. However, the latter would also introduce a bias, in that the set of VOIs would include voxels that were not active in the controls. As we were primarily interested in the load-dependency of activity in the working memory network, we decided to limit signal analysis only to voxels that were demonstrably involved in the working memory task without assuming that both groups would engage regions of the same size. The fact that levels of activity were the same for both groups in most clusters in spite of size differences supports the notion that the size issue did not introduce a systematic bias.

Our study has some potential limitations. Although comparable to other functional imaging studies investigating working memory in healthy subjects and in patients with schizophrenia, the sample size in our study was relatively small and the sample consisted entirely of females. This limits the generalization of our findings. It should be noted that in the present study no subjects were excluded on the basis of their performance on the task or because of the quality of the functional imaging data (i.e. none of the datasets exhibited clear motion artifacts). Further, our patient sample consisted of patients with mixed OCD symptomatology, which might have reduced the chance of finding significant correlations of performance or activity with the Y-BOCS scores.

In conclusion, our data corroborate the existence of a deficit in spatial working memory in OCD, especially at higher load-levels, and suggest that this is not related to a capacity problem of the working memory system, but is secondary to another disturbed aspect of executive functioning in OCD. The pattern of increased activity in the anterior cingulate might be related to the abnormal monitoring of performance, or some other disturbed (or compensatory) supervisory process, rather than to deficits in storing and manipulating information. Clearly, further research is needed to clarify the origin of the spatial working memory deficit and the role of the anterior cingulate in OCD. We are currently investigating the effects of pharmacological treatment of OCD on the load-activity pattern and performance found during the spatial *n*-back working memory task.

FIGURE 1

Illustration of the *n*-back task showing five trials of the 0-back and 3-back levels, together with the appropriate responses. Numbers are not presented during the task, but indicate the location of the stimuli and the corresponding responses.

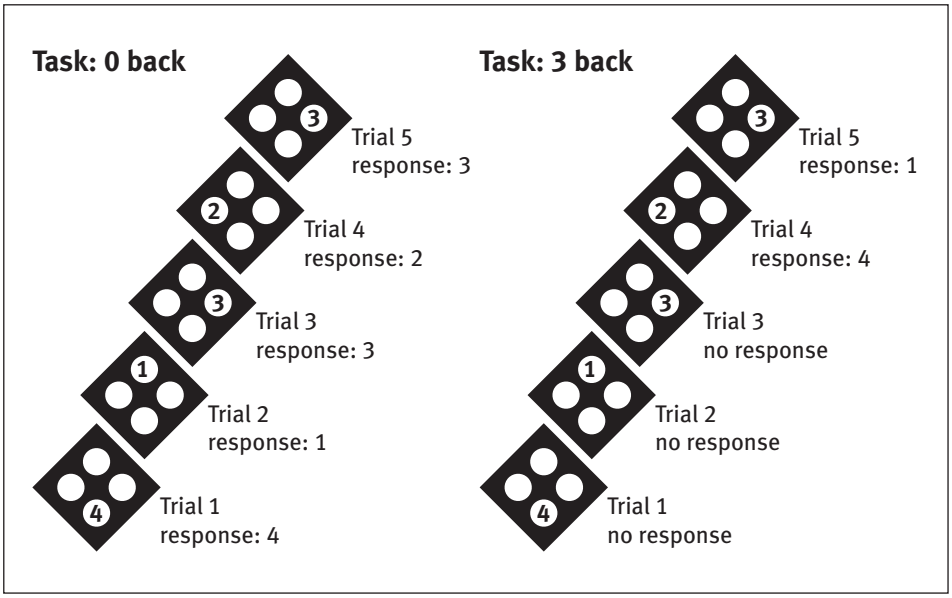



FIGURE 2

Performance of patients with OCD and matched controls on the *n*-back task. Graph representing mean percentage of errors (± sem) for each load level. (a): Significant difference between patients with OCD and controls, two-tailed Students *t*-test $p < 0.05$.

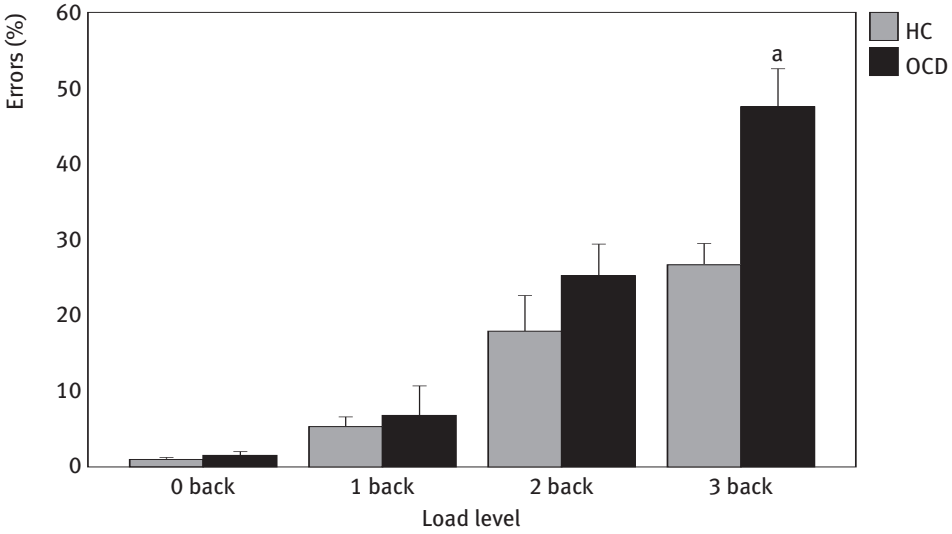
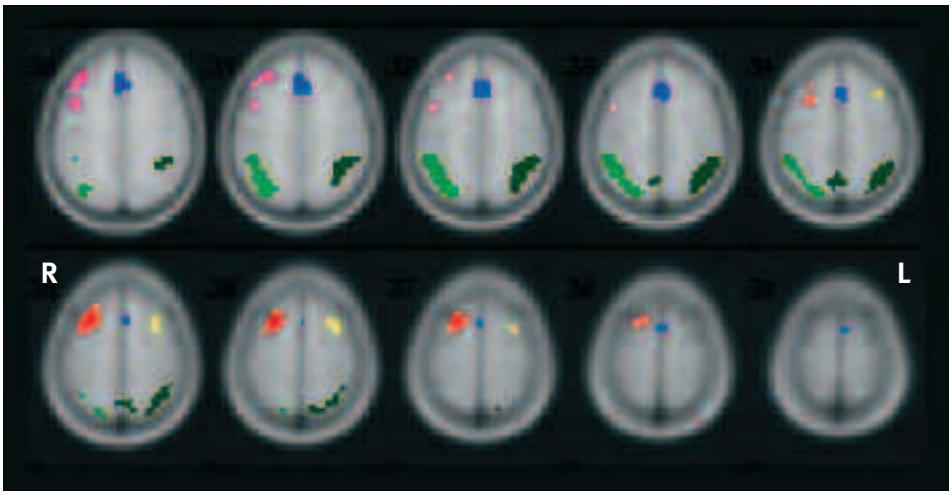


Figure 3

Transversal slices showing a number of group-wise clusters of activation, thresholded at t = 4.4 and with a cluster minimum of five voxels, projected on the Montreal Neuroimaging Institute average brain. OCD is obsessive-compulsive disorder, HC is healthy controls. R is right, L is left. Red is right prefrontal cortex (BA 6), yellow is left prefrontal cortex (BA 6), pink is right prefrontal cortex (BA 9/46), blue is anterior cingulate (BA 8), light green is right parietal cortex (BA 7), dark green is left parietal cortex (BA 40).

**OCD**




**HC**

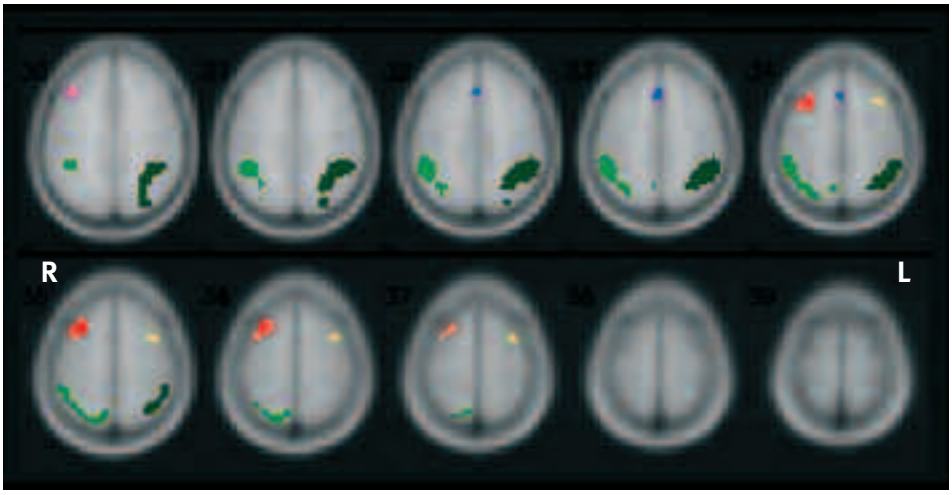


FIGURE 4

Load activity patterns of patients with OCD and matched controls in the resulting six common clusters on the *n*-back task. Activity versus rest is expressed as signal in arbitrary units (au). HC is healthy controls, OCD is obsessive-compulsive disorder.

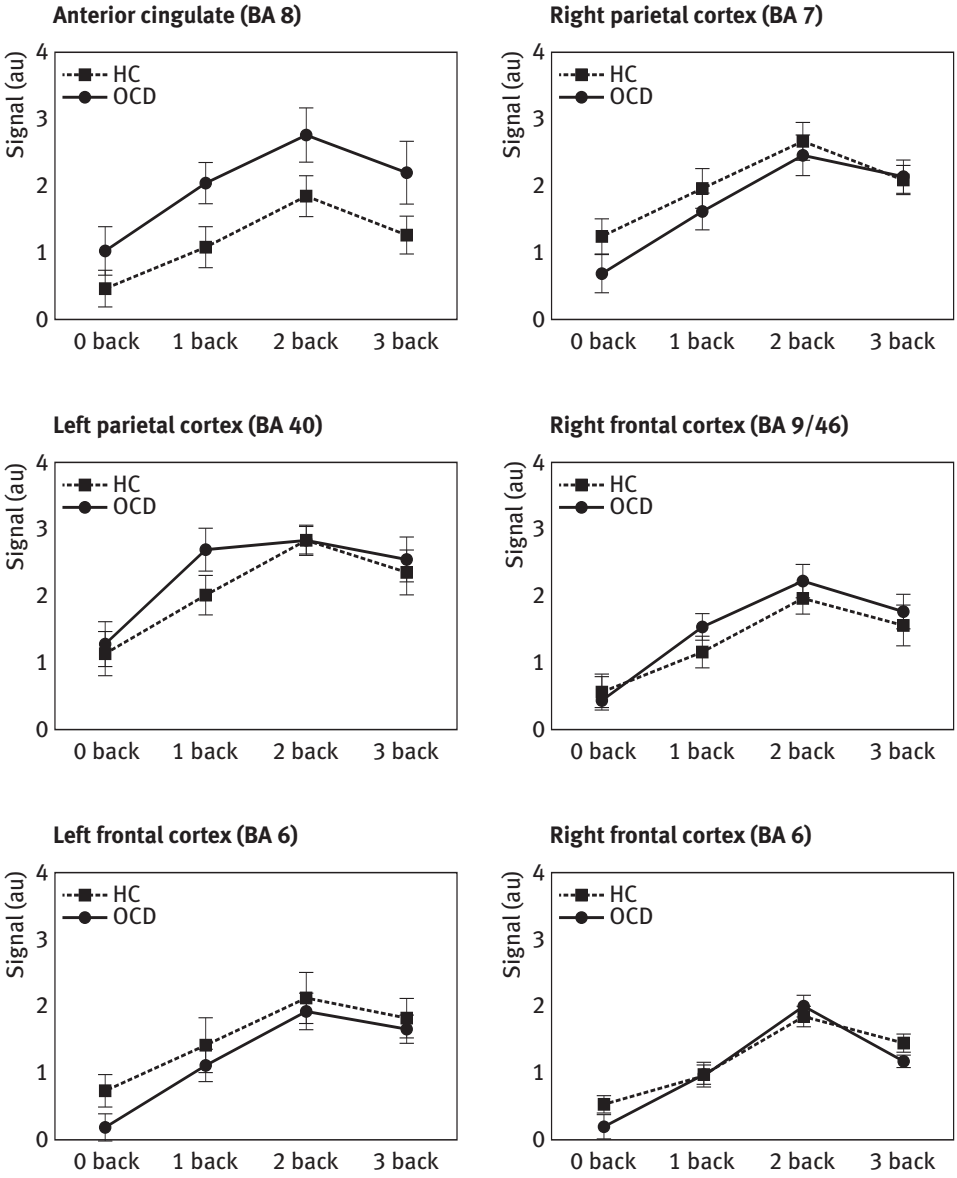


Table 1

Demographic and clinical characteristics of patients with OCD and pair-wise matched healthy controls

| Characteristics | Patients with OCD (N = 11) | Matched controls (N = 11) |
|---|---|---|
| Age (years) | 34.1 ± 9.6 | 34.8 ± 9.7 |
| Handedness | 0.95 ± 0.04 | 0.93 ± 0.03 |
| Sex | 11 females | 11 females |
| Level of education | middle 2, higher 9 | middle 2, higher 9 |
| Total Y-BOCS | 25.8 ± 3.1 | |
| Obsessions subscale | 12.9 ± 2.7 | |
| Compulsions subscale | 12.9 ± 1.4 | |
| Total HRDS | 8.0 ± 4.3 | |
| Total HAS | 11.3 ± 5.6 | |
| Medication | 6 naive, 5 drug free | |
| VAM-nervousness | 42.0 ± 22.0 | 33.0 ± 16.5 n.s. |
| VAM-anxiety | 36.5 ± 20.4 | 27.2 ± 14.0 n.s. |

Table 2

Regions involved in non-verbal working memory in patients with OCD and controls

| | OCD | | | | | Healthy controls | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Brodmann's area | NV | MNI Talairach coordinates | | | Brodmann's area | NV | MNI Talairach coordinates | | |
| Region | | | *x* | *y* | *z* | | | *x* | *y* | *z* |
| AC | 8 | 131 | -1 | 24 | 44 | 8 | 21 | 1 | 24 | 47 |
| PFC right | 9/46 | 186 | 43 | 31 | 30 | 9/46 | 19 | 47 | 41 | 19 |
| | 6 | 90 | 26 | 13 | 61 | 6 | 61 | 33 | 13 | 54 |
| PFC left | 6 | 28 | -29 | 13 | 58 | 6 | 17 | -36 | 8 | 58 |
| | 47 | 20 | -33 | 24 | 1 | | | | | |
| | 9/46 | 47 | -43 | 31 | 30 | | | | | |
| PC right | 7 | 211 | 21 | -74 | 53 | 7 | 211 | 29 | -66 | 54 |
| PC left | 40 | 232 | -49 | -49 | 53 | 40 | 176 | -47 | -52 | 51 |

OCD is obsessive-compulsive disorder, NV is number of voxels and MNI is Montreal Neuroimaging Institute. AC is anterior cingulate cortex, PFC is prefrontal cortex, and PC is parietal cortex. Overview of the resulting clusters of active voxels in patients with OCD and controls. Given are the approximate Brodmann area (BA) of the location of the peak activation, the number of activated voxels (NV) and the Talairach coordinates based on the MNI standard average brain.

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# Chapter IV

# Spatial working memory in obsessive-compulsive disorder improves with clinical response; a functional MRI study

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# Summary


## Background

To date, only a few studies have examined whether executive dysfunctions in obsessive-compulsive disorder (OCD) are state or trait dependent and none of these studies has used functional neuroimaging techniques. We used functional MRI to investigate the state or trait dependent nature of the spatial working memory deficit found in OCD.

## Methods

We conducted a functional MRI study before and after 12 weeks of pharmacological treatment in 14 psychotropic-free patients with OCD with no comorbid diagnoses. During each scan session subjects performed a spatial variant of a working memory task with four increasing levels of difficulty (*n*-back task).

## Results

Seven patients responded to treatment and seven did not. Responders and non-responders did not differ in clinical and demographical characteristics or brain activation patterns before treatment. Performance on the working memory task improved only in responders and was associated with a change in the overall pattern of brain activity during the task, but not with changes in the activity pattern of specific regions. We found no correlations between (changes in) scores on symptom scales, brain activity and performance.

## Conclusions

Spatial working memory deficits in OCD and their functional anatomical correlates, as assessed with a spatial *n*-back task, are, at least to some extent, state dependent.

# Introduction

Obsessive-compulsive disorder (OCD) is characterized by recurrent, persistent and intrusive thoughts or images that cause anxiety or distress (obsessions), and repetitive behaviors or mental acts aimed at reducing this distress or anxiety (compulsions). Patients recognize that the obsessions and compulsions are unreasonable and are products of their own mind. Recent epidemiological data suggest prevalence rates of OCD from 1,5% to 3%.[1-3]
Convergent evidence suggests a neurobiological basis for OCD, resulting in the current fronto-thalamo-striatal model of OCD. According to this model, obsessive-compulsive symptoms result from dysfunction of complex frontal, thalamic and striatal circuitry.[4;5] This circuitry is also known to be involved in executive functioning, i.e. higher-order processes necessary for effective and appropriate goal directed behavior, on the basis of which disturbances of executive functioning in OCD may be expected.
Indeed, studies examining cognitive and executive functioning in OCD have demonstrated deficits in several domains of executive functioning such as cognitive set-shifting, trial-and-error learning and inhibition capacities.[6-9] Subtle cognitive deficits in these domains have also been reported in sub-clinical populations.[10;11] More specifically, some recent studies, including the few functional imaging studies using a cognitive paradigm, have shown that OCD may be associated with specific cognitive deficits, taken to reflect fronto-striatal dysfunction.[12-15] One of the cognitive domains addressed in these studies is working memory, i.e. a system that regulates manipulation and short-term storage of information.[16] OCD patients perform poorly on tasks that engage spatial working memory (i.e. the working memory system that processes information on the location or position of items in space), especially when the task becomes more difficult.[12;13]
In a previous functional MRI study we assessed performance on a working memory task and the associated brain functioning in a carefully selected sample of patients and closely matched controls.[17] The working memory task employed in that study involves multiple levels of difficulty (load) and therefore enables visualization of the way in which the working memory system responds to increasing load. The advantage of this design is that it allows for determination of the relationship between level of difficulty, regional brain activity and performance. We used a spatial variant of the *n*-back working memory task that has been used in healthy volunteers and patients with schizophrenia.[18-20] In this task subjects see four large dots in a diamond shaped diagram with one dot changing color at a time (the stimulus). After each stimulus they have to indicate the location of a stimulus that has appeared a certain number of stimuli earlier (i.e. *n*-back). This variant of the *n*-back task consistently elicits activity bilaterally in dorsolateral prefrontal and parietal cortices, and in the anterior cingulate in patients with schizophrenia and in healthy controls. The involvement of these brain areas in (spatial) working memory has also been demonstrated in other functional imaging studies of working memory using other paradigms.[21-24] We found that patients with OCD performed poorly at the highest level of task difficulty but engaged the same brain regions as the matched healthy controls. Brain activity in a region covering the anterior cingulate cortex was significantly elevated in patients with OCD at all difficulty levels of this task.[17]
Although several studies have found executive dysfunctions and functional brain abnormalities in patients with OCD, to date only a few studies have examined whether these

dysfunctions are state or trait dependent and none of these studies has employed functional neuroimaging techniques. We therefore decided to investigate the state or trait dependent nature of the working memory deficit as found with the *n*-back task in OCD and the associated abnormal activity in the anterior cingulate cortex.[17] We conducted a functional MRI study before and after pharmacological treatment. To exclude the confound of prior treatment effects, we included only patients who were psychotropic-naïve or psychotropic-free for at least two weeks and who had not received cognitive behavioral therapy for at least three months. We hypothesized that the non-verbal spatial working memory deficit in OCD would improve (i.e. normalize) with successful treatment and thus be a trait dependent phenomenon.

# Methods and Materials

## Participants

Eighteen patients with OCD according to DSM-IV criteria and no other current Axis I or major Axis II pathology were enrolled. Patients were recruited from the outpatient department of the University Medical Center of Utrecht and participated in a large double blind study comparing the efficacy of paroxetine and venlafaxine in OCD, which is described elsewhere in greater detail.[25] Eleven subjects were right handed as assessed with the Edinburgh Handedness Score (EHS), had no history of illnesses with possible central nervous system sequelae and were in good physical health as confirmed by physical and laboratory examinations.[26] Screening for psychopathology was done by administering the Mini International Neuropsychiatric Interview IV (MINI-IV).[27] Diagnoses were confirmed by an experienced clinician (H.M, N.W). There were no patients with a lifetime history of psychosis, substance abuse, recurrent major depression, bipolar disorder, eating disorders, other anxiety disorders or tic disorders. Subjects used less than four units of coffee, two units of alcohol and six cigarettes a day. Patients were included when they had a minimum score of 16 on the Yale Brown Obsessive Compulsive Scale (Y-BOCS [28] and a maximum score of 13 on the Hamilton Depression Rating Scale (HAM-D [29a]). We also administered the Hamilton Anxiety Scale (HAM-A).[29b]

## Treatment

Subjects were scanned within two weeks after inclusion and subsequently started with the 12 weeks randomized clinical trial comparing the efficacy of paroxetine and venlafaxine in OCD. Using a fixed dosing schedule, dosages were titrated upward to paroxetine 60 mg or venlafaxine 300 mg daily in week seven and then continued till week twelve [25]. Patients were rescanned at the end of week 12. Immediately before all functional imaging sessions we administered a Visual Analogue of Mood Scale to assess nervousness and anxiety. At their first scan day patients were at least two weeks free of psychotropic medication and the severity of obsessive compulsive and depressive symptoms was assessed again. For patients who had used fluoxetine the medication washout period was extended to at least four weeks.

Patients did not receive any form of psychotherapy during the trial and cognitive behavioral therapy had been terminated at least three months before the first scan day. After complete description of the study to the subjects, written informed consent was obtained. The protocol was approved by the ethical committee of the University Medical Center of Utrecht.

## Working memory task

Subjects were trained on the working memory task for one hour before the start of the experiment. A video-projector was placed in the scanner control room to project stimuli from outside the control-room to a screen in front of the volunteer. A mirror enabled the subjects to see the screen.

Subjects had to perform a spatial variant of the *n*-back working memory task with four increasing levels of difficulty. The task was designed after Gevins [30] and has been used by our group and others in healthy volunteers and patients with schizophrenia.[18-20] Subjects looked at a screen, which showed four large dots in a diamond-shaped diagram indicating the four possible places where a stimulus could appear. The stimulus consisted of one dot changing color at a time. Subjects were instructed to respond to the stimulus by pushing one of four buttons on a pneumatic response button box with the right thumb. Layout of the four buttons corresponded spatially to the four possible positions in which the stimulus appeared. Responses had to be made either directly following the stimulus ('0-back'), or with a delay of one ('1-back'), two ('2-back') or three ('3-back') stimuli, hereafter referred to as 0B-1B-2B-3B. The level of difficulty was shown above the stimuli during the whole task. The different levels were run in blocks of 21 stimuli, with an interstimulus interval of 2.8 s, in total 59 s per block. The sequence of levels, including a baseline resting condition, was semi-randomized. In total each level was presented four times. During the rest condition no stimuli were presented and subjects simply looked at the background image of the task.

The design of the *n*-back task is such that in all levels, subjects have to respond to all stimuli, so the task requires a continuous monitoring and updating of information in working memory. The information that is presented during each trial is the same within all levels, as are the demands made on response selection and execution.

## Imaging procedure

After training subjects were allowed to familiarize with the scan setting. Extra care was taken to avoid provocation of OCS symptoms in patients with contamination obsessions, by changing sheets and by extensively cleaning the head support in the presence of patients. Immediately before the functional imaging we administered a Visual Analogue of Mood Scale (VAS) to assess nervousness and anxiety.

A total of 84 functional scans was acquired for each load level. FMRI scans were obtained with a Philips ACS-NT 1.5 T clinical scanner with PT6000 gradients, and a navigated BOLD 3D-PRESTO pulse sequence (parameters: TE/TR 37/24 ms, flip angle 10°, EPI factor 17, matrix 64*52*30, FOV 225*175*105, voxels 3.5mm isotropic, scan time 2.8 s) [31]. To compensate for the delay of the vascular response to neuronal activity, execution of the task started six seconds before the first functional scan. FMRI data were acquired in five blocks of 84 scans

(with 21 scans per load level or rest condition), lasting a total of approximately 20 minutes. The session was concluded with an anatomical scan (3D-FFE; TE/TR 4.6/30 ms; flip angle 30º; FOV 256 by 256 mm.; matrix 128 by 128 by 130 mm; slice thickness 1.2 mm; scan time seven minutes).

# Data Analysis

## Clinical characteristics

Response to treatment was conservatively defined as a decrease in the Y-BOCS total score of at least 35% at week 12 of the standardized pharmacotherapy. Differences between and within responders and non-responders in (changes in) scores on the rating scales were assessed using an ANOVA for repeated measures procedure or Mann Whitney U-tests or Wilcoxon signed rank tests when applicable.

## Performance

Performance on the *n*-back task was expressed as the average percentage incorrect or omitted responses for each subject on each different level of the task. Differences in performance between responders and non-responders were assessed using an analysis of variance procedure (ANOVA) for repeated measures with treatment-response as between-subject factor and level and time as within-subject factors. Changes in performance within groups were assessed using post-hoc Paired *t*-tests when applicable.

## fMRI data

The fMRI data were analyzed in three steps, similar to the procedure used in our previous studies and the methodology based on the random effects model as described by Ramsey et al.[17;32;33] The first step consisted of the generation of individual t-maps for each level of the task (contrasted with the rest condition), separately for pre- and post treatment datasets, analogous to a standard subtraction method.
Individual fMRI data were processed off-line on a HP™ workstation using PV-Wave™ processing software. All scans were registered to one high contrast functional scan to correct for rotation and translation between scans.[34] Scans were normalized for mean volume signal-intensity and a 3D gaussian filter (10,5 mm full width at half maximum) was applied to the functional scans. A voxel-wise multiple regression algorithm with four experimental factors (modeling the levels) and several signal drift factors was used to obtain individual activation t-maps for each of the four task levels vs. rest.[35] Three additional contrast maps were generated, for the contrast of the 1B-, 2B-, and 3B tasks vs. 0B to identify regions specifically associated with working memory, and exclude non-specific functions such as visual and motor processing.
In the next (second) step all individual activation maps were spatially normalized into stereotactic space by a linear registration to the Montreal Neuroimaging Institute (MNI) 305

average brain.[36] A group-wise t-map was obtained by using all individual contrast maps, and testing the values in each voxel against zero using the pooled variance calculated over all voxels. The resulting group-activation maps were thresholded at a t-value of 4.4. This value corresponds to a one-sided corrected p-value of 0.05, Bonferroni corrected for the total number of voxels.[37] Voxels with a t-value above 4.4 in any of the 'working memory' contrasts (1B-, 2B-, and 3B vs. 0B) were selected. Selected voxels that were neighbors at any point were clustered. A cluster minimum of five voxels was applied.
In the third and final step, the mean activity for every level was determined for each subject in each of the identified clusters. The mean activities were analyzed using ANOVAs for repeated measures procedure with response as between-subject factor and level, cluster and time as within-subject factors.

### Correlations

Correlations between activity in the clusters and performance at each level of difficulty were examined for all subjects together, and for responders and non-responders separately before and after treatment. Correlations with activity and with (changes in) performance at each load level were examined for the (changes in) Y-BOCS total score, the Y-BOCS obsessions and compulsions subscales, the HDRS-score, the HAS score, the VAS scores, medication history (naïve or not) and duration of illness. Correlations were assessed using Pearson and when applicable Spearman correlations coefficients. Significance level was set at $p = 0.05$ (two-tailed) and Bonferroni corrected for multiple comparisons. For all statistical evaluations SPSS (Version 9.0) software was used.

## Results

### Response to treatment

From the 18 patients who originally participated four patients were excluded from further analysis, two because they could not complete the treatment program and two others because of loss of performance data. Hence, the final analysis included 14 patients. There were seven responders and seven non-responders. There were no statically significant differences in the demographical and clinical characteristics of these two groups before treatment (see table 1). Although patients could be classified as having predominantly 'washing' or 'checking' symptomatology, most patients also had other obsessive-compulsive symptomatology.
Responders showed a mean decrease in Y-BOCS total score of 48.6%, (sd 14.1) with a significant decrease in HAS (Wilcox $Z = -2.37$, 0.018), but not in HDRS (Wilcox: $Z = -1.91$, 0.056). In non-responders there was also a significant decrease in total Y-BOCS score of 25.1% (sd 16.1), but there were no significant changes in HAS and HDRS. An ANOVA for repeated measures for the VAS scores showed no main effects and no significant interactions, indicating that anxiety and nervousness as elicited by the scanning procedure were comparable between the two scan sessions and did not differ between the two groups.

## Performance

ANOVAs for repeated measures and Bonferroni corrected post-hoc paired *t*-tests showed that performance improved significantly only in responders. First, an overall ANOVA for repeated measures for the responders and non-responders together showed a significant main effect of time ($F = 9.68$, df 1,12, $p = 0.009$), a significant time x treatment-response ($F = 6.72$, df 1, 12, $p = 0.024$), time x difficulty level ($F = 17.00$, df = 3, 10, $p = 0.000$) and a time x difficulty level x treatment-response interaction ($F = 4.32$, d.f. = 3,10. $p = 0.036$) and no significant between-subjects effects.
Next we performed ANOVAs for repeated measures for responders and non-responders separately to further analyze the interactions involving treatment response. In responders this ANOVA showed a significant main effect of time ($F = 29.91$, df = 1,6, $p = 0.002$), a significant main effect of difficulty level ($F = 23.50$, df = 3,4, $p = 0.005$) and a significant time x difficulty level interaction ($F = 23.39$, df = 3.9, $p = 0.005$). In non-responders only a main effect of difficulty level ($F = 20.43$, df = 3,4, $p = 0.002$) was found, indicating that treatment did not alter performance in this group.
Finally, Bonferroni corrected post-hoc paired *t*-tests for the performance in responders revealed a significantly decreased percentage of errors on the most difficult level after treatment ($t = 5.41$, df = 6, $p = 0.002$) (figure 1).

## Regions specifically involved in working memory

Identification of regions that were specifically involved in spatial working memory was based on clusters of at least 5 voxels with a t-value above 4.4 in one or more of the group 'working memory' contrast maps (1B-, 2B-, and 3B vs. 0B). A comparison of group-maps constructed for each group separately (responders and non-responders) did not reveal different patterns, i.e. responders and non-responders activated the same brain areas during the working memory task. Several bilateral clusters in the frontal and in the parietal cortex were identified. The clusters in the frontal cortex consisted of a region in the medial frontal cortex containing the anterior cingulate cortex and extending to the supplementary motor cortex, and a bilateral prefrontal region containing clusters in the dorsolateral prefrontal and premotor cortex. In the parietal cortex a bilateral cluster was present.

## Signal analysis in brain regions associated with working memory

ANOVAs for repeated measures for the activity levels in the seven identified regions showed that the activity patterns during the task in the two groups were similar before treatment. After treatment responders showed a significant change in the overall activity pattern of the seven regions (figure 2). There were no significant changes in the activity pattern of individual regions. In non-responders there were no significant changes in activity pattern after treatment.
For the signal analysis we first entered the t-values of individual subjects before treatment, averaged across voxels within each of the seven common regions identified, into ANOVAs for repeated measures. To allow for a sufficient number of degrees of freedom for the planned

ANOVAs for repeated measures, activity in the VOIs was normalized by subtracting the activity at the 0B level from 1-, 2- and 3-B.
The ANOVA for repeated measures for the activity in responders and non responders before treatment showed a significant main effect of difficulty level ($F = 13.86$, $df = 2,11$, $p = 0.001$), but no main effect of region and no significant interactions involving response indicating that the task related activity patterns in the two groups were similar before treatment.
An overall ANOVA for repeated measures for the two groups (factor 'response') together before and after treatment (factor 'time') showed a main effect of difficulty level ($F = 15.88$, $df = 2, 11$, $p = 0.001$), but no main effect of time or region. Time x difficulty level interaction, and time x difficulty level x response interaction were significant (($F = 3.96$, $df = 2, 11$, $p = 0.050$), and $F = 4.8$, $df = 2,11$, $p = 0.032$ respectively). There were no significant interactions involving the within-subject factor region.
Following up on the time x difficulty level x response interaction, post-hoc paired *t*-tests for the average activity at each difficulty level indicated that the pattern changed in responders only. Responders showed a significantly decreased activity at the 1B and 2B level ($p = 0.007$ and $p = 0.006$ respectively), resulting in a more linear increase of the activity pattern, as opposed to the non-responders who maintained the drop in the activity at the 3B level.

### Correlations

Before and after treatment there were no significant Bonferroni corrected correlations between the activity in any of the clusters or the mean overall activity per load level for all clusters, and the performance at any load level. There were also no significant Bonferroni corrected correlations between the activity in any of the clusters or the mean overall activity per load level for all clusters and the (changes in) performance or (changes in) scores on the clinical rating scales and the medication history.

## Discussion

Treatment-free patients with OCD with no comorbid diagnoses were tested on a parametrically controlled spatial *n*-back working memory task before and after pharmacotherapy. Clinical response of OCD symptoms was found to be associated with an improvement of the performance on the working memory task and with an overall change in brain activity during increasing task difficulty. This indicates that spatial non-verbal memory deficits in OCD and their functional anatomical correlates, as assessed with this *n*-back task, are, at least to some extent, state dependent.
The brain circuit subserving spatial working memory as determined in our study involved the medial frontal lobe, anterior cingulate, and the dorsolateral prefrontal and parietal cortex bilaterally. This set of areas is typical for this task, as has been reported in previous functional imaging studies of non verbal working memory that used the same spatial variant of the *n*-back task.[18-20]
At baseline the brain activity pattern of the patients during increasing task difficulty was comparable to that found in our previous study.[17] This brain activity pattern indicated that in

patients with OCD worsening of performance with increasing difficulty of the task is not due to a reduced activity of the working memory system. After treatment, we found in responders a combination of a better performance and a more linear increasing brain activity pattern during increasing task difficulty. This reflects that the working memory system was better capable of processing information in these patients.

To date, only a limited number of studies have examined the effect of treatment status or response on neuropsychological performance in OCD. So far, these studies have yielded inconsistent results. Most studies found no effect of treatment on neuropsychological performance, but some reported limited improvement or even worsening of performance.[38-41] However, several studies had methodological limitations, such as the inclusion of patients with comorbidity or different treatment status or the use of less specific neuropsychological tests.[43] Furthermore, only a few studies used a within-subject design. None of these studies used an experimental paradigm comparable to the spatial *n*-back task, so it is not possible to compare our results directly.

Our data indicate that the nonverbal spatial working memory deficit in OCD as assessed with the *n*-back task and the associated brain activity pattern have a state-dependent component. This suggests that that the brain circuitry involved (or one or more of its components) is related to the severity of OCD symptomatology. This relationship could be a causal or a more epiphenomenological one. It has been suggested earlier that a deficit in specific aspects of non-verbal memory may give rise to the checking and doubt found in many patients with OCD.[44] Several neuropsychological studies have indeed reported deficits such as a reduced memory for actions or a reduced confidence in own memory in patients with OCD that could explain the frequent checking and doubt in many forms of OCD.[45] On the other hand, a deficit in non-verbal memory would not explain many other symptoms of OCD, such as aggressive obsessions or superstitious rituals.[46] Similar to our study, most neuropsychological studies investigating (working) memory in OCD found no or only very weak correlations between test measures and symptomatology, indicating that a non-verbal or spatial (working) memory deficit should not be considered causal for OCD. Furthermore, findings from recent studies suggest that a reduced performance of patients with OCD on working memory tasks may be secondary to a reduced capacity to develop or apply an efficient strategy and not to a dysfunction of the working memory system proper.[12;13;43;47] We hypothesized earlier that the hyperactivity in the cingulate area found in patients with OCD when performing the *n*-back task might be associated with such a reduced capacity to develop or apply a strategy [17]. However, the improvement of performance on our *n*-back working memory task in responders was associated with a global change of the brain activity pattern during increasing difficulty and was not limited to the cingulate, which seems to argue against the notion of the anterior cingulate being hyperactive because of strategy problems.

To our best knowledge this is the first study in patients with OCD to directly investigate the effect of clinical improvement on an aspect of executive dysfunction and the associated brain activity pattern. We used a carefully selected sample of patients, a standardized pharmacotherapy and a task with increasing difficulty levels that enables visualization of the way the non-verbal spatial working memory system responds to increasing load. It should be noted that in the present study no subjects were excluded on the basis of their performance

on the task or because of the quality of the functional imaging data (i.e. none of the datasets exhibited clear motion artifacts).

There are also some limitations to our study to consider. Although comparable to other studies examining executive functioning in OCD, the sample size was relatively small. Our patient sample consisted of patients with mixed OCD symptomatology, which might have reduced the chance of finding significant correlations of (changes in) performance or activity with the Y-BOCS scores. We did not use a control group of matched healthy volunteers, which would have allowed us to assess more specifically if performance and the associated brain activity patterns tend to normalize with response. It cannot be ruled out that the spatial working memory deficit in OCD also has a trait dependent component. However, this issue can only be addressed adequately in a group of patients with a full remission of symptoms, which is a rarely the case in OCD. In our study subjects were only examined after twelve weeks of standardized pharmacotherapy and not after shorter intervals. Hence it was not possible to examine if the improvement in performance on the *n*-back task preceded a clinical response, i.e. was an early marker for response. Finally, one could argue that the absence of a control group does not allow for an assessment of possible learning effects. However, all subjects were trained for one hour before each session, which was sufficient to reach a plateau in performance, thereby reducing possible learning effects. Furthermore, it has been shown by others that the group-average pattern and magnitude of activation in an *n*-back working memory task does not change with repeated testing. This was observed for healthy controls as well as for schizophrenic patients [21].

In conclusion, our data show that the spatial non-verbal working memory deficit in OCD, as assessed with our *n*-back task, improves with response to treatment and that this improvement is associated with a more linear pattern of the activity of the spatial working memory system during increasing task difficulty. This indicates that spatial non-verbal memory deficits in OCD and their functional anatomical correlates are, at least to some extent, state dependent.

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TABLE 1

Demographic and baseline clinical data of responders and non-responders

| Subject characteristics | Responders (n = 7) Mean (± SD) | Non-Responders (n = 7) Mean (± SD) | *p* |
|---|---|---|---|
| Age (y) | 27.6 ± 3.2 | 29.0 ± 2.8 | n.s. |
| Gender (M/F) | 4/3 | 3/4 | n.s. |
| Y-BOCS total | 24.4 ± 3.8 | 24.7 ± 2.2 | n.s. |
| Y-BOCS obs. | 11.7 ± 1.8 | 12.5 ± 1.6 | n.s. |
| Y-BOCS comp. | 12.7 ± 2.3 | 12.1 ± 1.7 | n.s. |
| HDRS | 7.5 ± 3.8 | 7.8 ± 4.2 | n.s. |
| HAS | 10.0 ± 4.0 | 11.2 ± 5.4 | n.s. |
| Psychotropic naïve/free | 3/4 | 3/4 | n.s. |
| Onset early/late | 3/4 | 2/5 | n.s. |
| Checkers/washers | 4/3 | 3/4 | n.s. |

OCD is obsessive-compulsive disorder, Y-BOCS is Yale Brown Obsessive Compulsive scale, HAM-D is Hamilton Depression scale, and HAM-A is Hamilton Anxiety scale

Figure 1

Performance on the *n*-back task of responders and non-responders before and after treatment. Resp-pre is responders before treatment, non-pre is non-responders before treatment, resp-post is responders after treatment, non-post is non-responders after treatment. (a) Significant difference between responders before and after treatment, two-tailed (p = 0.002).

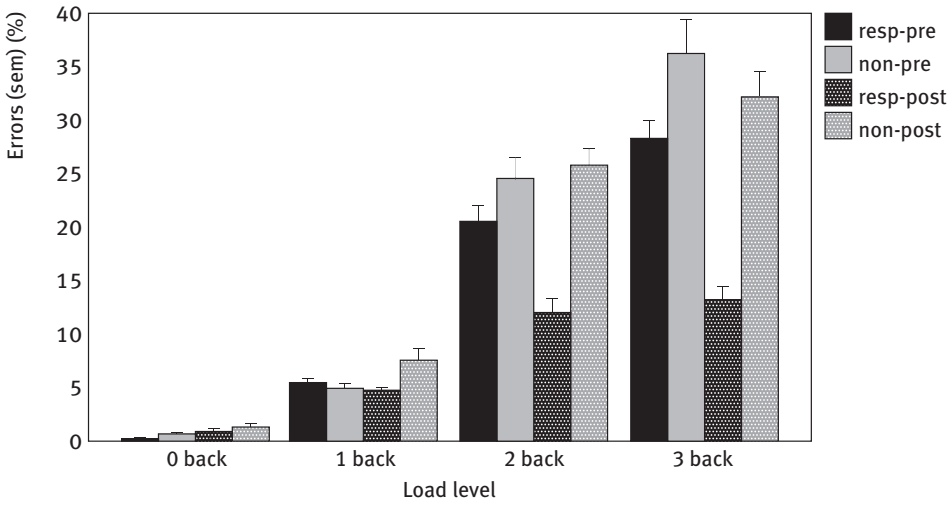
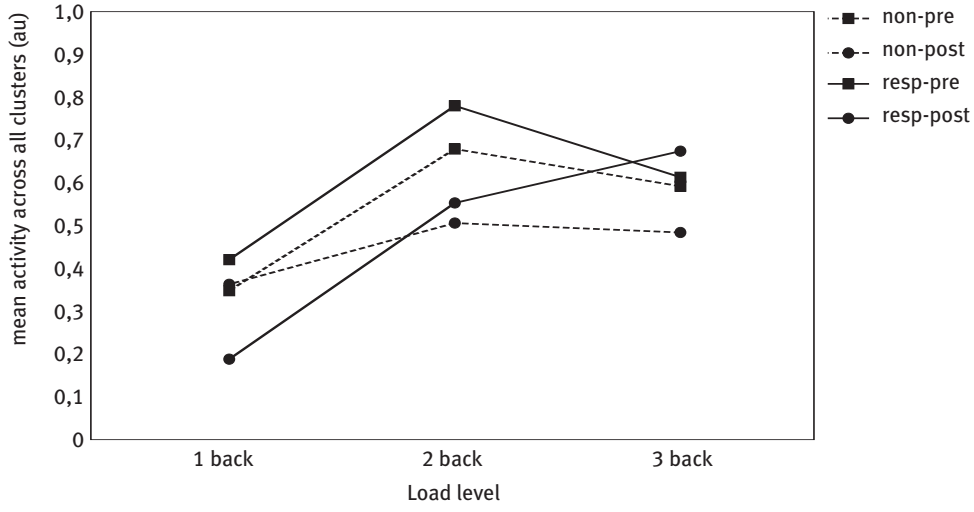



Figure 2

Mean normalized activity across all clusters per load level for responders and non-responders, before and after treatment. Activity is expressed in arbitrary units (au). Non-pre is non-responders before treatment, non-post is non-responders after treatment, resp-pre is responders before treatment, and resp-post is responders after treatment.



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*Section 2*

# *Neurochemistry*

# Chapter V

# Enhanced densities of dopamine transporters in psychotropic-naïve patients with obsessive-compulsive disorder shown by [123I]Beta-CIT SPECT

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# Summary


## Objective:

In obsessive-compulsive disorder (OCD) perturbations of the serotonergic and dopaminergic systems are postulated, but the functional anatomy of these neurotransmitter systems in OCD has never been investigated in psychotropic-naïve patients with no comorbid diagnoses.

## Method

[$^{123}$I]beta-CIT binding patterns for dopamine and serotonin transporters in the brain were measured in 15 psychotropic-naïve adult outpatients with OCD and no comorbidity and in 15 pair-wise matched healthy subjects. Volumes of interest were constructed on magnetic resonance imaging scans and coregistered with single photon emission tomography scans. Binding ratios were compared and possible correlations between binding patterns and obsessive-compulsive symptomatology were assessed.

## Results

There were significant differences between patients and subjects in the binding pattern of [$^{123}$I]beta-CIT for the dopamine transporter in the left caudate and left putamen. Patients had higher binding ratios than controls. No differences were found in the less specific binding pattern of [$^{123}$I]beta-CIT for serotonin transporters in the selected volumes of interest. Hemispheric within-group comparisons revealed no asymmetry effects.

## Conclusions

The results of our study provide direct evidence for an involvement of the dopaminergic system in the pathophysiology of OCD.

# Introduction

Obsessive-compulsive disorder (OCD) is characterized by recurrent, persistent and intrusive thoughts or images that cause anxiety or distress (obsessions), and repetitive behaviors or mental acts aimed at reducing this distress or anxiety (compulsions). Patients recognize that these obsessions and compulsions are unreasonable and products of their own mind. Once considered rare, recent epidemiological data suggest prevalence rates of OCD from 1,5% to 3%.[1;2] In general, OCD symptoms can best be managed with serotonin reuptake inhibitors (SRIs) and/or behavioral therapy. The selective response of OCD patients to SRIs has led to the hypothesis that changes in the central serotonergic systems may be the mechanism by which these compounds exert their effect.[3] Direct evidence that serotonergic perturbations are implicated in the neurobiology of OCD, however, is sparse. Studies with serotonergic pharmacological challenges and CSF metabolite studies have yielded data that are too inconsistent, or too open to different interpretations, to serve as a valid basis for dissecting out the neurobiology of OCD.[3-5] Growing evidence that atypical antipsychotics, such as risperidone and quetiapine, may augment the response to SRIs in refractory OCD patients and in patients with comorbid tics and studies showing an exacerbation of symptoms after administration of a dopamine agonist, would seem to point to an increased activity of dopaminergic systems in OCD.[6;7] The role of dopamine in stereotypic behaviors in animal models and the preclinical evidence of important interactions between serotonergic and dopaminergic systems further strengthen the putative role of dopamine in OCD.[8;9] Studies examining the concentration of the dopamine metabolite homovanillic acid and the dopaminergic regulation of the hypothalamo-pituitary-adrenal axis lend further support to a possible role of dopamine in the pathophysiology of OCD.[10;11] Neuroimaging studies have been very influential in shaping neurobiological models of OCD. Converging data have implicated a network of brain regions, including orbitofrontal cortex, striatum and thalamus, in the pathophysiology of OCD. Most regions of the putatively involved network in OCD are densely innervated by serotonergic and/or dopaminergic neurons.[12] However, despite the advent of several ligands for dopaminergic and serotonergic binding sites suitable for positron emission tomography (PET) or single photon emission computed tomography (SPECT), the functional anatomy of these neurotransmitter systems in OCD has scarcely been investigated. A commonly used ligand is [$^{123}$I]beta-CIT ($^{123}$ I labeled 2ßcarbomethoxy3ß(4iodophenyl)tropane), a SPECT ligand enabling visualization of both serotonin (5-HTT) and dopamine (DAT) transporter in the brain. [$^{123}$ I]beta-CIT has already been used extensively to investigate several psychiatric and neuropsychiatric disorders.[13] Binding of [$^{123}$ I] beta-CIT in the striatal region has been shown to reflect mainly binding to the DAT, binding to the 5-HTT occurs predominantly in the thalamus, midbrain and pons, but the binding in these regions might also reflect densities of other monoamine transporters to an unknown proportion.[14;15] Differences in binding characteristics of [$^{123}$ I]beta-CIT for the DAT and 5-HTT also make temporal separation of the transporter occupancy possible.[16;17] Due to these characteristics densities of both DAT and 5-HTT can be visualized in the same subject after a single administration of the ligand. The present study sought to examine possible differences in binding patterns of [$^{123}$ I]beta-CIT in patients with OCD and age, sex and handedness pair-wise matched healthy controls. In order to further reduce the number of

potential confounders only psychotropic-naive patients with OCD with no comorbid diagnoses and with no previous history of any other major psychopathology were included. We hypothesized that as a result of a putatively increased activity of dopaminergic systems in OCD, the binding patterns of [$^{123}$ I]beta-CIT in OCD would reflect higher densities of DAT.

# Methods and materials

## Subjects

Psychotropic-naïve patients with OCD with no comorbid diagnoses were recruited from the 375 patients with OCD as primary diagnosis referred to the anxiety research unit of the Department of Psychiatry at the University Medical Center of Utrecht from 1997 to 2001. Most patients came from direct physician referrals. Healthy controls were enrolled through advertisements in flyers and newspapers or obtained from an existing database. Only subjects without a lifetime history of psychosis, substance abuse, recurrent major depression, bipolar disorder, eating disorders, other anxiety disorders, tics and stuttering were included. Furthermore, all subjects had no first-degree history of a major DSM-IV axis I disorder (except for OCD in patients) or tics. All subjects had no lifetime history of illnesses with possible central nervous system sequelae and were in good physical health, as confirmed by physical and laboratory examinations. Subjects consumed less than six cups of coffee, four units of alcohol and six cigarettes a day. Screening for current and prior adult psychopathology was done by administering the Mini International Neuropsychiatric Interview IV (MINI-IV).[18] Diagnoses were confirmed by an experienced clinician (H.M, N.W.). Handedness was determined by administering the Edinburgh Handedness Scale.[19] Patients had to have a minimum score of 16 on the Yale Brown Obsessive Compulsive Scale (Y-BOCS) and a maximum score of 13 on the Hamilton Depression Rating Scale (HAM-D).[20-22] Subjects underwent imaging procedures within two weeks after screening. Patients had not received any form of psychotherapy, especially cognitive behavioral therapy, within the three months preceding the study. The protocol was approved by the ethical committee of the University Medical Center of Utrecht. After complete description of the study to the subjects, written informed consent was obtained.

## Image acquisition and analysis

At the first day of SPECT scanning, subjects received an intravenous injection of approximately 150 MBq of [$^{123}$I]beta-CIT (MAP Medical Technologies, Finland, radionuclidic purity ($I^{125}$ /$I^{123}$) of at least 9,5 x $10^{-3}$ at calibration time and a radiochemical purity of at least 95%). We used a Picker Prism 3000 triple-headed gamma camera with ultra high resolution fan beam collimators and a full-width at half-maximum of approximately 12 mm. Four hours after the injection the first scan was made to assess the binding in the 5-HTT rich regions. Between 22-24 hours after the injection the second scan was performed to measure the binding to the DAT.[16] Subjects refrained from coffee and nicotine in the six to 10 hours preceding each SPECT scan. Immediately after the first scan, subjects received 20 mg of

paroxetine to displace the radiolabeled beta-CIT from the 5-HTT, to enable more precise determination of binding to the DAT.[16] Several studies have demonstrated that the occupation of the serotonin transporters is virtually maximal at modest oral dosages (i.e. 10 mg) of paroxetine and other potent 5-HT re-uptake blockers.[14;23] To control for possible differences in metabolism between subjects we choose a dosage of 20 mg. Paroxetine was well tolerated by all subjects. During scanning subjects were in supine position with eyes and ears open and with their head fixated in a head holder. We ensured that patients stayed awake and did not move. For an accurate determination of each subject's volumes of interest (VOIs), all subjects also underwent structural magnetic resonance imaging (MRI) (3D-FFE; TE/TR 4.6/30 ms; flip angle 30º; FOV 256 by 256 mm.; matrix 128 by 128 by 130 mm; slice thickness 2 mm) two hours before the injection of [$^{123}$I]beta-CIT. MRIs were reoriented to the standardized coordinate system of the Montreal Standard brain.[24] VOIs were delineated manually on the reoriented MRIs by a researcher (J.H.) blind to subjects' identity and diagnosis, by means of the Display software from Brain Imaging Center of the Montreal Neuroimaging Institute.[25] Because previous studies suggested possible hemispheric asymmetries of the DAT densities in healthy subjects and loss of this asymmetry in specific psychiatric populations, we decided to examine VOIs bilaterally.[26;27] VOIs for the 5-HTT rich regions included the left and right thalamus, the midbrain and the pons, and for the DAT the left and right caudate nucleus, and the left and right putamen. The cerebellum was used as a reference region, representing the non-specific binding for [$^{123}$I]beta-CIT.

To allow for exact co-registration of MRI and SPECT scans, fiducial markers were used. Fiducial markers were cone-shaped with cross-shaped feet and placed on the nose bridge and preauricular above the mandibular joints. The position of each marker was indicated with four dots on subjects' skin to allow for repositioning of markers immediately before the SPECT scans. Vitamin A and Co$^{57}$ were used as contrast agents for the MRI and SPECT scan, respectively. The energy peak for [$^{123}$I]beta-CIT was set at 160 keV with a window of 20% and at a peak of 120 keV with a window of 15% for Co$^{57}$. After standard processing, brain SPECT images were resliced to isotropic voxels with dimensions of 2 mm and further treated as 3D volumes to coregister within the three dimensional orientation of the MRIs. Co-registration was performed semi-automatically based on the position of the fiducial markers, using the Register multimodality software package and additional software developed at the Brain Imaging Center of the Montreal Neurological Institute [25]. The researcher performing the co-registration (N.W) was blind to subject identity and diagnosis.

For each separate VOI the ratio of the specific binding of [$^{123}$I]beta-CIT was calculated according to methodology used in previously published [$^{123}$I]beta-CIT studies as the average radioactivity count per voxel per VOI minus the average radioactivity count per voxel in the cerebellum/average radioactivity count per voxel in the cerebellum.

## Statistical analyses

Age was compared using a Students *t*-test. The intra-rater and inter-rater quality for the VOIs procedure was assessed by calculating intraclass correlations according to the method used by Bartko and Carpenter.[28] The specific binding ratios for [$^{123}$I]beta-CIT for each VOI were compared using Mann-Whitney U tests. Within group comparisons of hemispheric binding

ratios in bilateral VOIs were performed using Mann-Whitney U tests. Spearman rank correlations were calculated to assess correlations between specific binding ratios and Y-BOCS total and subscale scores. Two-tailed significances are reported throughout.

# Results

From the 375 patients with OCD as primary diagnosis referred to our specialized unit from 1997 to 2001, 104 had never received treatment with an SRI.[29] Unfamiliarity with OCD treatment guidelines, as well as several patient related factors may underlie this lack of adequate treatment. Fifty patients were psychotropic-naïve. Eighteen psychotropic-naïve patients fulfilled the inclusion criteria and finally 15 patients participated. Controls were mainly recruited from the existing database. Six potential controls refused participation. All subjects completed the study. Patients and controls were perfectly matched for gender and did not differ significantly in age (patients 31.4 ± 9.0, controls 32.0 ± 9.5 years) and handedness. Demographic and clinical characteristics are shown in Table 1. Almost all subjects were non-smoker. The patient group was heterogeneous for symptomatology. Five patients had predominantly obsessions of contamination and compulsions of washing, six obsessions of doubt and compulsions of checking, two predominantly aggressive obsessions and compulsions of counting and two mixed symptomatology. Most patients had a juvenile onset (before the age of 18) of OCD. Although most patients had some aspects of depressive symptomatology, as reflected in the average Hamilton depression scores, none fulfilled criteria for a depressive episode or dysthymia or any other comorbid disorder at screening. Four patients had a prior single episode of a DSM-IV depressive episode NOS (in two patients with dysthymic and in two with more depressive features). One patient had a history of two DSM-IV depressive episodes NOS, one with dysthymic and one with more depressive features. One patient had received a form of supportive psychotherapy for his depressive symptoms.

Six patients had never received any form of treatment for their OCD. Six others had received a form of supportive or psychoanalytic therapy. Three patients had received a form of cognitive behavioral therapy for a short period of time and without any noticeable effect. In these patients the cognitive behavioral therapy was stopped at least 18 months before scanning.

In one patient the first SPECT scan (at 4 hours after injection) could not be reliably co-registered to the MRI because of motion artifacts, so the final analysis for the binding in the 5-HTT rich regions involved 14 patients and 14 pair wise-matched controls. The intraclass correlation coefficients for the intra-rater and inter-rater reliability of the VOI procedure were between 0.89 and 0.98 (mean 0.94, SD ± 0.04) and between 0.86 and 0.99 (mean 0.95 ± SD 0.05) respectively.

Mann-Whitney U-tests revealed a significantly higher average binding ratio to the DAT in the left caudate ($p = 0.004$) and in the left putamen ($p = 0.005$) of patients with OCD, compared to the matched healthy controls (Figure 1). There were no significant differences in average binding ratios to the DAT in the right caudate and right putamen (Table 2.) Patients with juvenile onset and patients with adult onset had similar average binding ratios to the DAT. There were also no significant differences in average binding ratios between the different

subtypes of OCD. Hemispheric within group comparisons for patients and controls revealed no significant asymmetry effects. No significant correlations were found between binding ratios to the DAT and scores on the Y-BOCS total and subscales or duration of illness.
No significant differences in binding patterns were found between patients with OCD and healthy controls in the 5-HTT rich regions, i.e. the left and right thalamus, midbrain and pons (Table 2). Hemispheric within group comparisons revealed no asymmetry effects. No significant correlations were found between binding ratios in the thalamus, midbrain and pons, and scores on the Y-BOCS total and subscales and the duration of illness.

# Discussion

We found significantly higher binding ratios of [$^{123}$I]beta-CIT, an index of dopamine transporter density, in the left basal ganglia of psychotropic-naïve patients with OCD with no comorbid diagnoses, compared to age and sex pair-wise matched healthy controls. No abnormalities in binding ratios to the 5-HTT rich regions in the midbrain, thalamus or pons were found.
To our best knowledge this is the first study examining central 5-HTT and DAT densities in a carefully selected group of psychotropic naïve patients with OCD. Interestingly, in a recent [$^{123}$I]beta-CIT SPECT study in Tourette's syndrome, a disorder that is purported to have also basal ganglia abnormalities, no abnormalities in 5-HTT and DAT densities were found in the basal ganglia, midbrain and thalamus.[30] Results obtained in OCD with functional neuroimaging studies using other methodologies most consistently show abnormalities in the right caudate and right orbitofrontal cortex, normalizing after treatment.[31] Although this seems suggestive of some form of lateralized functional abnormality in OCD, this is not postulated in the prevailing neurobiological model of OCD.
We did not find hemispheric asymmetries of binding ratios for the DAT and 5-HTT in any of the bilateral brain structures of both patients with OCD and healthy controls. The results of previous studies examining hemispheric asymmetries of the DAT densities in healthy subjects and neuropsychiatric conditions are inconsistent with these findings. Differences in radioactive ligands, neuroimaging techniques and the number of subjects may account for these discrepancies. Thus, in a small PET study examining DAT densities in patients with schizophrenia and healthy controls with a radiolabeled form of 2-beta-carbomethoxy-3-beta-(-4-fluorophenyl)tropane ([$^{18}$F]-CFT), hemispheric asymmetry was only found in the caudate of healthy controls.[26] In contrast, a SPECT study with a radiolabeled cocaine analog (99Tc TRODAT) in healthy volunteers did not reveal hemispheric asymmetries in binding ratios to the DAT in caudate and putamen.[32] However, in a very large [$^{123}$I]beta-CIT SPECT study examining age-related decline in DAT densities in 126 healthy subjects, higher binding ratios in the left caudate and putamen were found.[27] Although standard templates were used instead of VOIs defined on co-registered MRIs, these findings suggest that the sample in our study may have been too small to detect hemispheric asymmetries within groups.
The data from our present study in psychotropic-naive patients clearly suggest a role for the DAT in the pathophysiology of OCD. Theoretically, the higher dopamine transporter densities in the left basal ganglia of psychotropic-naïve patients with OCD, as measured by the binding

ratios of [$^{123}$I]beta-CIT, may be either due to a primary abnormality at the level of the transporter or secondary to other abnormalities. Higher transporter densities may result from a higher homeostatic tone of the dopaminergic system, with lower densities of D1 and D2 receptor.[33;34] The possible role of a higher dopaminergic activity in the left basal ganglia in the pathophysiology of OCD still needs to be elucidated. Both dopamine (through D1 and D2 receptors) and serotonin (e.g. through 5-HT2 receptors) are known to have a modulatory influence on the activity of excitatory (i.e. glutamate) and inhibitory (i.e. GABA) neurotransmitters in the basal ganglia and their cortico-thalamo-limbic connections. Furthermore, both the serotonergic and dopaminergic system are known to modulate each others activity in parts of the fronto-thalamo-basal ganglia circuitry supposedly involved in OCD.[35-37] Data on the exact nature of these interactions are still inconclusive. Finally, based on the results of the present study it is not possible to dissect out whether dopaminergic abnormalities are causal or epiphenomenonal to OCD.

Our study has several strong points. Patients and controls were pair-wise matched and the patient group consisted of a population with no comorbid diagnoses (especially tics), which had never been exposed to psychotropic drugs and for the most part also not to psychotherapy. Furthermore, SPECT data were analyzed using co-registered MRI, allowing for more precise determination of the VOIs.

There are also some possible limitations to this study. The patient group was heterogeneous for OCD symptomatology, reducing the chance of finding abnormalities related to a particular subtype of OCD.[38]. We did not match female subjects for the stage of menstrual cycle, but the stage of menstrual cycle was noted at time of scanning. Four female patients were scanned in the first two weeks of their menstrual cycle, the remaining four (two patients and two controls) in the last two weeks. Although we included several important parts of the putative disturbed fronto-thalamo-cortical circuitry in OCD in our VOIs, other areas could not be investigated in this study. Considering the dispersion of the data, the power of our study may have been too small to detect a bilateral increase in dopamine binding potential in the basal ganglia. Such a bilateral increase in dopamine binding potential could theoretically result from differences in the frequency of the DAT SLC6A3 genotype, in previous studies associated with DAT availability.[39].

We found no abnormalities in binding ratios for the 5-HTT rich regions of psychotropic-naïve patients with OCD. However, [$^{123}$I]beta-CIT binding to these regions is probably also reflecting availability of other monoamine transporters to an unknown proportion. The time point for visualization for may have further limited the possibility of finding abnormalities at the level of the 5-HTT, as is illustrated by the study of Willeit et al. in seasonal affective disorder.[40]. In the latter study the 5-HTT was visualized at 4 hours and at 24 hours after injection of the ligand, when a pseudoequilibrium state is reached. Differences were found only in the SPECT acquisitions at 24 hours after the injection. In the present study a 5-HTT inhibitor was administered after the first scan on order to displace [$^{123}$I]beta-CIT from the 5-HTT. Hence, the 5-HTT could not be visualized at 24 hours after the injection.

Finally, it should be mentioned that although SPECT is easier to use, has a higher safety index and is less expensive than PET, it has also relative disadvantages like the poorer anatomical resolution and the use of semi-quantitative techniques.

Notwithstanding the possible limitations, our data clearly indicate a role for dopamine in the

pathophysiology of OCD. This finding needs to be replicated and should be further explored in studies examining the effect of pharmacotherapy and psychotherapy on both serotonergic and dopaminergic transporter densities in OCD, and in studies further dissecting the possible involvement of neurotransmitter systems in this disorder.

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Table 1

Demographic and clinical characteristics of patients with OCD and pair-wise matched healthy controls

| | Patients with OCD (n = 15) | Matched controls (n = 15) |
|---|---|---|
| Age (years) | 31.4 ± 9.0 | 32.0 ± 9.5 |
| Handedness | 0.96 ± 0.03 | 0.94 ± 0.04 |
| Sex | 11 males | 11 males |
| 4 females | 4 females | |
| Nicotine use | 12 non-smokers | 11 non-smokers |
| Onset | 10 juvenile, 5 adult | |
| Years of illness | 12.2 ± 7.2 | |
| Total Y-BOCS | 23.4 ± 4.2 | |
| Obsessions subscale | 12.0 ± 2.1 | |
| Compulsions subscale | 11.4 ± 2.6 | |
| Total HDRS | 8.4 ± 4.1 | |

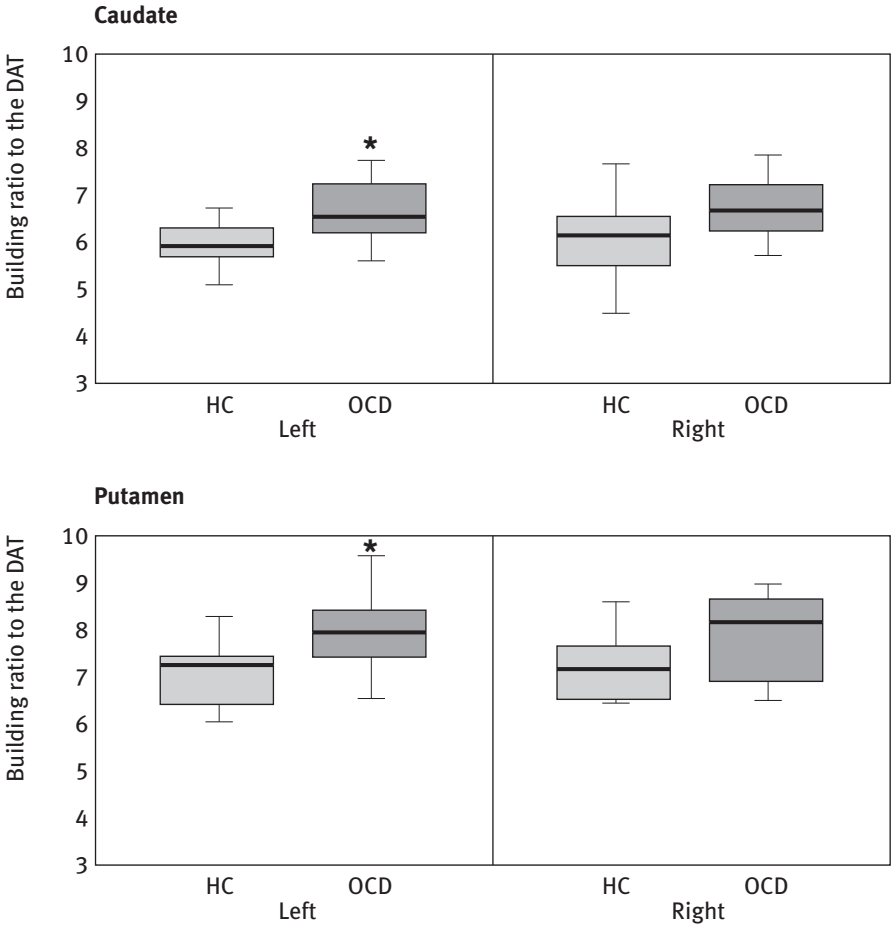
Table 2

Dopamine transporter (DAT) and serotonin transporter (5-HTT) binding ratios in the volumes of interest in psychotropic-naïve patients with OCD and matched healthy controls

| VOI | OCD | controls | p value |
|---|---|---|---|
| DAT (± SD) | | | |
| Left caudate | 6.80 ± 0.64 | 5.99 ± 0.78 | 0.004 |
| Right caudate | 6.78 ± 0.67 | 6.16 ± 0.85 | 0.045 |
| Left putamen | 8.00 ± 0.74 | 7.04 ± 0.79 | 0.006 |
| Right putamen | 7.97 ± 0.89 | 7.16 ± 1.23 | 0.050 |
| 5-HTT (± SD) | | | |
| Left thalamus | 8.38 ± 1.46 | 8.34 ± 0.75 | 0.946 |
| Right thalamus | 8.24 ± 1.55 | 8.51 ± 0.72 | 0.458 |
| Midbrain | 10.74 ± 1.90 | 11.04 ± 1.31 | 0.683 |
| Pons | 8.34 ± 1.77 | 8.74 ± 0.63 | 0.813 |

Figure 1

Box plots for specific binding ratios of [$^{123}$I]beta-CIT to the dopamine transporter in the left and right caudate and putamen of patients with OCD (N = 15) and controls (N = 15). Dark horizontal lines indicate median; boxes, 75% confidence intervals, and limit lines the range. Asterisk indicates a significant difference (P value of ‹ 0.00625, corrected for multiple comparisons).



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# Chapter VI

# Low level of dopaminergic $D_2$ receptor binding in obsessive-compulsive disorder

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# Summary


## Background:

Despite growing evidence for involvement of the dopaminergic system in dopamine in obsessive-compulsive disorder (OCD), the functional anatomy of the dopaminergic system in the basal ganglia has been investigated sparsely.

## Methods

The dopamine $D_2$ receptor binding was assessed in ten medication free OCD patients and ten healthy controls, matched for age, gender, and handedness. The binding potential was measured using single photon emission computerized tomography (SPECT) and infusion of the $D_2$ receptor radiotracer [$^{123}$I] iodobenzamide ([$^{123}$I] IBZM). With magnetic resonance imaging (MRI) as reference, regions of interest (caudate and putamen) were delineated for each hemisphere and co-registered with the corresponding SPECT scans.

## Results

The dopamine $D_2$ receptor binding in the left caudate nucleus was significantly lower in the patients with OCD than in healthy controls ($F_{1,18} = 7.0$, $p = 0.016$). In addition, an interhemispheric difference was observed in the patients' sample. Both the $D_2$ receptor binding potential (df: 9, $p = 0.012$), and the volume (df: 9, $p = 0.029$) of the left caudate nucleus were statistically significantly reduced relative to the right caudate nucleus.

## Conclusions

This study provides in vivo evidence for abnormalities in the binding potential of the dopamine $D_2$ receptor, which suggest the direct involvement of the dopaminergic system in the pathophysiology of OCD.

# Introduction

Over the past two decades, several investigators have suggested that obsessive-compulsive disorder (OCD) might be related to a dysfunction of brain serotonin systems, mainly because of the anti-obsessional efficacy of selective serotonin reuptake inhibitors (SSRIs).[1] In recent years, evidence has accumulated showing that – in addition to the serotonergic system – the dopaminergic system may also be involved in OCD.[2] A role for dopamine in the pathophysiology of OCD is supported by preclinical and clinical evidence.
Preclinical evidence includes experimental animal models of induced stereotypies through increased dopaminergic transmission.[3] In fact, putative animal models for OCD depend primarily on changes in the dopaminergic system; the $D_2$ receptor is of primary interest, as rats treated chronically with the selective $D_{2/3}$ receptor agonist quinpirole develop compulsive checking behavior.[4] Clinical evidence include the observation that insults to basal ganglia structures, intimately linked to rich dopaminergic innervations, have been associated with the emergence of obsessive–compulsive behavior.[5] Furthermore, pharmacological agents influencing the dopaminergic system such as methylphenidate, cocaine and bromocriptine, have been shown to induce obsessive-compulsive symptoms.[6] Finally, imaging studies of the neurobiological processes in OCD have pointed consistently to abnormalities in the cortico-striatal-thalamo circuits (especially the caudate nucleus).[7] There is considerable experimental evidence sustaining that the dopaminergic system plays a pivotal role in the function of these cortico-striatal-thalamo circuits by fine-tuning the patterns of activity in the direct and indirect pathway.[8]
Despite the growing evidence for contributions of the dopaminergic system and basal ganglia in OCD the functional anatomy of the dopaminergic system has scarcely been investigated directly. To study the dopaminergic system in OCD, we used [$^{123}$I] IBZM as a radioligand, and SPECT along with MRI scans to determine whether there are differences in the $D_2$ binding potential in the striatum (caudate and putamen) between patients with OCD and healthy controls. We hypothesized that the dopamine $D_2$ receptor binding potential would be reduced in OCD patients owing to a hyperactive striatal circuit.[7]

## Methods and Materials

The subjects in this study were 10 patients with OCD and ten healthy controls who gave written informed consent for participation in this study. The study had been approved by the University of Utrecht Medical Ethical Review committee (Utrecht, The Netherlands). The Mini-International Neuropsychiatric Interview was used to ascertain that patients met the DSM-IV criteria of the primary OCD diagnosis, and that healthy controls were free of psychiatric diagnoses [9]. All subjects were right-handed and physically healthy, as confirmed by physical and laboratory examinations. None of the patients or controls smoked at the time of their participation in the study.

## Patients

Patients (seven females/three males) were recruited from the outpatient department of the University Medical Center of Utrecht. Study criteria for the patient's sample included: 1) aged between 18 and 65 years; 2) diagnosis of primary OCD according to the DSM-IV criteria; 3) a score of at least 18 on the Yale-Brown obsessive-compulsive scale (Y-BOCS), or at least 12, if only obsessions or compulsions were present 4) absence of psychotropic medication within the last month preceding the study; 5) absence of behavioral therapy within six months preceding the study; 6) no current major depression, which was ascertained by the 17-item Hamilton Depression Rating Scale (HAM-D) on admission ; 7) absence of any other DSM-IV disorder, a history of substance abuse, or dependence; 8) absence of organic mental or neurological disorders; 9) absence of pregnancy.[10]
Because there might be an association between altered striatal dopamine $D_2$ function and the dopamine $D_2$ genotypes, patients were genotyped for the TaqIa, and Ser311/Cys variants of the dopamine $D_2$ receptor.[11] Oligonucleotide primers (5'-CGTCGACGGCTGGCCAAGTTGTCTA and 5'-CCGTCGACCCTTCCTGAGTG-TCATCA) were used to amplify a 310 bp region surrounding the TaqIA site. The polymerase chain reaction (PCR) was performed according to the following conditions: 94°C for 1 min, 50°C for 1min, 72°C for 1,5min for 35 cycles. Digestion of 10µl of PCR product was accomplished by incubation overnight with 5 units of TaqI restriction enzyme at 65°C. After incubation with TaqI, the A1 allele remains intact while the A2 allele is cut into a 130 bp piece and a 180 bp piece. All three fragments were resolved on a 1,5% agarose gel and visualized by staining with ethidium bromide.

## Controls

Healthy controls (seven females/three males) were recruited from an existing database or by advertising. Inclusion criteria for the control sample included 1) aged between 18 and 65 years; 2) absence of any psychiatric illness; 3) absence of organic mental and neurologic disorders, or a medical illness; 4) absence of any medication within last month preceding the study; 5) absence of pregnancy. As there is evidence for gender differences in dopamine $D_2$ receptor levels, and age related $D_2$ receptor loss, comparison controls were matched pair-wise for gender and age.[12;13]

## SPECT

Subjects received an intravenous injection of approximately 185 MBq (5 mCi) of $^{123}$-IBZM ((123I)S-(–)-N-((1-ethyl-2-pyrrolidinyl)methyl)-2-hydroxy-3-iodo-6-methoxybenzamide) (Amersham-Cygne, Eindhoven; The Netherlands, radionuclidic purity (I125 /I123) of at least 9,5 x 10-3 at calibration time and a radiochemical purity of at least 95%). To decrease radiation exposure to the thyroid gland, all subjects received 170 mg/day of potassium iodide during one week, starting from two days before the scan. Imaging was performed on a Picker Prism 3000 triple-headed gamma camera with ultra high-resolution fan beam collimators Full Width Half Max of approximately 12 mm. The following scanning parameters were used: continuous mode, 128x128 matrix, angular range: 120°, angular step: 3°, number of steps: 40. The scanning session was performed at 120-180 minutes after the injection.

## MRI

To provide anatomical reference and to rule out structural lesions, we obtained a structural magnetic resonance imaging (MRI) brain scan (3D-FFE; TE/TR 4.6/30 ms; flip angle 30º; FOV 256 mm by 256 mm.; matrix 128 by 128 by 130 mm; slice thickness 2 mm) two hours before the injection of [$^{123}$I] IBZM. This was a T1-weighted structural image, acquired on a Philips NT (Best, the Netherlands) scanner operating at 1.5 T. MRI scans were reoriented to the standardized coordinate system of the Montreal standard brain.[14] Volumes of interest (VOI) for the dopamine $D_2$ receptor included the left and right caudate nucleus, and the left and right putamen, with the cerebellum as reference region. A researcher blind to subject's identity and diagnosis manually delineated the VOI on the reoriented MRI using Display software from the Brain Imaging Center of the Montreal Neuroimaging Institute.[15] The VOIs were manually delineated on a MRI slice thickness of 2 mm. Volumes were measured by adding all segmented voxels and then multiplying them by the volume of a single voxel.

## Co-registration

Fiducial markers, containing vitamin A and $Co^{57}$ as contrast agents for the MRI and SPECT scan, respectively, were used for exact co-registration of the MRI and SPECT scan. The energy peak for [$^{123}$I] IBZM was set at 160 keV with a window of 20%, and for $Co^{57}$at a peak of 120 keV with a window of 15%. After standard processing, SPECT-images were resliced to isotropic voxels of 8 $mm^3$ and treated as 3D volumes to enable co-registration with the MRI. Co-registration was performed semi-automatically on the basis of the position of the fiducial markers, using the Register multimodality software package from the Brain Imaging center of the Montreal Neuroimaging Institute.[16] The binding potential ($B_{max}/K_d$) for each separate VOI was calculated by using the cerebellum as a reference tissue (average count radioactivity per VOI/ average count radioactivity in the cerebellum).

## Statistical analysis

The binding potentials for [$^{123}$I] IBZM to the dopamine $D_2$ receptor in patients and controls were compared using one-way analysis of variance (ANOVA). To control for volume, one-way analysis of covariance (ANCOVA) was performed with volumes of interest as covariate. The intrarater reliability of the VOI procedure (caudate, putamen and cerebellum) was assessed through an additional blind morphometric analysis of eight scans, which were randomly chosen and cloned for this purpose. An intra class correlation was calculated using a two-way mixed effects model.[17] The intraclass correlation coefficients for the intra-rater and inter-rater reliability of the VOI procedure were between 0.89 and 0.98 (mean 0.94, SD ± 0.04) and between 0.86 and 0.99 (mean 0.95 ± SD 0.05) respectively. Within group comparisons of hemispheric binding potentials in bilateral VOIs were performed using a paired *t*-test. Pearson correlations were calculated to assess correlations between dopamine $D_2$ binding potentials and clinical measures. All tests were two-tailed, with a significance level of 0.05.

# Results

Study sample

Clinical characteristics of OCD patients and dopamine $D_2$ receptor phenotypes are shown in Table 1. Patients had a mean Y-BOCS score of 25.9 ± 6.5 and a mean HAM-D score of 12.3 ± 4.5. Three of the ten patients had a first-degree relative with OCD (patient 1,4, and 5), two had a first-degree relative with major depressive disorder (patient 3 and 9), and five had no familial psychiatric morbidity. Except for two patients, who had a comorbid single episode major depressive disorder (patient 6 and 9), none of the patients met criteria for another Axis I disorder or an Axis II (personality) disorder. Two patients had never received any pharmacological treatment, three patients had been treated once with SSRIs, two patients had been treated twice, and three patients had three previous episodes treated with SSRIs. None of the patients was ever treated with an antipsychotic. On admission, three of the ten patients were treated with SSRIs (2 patients used 20 mg of paroxetine daily and 1 patient used 40 mg of paroxetine daily). In these cases, medication was discontinued and patients were kept medication free for one month before the study. There was no difference in age between patients (36.4 ± 12 years) and controls (33.7 ± 10 years) ($F: _{1,18} = 0.23$, $p = 0.59$). None of the control subjects had ever been treated with psychotropic medication.

## D2 receptor binding ratios

Values of dopamine $D_2$ receptor binding potential in the caudate and putamen are shown in Table 2. Dopamine $D_2$ binding potentials were statistically significantly lower for the left caudate ($F: _{1,18} = 7.0$, $p = 0.016$) compared with those of control subjects. This effect remained statistically significant, even when corrected for volumes of the left caudate nucleus ($F: _{1,18} = 5.8$, $p = 0.025$). In the patient sample, a statistically significant interhemispheric difference was detected in the caudate nucleus: the left caudate had a lower dopamine $D_2$ receptor binding potential than the right caudate ($t: 3.125$, $df: 9$, $p = 0.012$) (Table 3). The differences of the dopamine $D_2$ binding potentials in right caudate and putamen between patients and controls were not statistically significant, and no interhemispheric differences were observed in the controls sample.

## Volumes of interest

Because an MRI reference brain was used, we included the volumes of the regions of interest in the analysis as well. No statistically significant difference in volumes of the caudate and putamen was observed between patients and controls. In the patient's sample, however, we detected a statistically significant reduced volume of the left caudate relative to the right caudate, 2793 ± 441 and 2919 ± 497, respectively ($df: 9$, $p = 0.029$). No interhemispheric differences were observed in the control subject sample (Table 3).
We found no statistically significant correlation between clinical measures, such as age of onset, duration of illness, Y-BOCS-obsessions, -compulsions and -total scores, or HAM-D scores with the dopamine $D_2$ receptor binding potentials in caudate and putamen.

# Discussion

The major finding of this study is that patients with OCD have lower dopamine $D_2$ binding ratios in the left caudate nucleus relative to controls. We also observed lower $D_2$ binding ratios in and a reduced volume of the left caudate nucleus compared to the right caudate nucleus in patients with OCD. Although our results should be considered preliminary owing to the small sample size, this report is the first to demonstrate in vivo dopamine $D_2$ changes in patients with OCD.

It is not possible to compare our data with similar studies, but our results corroborate other neurobiological findings in OCD. Structural abnormalities of the caudate nucleus have previously been found in a number of morphometric MRI studies.[18;19] It is of note that changes in the caudate nucleus may be specific to OCD, and are not just part of the anxiety penumbra.[20] Functional imaging studies have shown both increased and decreased activity in the caudate.[21;22] Despite various discrepancies, caudate abnormalities have been detected in the majority of neuroimaging studies. Our data add to the accumulating evidence that the caudate is implicated in OCD. The interhemispheric difference of the caudate nucleus in our population suggests a laterality in the pathophysiology of OCD that is partially consistent with other reports.[7] However, it should be noted that the observed laterality might be due to a physiological asymmetry with higher binding potential on the right side.[23] On the other hand, the absence of this effect of laterality in the putamen and in the control group might be the result of a lack of statistical power due to our small sample size.

Until now, except for some discrete observations, there has been no direct evidence implicating the dopamine $D_2$ receptor in OCD. Brambilla et al. have suggested that the blunted growth hormone response to apomorphine stimulation in patients with OCD might result from subsensitive $D_2$ receptors.[24] Preclinical evidence includes the observation that rats treated chronically with the dopamine $D_2/D_3$ receptor agonist quinpirole develop compulsive checking behavior.[4] Inositol, which has demonstrated clinical efficacy in OCD, has been shown to induce a significant increase in striatal $D_2$ receptor density in guinea pigs.[25] Clomipramine, the most studied and effective anti-OCD drug yet, was shown to possess mild but significant dopamine $D_2$ receptor blocking activity.[26] Other indirect clinical evidence includes the successful treatment of treatment-refractory OCD with dopamine $D_2$ receptor antagonists as adjunct to SSRIs.[27;28]

At this point, it is difficult to establish the direct cause or underlying mechanism of the decreased [$^{123}$I] IBZM binding in our study. The decreased [$^{123}$I] IBZM binding may be explained either by a lower number of available $D_2$ receptors due to (1) structural degeneration of the postsynaptic striatal cells, (2) genetic variability of the $D_2$ receptor gene or (3) down-regulation of the $D_2$ receptor by competition with high concentrations of endogenous dopamine.

A structural degeneration of the postsynaptic striatal cells in OCD is supported by the observation of decreased caudate volumes in morphometric imaging studies [7]. On the other hand, Sawle et al. did not find any alteration in [$^{18}$F]-6-Fluorodopa uptake into the caudate and putamen in a small Positron Emission Tomography (PET) study involving six OCD patients with obsessional slowness.[29] A decrease in [$^{18}$F]-6-Fluorodopa uptake is believed to reflect a reduction in the number of nigrostriatal dopaminergic neurons.[29]

The lower dopamine $D_2$ densities in patients with OCD could also be the result of variants of the dopamine $D_2$ receptor genotype. The A1 allele of the TaqIa RFLP in the dopamine D2 receptor gene has been associated with low striatal $D_2$ availability in vivo in healthy volunteers.[11] In our sample, however, only two of nine patients had the A1 allele of the TaqIa in the dopamine $D_2$ receptor gene. In addition, one would expect a decrease of the $D_2$ receptor density in both hemispheres if the specific $D_2$ receptor genotype primarily determined the $D_2$ receptor distribution.

Finally, one may consider down-regulation of the $D_2$ receptor. Because $D_2$ receptors are up- or down regulated in response to lower or higher synaptic dopamine availability, down-regulation of the receptor concurs with higher synaptic concentrations of dopamine. As of yet, there is little conclusive evidence of increased dopamine activity in OCD.[30] The few direct biochemical investigations of dopamine in OCD patients have mostly yielded normal results.[31-34] Because serotonin neurons may exert a tonic inhibitory influence on the dopamine function, it has been suggested that a putative serotonergic deficiency in OCD patients results in an increased secretion of dopamine, and subsequently in postsynaptic dopamine $D_2$ down-regulation.[2] A role for increased dopamine concentrations in the striatum is supported by SPECT studies investigating the dopamine transporter (DAT) binding ratio. Kim et al. found an increased dopamine transporter (DAT) binding ratio in the right basal ganglia and a tendency towards an increased DAT binding ratio in the left basal ganglia with [$^{123}$I] IPT SPECT in 15 OCD patients.[35] Pogarell et al., on the other hand, reported no significant differences in striatal [$^{123}$I] Beta-CIT binding between nine patients and ten controls.[36] Because higher DAT densities are believed to mirror a higher homeostatic tone of the dopaminergic system, the most straightforward, albeit preliminary, explanation for a decreased [$^{123}$I] IBZM binding in our study would be that it reflects a higher synaptic concentration of dopamine associated with a secondary down-regulation of the $D_2$ receptor.

A limitation of the study is the small sample size. The power of our study may have been too small to detect bilateral changes, or changes in the putamen. Another important limitation of the study is that [$^{123}$I] IBZM as a SPECT tracer has been reported to reflect dopaminergic $D_2$ as well as $D_3$ receptor binding.[37] Our data might thus be less specific for the $D_2$ receptor binding potential than assumed in advance. On the other hand, the density of the dopamine $D_3$ receptor in the striatum is insignificant in proportion to the density of the $D_2$ receptor. An additional challenge with amphetamine might improve our study design further, because [$^{123}$I] IBZM binding after acute amphetamine administration has been validated as an indirect measure of the change in synaptic dopamine concentration. Alternatively, we could have used the dopamine depletion paradigm (e.g., using alpha-methyl-paratyrosine (AMPT) to measure baseline striatal dopamine release).[38;39]

To conclude, the findings from this study provide strong evidence for the direct involvement of the dopaminergic system in the pathophysiology of OCD.

TABLE 1

Clinical characteristics and $D_2$ receptor genotypes of the patient sample

| nr | sex | age | age at onset | length illness | Principal OCD-symptoms | Y-BOCS | HAM-D | TAQ I | SER/CYS |
|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 37 | 25 | 12 | Contamination/washing | 34 | 17 | A2A2 | SER/SER |
| 2 | F | 20 | 15 | 5 | Contamination | 14* | 14 | A1A2 | SER/SER |
| 3 | F | 24 | 7 | 17 | Contamination/washing | 22 | 13 | A2A2 | SER/SER |
| 4 | M | 18 | 12 | 6 | Aggressive obsessions/checking | 31 | 9 | A2A2 | SER/SER |
| 5 | F | 37 | 17 | 20 | Contamination/washing | 29 | 10 | A1A2 | SER/SER |
| 6 | F | 38 | 30 | 8 | Perfectionism/checking | 16 | 5 | N.A. | N.A. |
| 7 | F | 52 | 22 | 30 | Obsessional doubt/checking | 27 | 8 | A2A2 | SER/SER |
| 8 | M | 54 | 14 | 40 | Sexual obsessions/checking | 27 | 16 | A2A2 | SER/SER |
| 9 | F | 32 | 11 | 21 | Symmetry/checking | 33 | 13 | A2A2 | SER/SER |
| 10 | M | 30 | 13 | 17 | Somatic obsessions/checking | 28 | 18 | A2A2 | SER/SER |

OCD, obsessive-compulsive disorder; Y-BOCS, Yale Brown Obsessive-Compulsive Scale; HAM-D, Hamilton Depression Scale; F, female;M, male; N/A, not applicable

* Only obsessions

TABLE 2

[$^{123}$I] IBZM SPECT $D_2$ binding potentials in caudate and putamen in OCD patients and healthy controls

| | [$^{123}$I] IBZM SPECT $D_2$ | | | | | | |
|---|---|---|---|---|---|---|---|
| | Patients | | Controls | | Analysis | | |
| Brain region | Mean | SD | Mean | SD | F | p | Difference |
| Caudatus | 0.030 | 0.006 | 0.038 | 0.008 | 5.4 | 0.033 | 0.008 |
| Left | 0.029 | 0.006 | 0.038 | 0.008 | 7.0 | 0.016 | 0.009 |
| Right | 0.031 | 0.007 | 0.037 | 0.008 | 3.3 | 0.086 | 0.006 |
| Putamen | 0.022 | 0.009 | 0.028 | 0.009 | 2.3 | 0.142 | 0.006 |
| Left | 0.021 | 0.009 | 0.028 | 0.009 | 2.4 | 0.134 | 0.007 |
| Right | 0.023 | 0.010 | 0.029 | 0.009 | 2.0 | 0.170 | 0.006 |

[$^{123}$I] IBZM, [$^{123}$I] iodobenzamide; SPECT, single photon emission computed tomography;OCD, obsessive-compulsive disorder.

Table 3

Interhemispheric difference of [$^{123}$I] IBZM SPECT $D_2$ binding potentials and volumes of interest in OCD patients in $mm^3$

| | Left | | Right | | | |
|---|---|---|---|---|---|---|
| Brain region | Mean | SD | Mean | SD | F | p |
| Caudatus | | | | | | |
| Ratio | 0.029 | 0.006 | 0.031 | 0.007 | 0.7 | 0.01 |
| Volume | 2716 | 480 | 2835 | 543 | 2.4 | 0.03 |
| Putamen | | | | | | |
| Ratio | 0.021 | 0.009 | 0.023 | 0.009 | 1.6 | 0.45 |
| Volume | 1690 | 668 | 1728 | 711 | 2.1 | 0.70 |

[$^{123}$I] IBZM, [$^{123}$I] iodobenzamide; SPECT, single photon emission computed tomography; OCD, obsessive-compulsive disorder.

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# Chapter VII

# Summary and general discussion

Obsessive-compulsive disorder (OCD) is a frequent, incapacitating and usually chronic psychiatric disorder with substantial direct and indirect costs, characterized by recurrent, persistent and intrusive thoughts or images that cause anxiety or distress (obsessions), and repetitive behaviors or mental acts aimed at reducing this distress or anxiety (compulsions). Patients recognize that these obsessions and compulsions are unreasonable and products of their own mind. As described in the introduction of this thesis, obsessive-compulsive disorder has been conceptualized primarily as a form of neurosis for a long time and was believed to be a rare disorder responding poorly to (psychoanalytic) therapy. However, evidence accumulating since the second half of the twentieth century, has suggested a neurobiological basis for OCD.
Just as in many other major psychiatric disorders, in OCD the advent of neuroimaging techniques has brought new opportunities for research into its neurobiology. In the research for this thesis two functional neuroimaging techniques, functional magnetic resonance imaging (fMRI) and Single Photon Emission Tomography (SPECT) were used to further explore neuropsychological functioning and neurochemistry in OCD.

# Section 1
# Cognitive functioning

## Antisaccade studies

OCD symptomatology is mediated by specific neuronal circuitry involving parts of the frontal cortex, the basal ganglia, the thalamus and parts of the limbic system.[1] Dysfunctions of this complex circuitry result in disturbances of executive functioning (i.e. higher-order processes necessary for effective and contextually appropriate goal directed behavior) that may underlie parts of the symptomatology of OCD.[2;3] The distinctive phenomenology of OCD, with patients being unable to suppress their obsessions and compulsions, has led to the hypothesis that a deficit in one specific aspect of executive functioning, the capacity to voluntarily inhibit, may be a common denominator of the cognitive disturbances in OCD. Strong support for this hypothesis comes from studies finding a reduced performance in OCD on specific oculomotor tasks requiring inhibition of a reflexive saccade (antisaccade tasks). Saccadic movements are known to be subserved by fronto-thalamo-striatal circuitry.[4]
Chapter I presents the results of the first study to examine whether antisaccadic abnormalities in OCD represent a stable feature of the disorder or a feature that normalizes with treatment, i.e. are a state dependent phenomenon. In the first part of the study we compared the performance of 14 adult psychotropic-naïve patients with OCD with no comorbidity and 14 matched healthy controls on a saccadic, a fixation and an antisaccade task. Subsequently, we investigated the effects of response to treatment on the performance on the same three oculomotor tasks in a group of 17 psychotropic-free or naïve patients with OCD with no comorbidity. Compared to the healthy controls, the patients with OCD showed normal error rates on the antisaccade and fixation tasks, but needed more time to initiate antisaccades. This finding indicates that patients with OCD have no gross impairment of

oculomotor inhibitory capacities and does not support the notion of impaired inhibition being a common denominator of cognitive disturbances in OCD. Instead, patients with OCD may display a disturbance of the capacity to deliberately initiate a saccade to an imagined target, as is the case in the antisaccade task. This would be in line with the findings in some other recent studies, suggesting that patients with OCD have an impaired ability to use internal representations for the guidance of behavior.[5;6] In the second part of the study we found no effects of pharmacotherapy or response on performance on the three oculomotor tasks, indicating that the specific pattern of oculomotor performance in OCD seems to constitute a state-independent phenomenon, i.e. a stable feature of the disorder.

## Limitations and further research

Although the oculomotor studies described in chapter II were performed in groups of carefully selected patients and controls and can be considered adequately designed, future oculomotor studies in OCD should take some limitations of our design into account. Although saccadic measures have been shown to be a relative stable in other groups of patients and in healthy volunteers, we did not directly assess test-retest variability in our sample of patients with OCD and in the matched healthy controls. Further, we only examined error rate and latency of (anti)saccades, leaving several other oculomotor parameters outside consideration.

The results of the oculomotor study in the second part of chapter II suggest that specific antisaccadic abnormalities may be a stable feature of OCD. Future projects should aim at exploring possible oculomotor abnormalities in the relatives of patients with (hereditary) OCD, and at identifying the functional anatomical substrate and its dynamics in patients with OCD in neuroimaging studies. Comparable research has already been performed in schizophrenia.[7]

## Working memory

Neuropsychological studies have shown that obsessive-compulsive disorder (OCD) is also consistently associated with a specific deficit in spatial working memory, another aspect of executive functioning, especially when task difficulty is high. The spatial working memory system in OCD had never been investigated before with functional neuroimaging techniques. Chapter III presents a functional MRI study in which performance on a working memory task with increasing levels of difficulty (*n*-back), as well as the underlying neuronal substrate and its dynamics, were assessed in 11 treatment-free female patients with OCD with no comorbidity and 11 pair-wise matched healthy controls. Patients with OCD performed poorly at the highest level of task difficulty and engaged the same set of brain regions during the task as the matched healthy controls. Only in a region covering the anterior cingulate the activity was significantly elevated in patients with OCD at all levels of the task. The activity pattern in the other brain regions was comparable to that in controls. These findings do not provide evidence for a deficit of the spatial working memory system proper. Earlier it has been suggested that deficits in specific aspects of (working) memory may give rise to the checking and doubt found in many patients with OCD. Several neuropsychological studies

have indeed reported deficits like a reduced memory for actions or reduced confidence in memory in patients with OCD, that could explain the frequent checking in many forms of OCD.[8] On the other hand, a deficit in non-verbal memory would not explain many other symptoms of OCD, like for example aggressive obsessions or superstitious rituals.[9]
In line with other recent investigations we have suggested that the observed deficit in spatial working memory may be secondary to another disturbed aspect of executive functioning in OCD.[10] Indeed, some recent studies have demonstrated that patients with OCD are less likely to spontaneously generate effective strategies for the performance of certain memory tasks.[5;11;12]
Our finding of an elevated activity in a region covering the anterior cingulate is in concordance with the results of several neurosurgical studies and findings in neuroimaging resting-state and provocation studies, implicating the anterior cingulate in OCD.[2]
Interestingly, studies examining the role of the anterior cingulate in executive functioning in healthy volunteers and non-human primates have led to hypotheses that the anterior cingulate plays a key role in the implementation or evaluation of a strategy.[13;13;14]
Chapter IV presents the results of a subsequent study examining the effect of clinical response on the dynamics of the working memory system in OCD, as assessed with the *n*-back working memory task and fMRI. Fourteen patients with OCD with no comorbidity were examined before and after pharmacological treatment. Performance on the working memory task improved only in responders and was associated with a change in the overall pattern of brain activity during the task, but not with changes in the activity pattern of specific regions. This suggest that spatial working memory deficits in OCD and their functional anatomical correlates are, at least to some extent, related to OCD symptomatology, i.e. state dependent.
In chapter III it was hypothesized that the anterior cingulate was hyperactive in OCD during the *n*-back working memory task as a result of its putative involvement in the implementation or control of strategy. However, the improvement of performance on the *n*-back working memory task in the responders in our second study was associated with a global change of the brain activity pattern during increasing difficulty and was not limited to the cingulate, which seems to argue against the notion of the anterior cingulate being hyperactive in OCD because of strategy problems only. Alternative explanations might be that in responders, in contrast to non-responders, the output of the hyperactive 'strategy implementing' cingulate could lead to a more efficacious global activity pattern, or that the improvement was essentially the result of changes in the functioning of brain regions other than the cingulate.

## Limitations and further research

The functional MRI studies in section I of this thesis used an approach in which brain regions involved in working memory were segregated from others, an approach known as functional segregation. Subsequently the dynamics of brain activation during the working memory task were examined in the identified regions. We did not examine functional connectivity, i.e. the dynamics of the activity pattern between regions. This could possibly have shed more light on the role of the hyperactive anterior cingulate. Methods for the analysis of data that allow for the examination of functional or effective connectivity have been introduced in the field of functional neuroimaging recently. Anatomical connectivity, i.e. the pattern and quality of

anatomical connections between regions, was also not examined in the present studies. With recently developed structural MRI techniques, based on diffusion weighted MRI, it is now possible to visualize white matter tracts and examine their integrity in vivo. In OCD both anatomical and functional connectivity approaches have not been applied widely, but it is to be expected that research into executive dysfunctions will greatly benefit from them.
In the study described in chapter IV the effect of response on working memory and the associated brain activity was examined, but we did not assess test-retest variability and did not include a matched healthy control group. Hence, it was not possible to directly assess if in responders the brain activity related to working memory tended to normalize or was still abnormal but more efficient.
The two fMRI studies in this thesis are amongst the first functional imaging studies using a cognitive paradigm in OCD and focused on a specific aspect of executive dysfunction in OCD. In several other major psychiatric disorders a similar trend had evolved already earlier, notably in schizophrenia and depression. Apart from attempts to gain more insight in the pathophysiological mechanisms involved in psychiatric disorders, neuroimaging studies also increasingly aim at the identification of potential 'biological' markers for the presence of a disorder, the presence of vulnerability or to evaluate effectiveness.[15] Eventually, one also hopes to identify more elementary, genome related phenomena (endophenotypes), as opposed to the 'endpoint' variable clinical presentation (the phenotypes). Endophenotypes can be used to identify the 'downstream' aspects of (different) clinical presentations, as well as the 'upstream' consequences of genes. In the field of OCD there is still a relative paucity of this type of studies.
Although antisaccades and spatial working memory may appear to be unrelated at first sight and were addressed separately in this thesis, several studies do suggest that they are connected. Thus, lesions and neuroimaging studies have shown that both the generation of antisaccades and working memory rely on an intact functioning of the dorsolateral prefrontal cortex and its related circuitry. Further, working memory processes may serve a critical role in the suppression of reflexive saccades, as was shown in studies using a dual task paradigm in which subjects had to perform an antisaccade task while simultaneously performing a (*n*-back) working memory task.[16;17] Future research into the nature of the antisaccadic abnormalities in OCD could benefit from the use of such a dual task paradigm, especially in combination with functional MRI.

# Section 2

# Neurochemistry

## Dopamine and serotonin

The selective improvement of OCD symptomatology after long-term administration of serotonin reuptake inhibitors has led to the hypothesis that changes in the central serotonergic systems may be the mechanism by which these compounds exert their effect.[18] Evidence that serotonergic perturbations are directly implicated in the neurobiology of OCD,

however, has been sparse. Recent data suggests that other neurotransmitter systems, especially the dopamine system, may also be involved.[19;20] The prevailing fronto-thalamo-striatal model of OCD postulates a hyperactive striatal circuit as a result of an increased dopaminergic input.[1] However, despite the advent of several radiolabeled ligands, i.e. chemicals with a high affinity for dopaminergic or serotonergic binding sites suitable for neuroimaging techniques like single photon emission computed tomography (SPECT) or positron emission tomography (PET), the functional neuroanatomy of serotonergic and dopaminergic neurotransmitter systems in OCD has not been investigated extensively before. In chapter V the binding patterns of the radiolabeled [$^{123}$I]beta-CIT for dopamine and serotonin transporters in the brain were compared between 15 psychotropic-naïve patients with OCD with no comorbidity and 15 pair-wise matched healthy controls. Volumes of interest were constructed on MRIs and co-registered with the SPECT scans. We hypothesized that as a result of a putatively increased activity of dopaminergic systems in OCD, the binding patterns of [$^{123}$ I]beta-CIT in OCD would reflect higher densities of dopamine transporters. Patients with OCD had indeed significantly higher binding ratios for [$^{123}$I]beta-CIT in the left caudate and left putamen. No differences were found in the less specific binding pattern of [$^{123}$I] beta-CIT in the volumes of interest selected for the serotonin transporter.

In chapter VI the binding patterns of the radiolabeled ligand [$^{123}$ I] IBZM for the D2 receptor, an important dopaminergic receptor subtype, were compared between 10 patients with OCD and 10 healthy controls. Volumes of interest were constructed on MRIs and co-registered with the SPECT scans. We hypothesized that as a result of the putatively increased activity of dopaminergic systems in OCD the D2 receptor would have been down-regulated, i.e. having a reduced density or binding capacity in the striatum (caudate and putamen). Indeed, patients with OCD showed a lower binding ratio for IBZM in the left caudate.

The two SPECT studies in section II provided direct evidence for dopaminergic alterations in OCD. As increased levels of dopamine will eventually lead to an increase in dopamine transporter densities and a down-regulation of the number of D2 receptors, the results from both studies support the notion of an increased striatal dopaminergic transmission as postulated in the fronto-thalamo-striatal model proposed by Saxena at al.[1] According to this model there is an imbalance between the activity of the direct, activating, pathway and the indirect, inhibiting, pathway in OCD. Stimulation at the D1 receptor activates the direct pathway; stimulation at the D2 receptor deactivates the indirect pathway, the net result of higher dopamine levels being an increased activity in specific fronto-thalamo-cortical circuitry.

Increased levels of dopamine in OCD are also in line with evidence suggesting an abnormal responsiveness of the amygdala, a brain region involved in fear conditioning and the modulation of affective responses to stress.[21;22] When higher dopamine levels increase the transmission in the mesolimbic pathway, the prefrontal cortex has been shown to be less capable of attenuating activity of the amygdala.[23;24] Finally, the results of the two SPECT studies are in line with evidence suggesting that OCD and addiction may share common neurobiological, especially dopaminergic, mechanisms.[25-27]

## Limitations and further research

Although the SPECT studies in this section used co-registration of MRI for more precise determination of the volumes of interest and included carefully selected patients and controls, there are also some limitations to consider. Both studies had relatively small sample sizes and it should be mentioned that although SPECT is easier to use, has a higher safety index and is less expensive than PET, it has also relative disadvantages like a poorer anatomical resolution and the use of semi-quantative techniques (PET). Further, the two SPECT ligands that were used have a less specific binding-pattern than several (newer) PET and SPECT ligands.

Future ligand studies in OCD should further explore the findings described in Section II in studies examining the effects of pharmacotherapy, psychotherapy or pharmacological challenges on both the serotonergic and dopaminergic systems and their interactions in OCD.

## General remarks

The studies in this thesis were almost all performed in carefully selected adult patients with OCD with no comorbidity at the time of inclusion. However, in OCD it is the rule rather than the exception that (life-time) comorbidity is present. Hence, the generalizability of our findings in these selected samples of patients with OCD may be limited. Another limitation of all studies is that patients with various types of OCD symptomatology were included. Several studies using factor analysis have shown that OCD symptomatology can be divided into three to five symptom clusters, with changes usually occurring within rather than between symptom clusters.[28;29] Evidence is accumulating that the specific symptom clusters may differ in their neurobiological substrates.[30] Clearly, future neuroimaging studies aimed at elucidating the pathophysiology of OCD or identifying biological markers in OCD, should take this in account.

All studies in this thesis used a categorical approach: a diagnosis of OCD and a cut-off score at the primary symptom scale (Y-BOCS) were required for subjects to be included. However, there is evidence suggesting that OCD may be better understood from a continuum perspective. Thus, studies have shown that sub-clinical obsessive-compulsive symptomatology is present in a substantial percentage of the general population and is associated with disturbances of executive functioning.[31;32] However, only a few functional imaging studies have been performed in these subclinical populations yet.

The studies in this thesis have shown that OCD is associated with specific deficits in executive functioning (and associated abnormalities in brain activity) and with specific dopaminergic abnormalities. As several aspects of working memory and antisaccades are probably intertwined and both are known to be influenced by dopaminergic transmission, it would have been a major advantage if the studies in this thesis would have been performed in the same sample of patients.[16;33-35] This would have made it possible to examine possible correlations between working memory function, saccades measures and dopaminergic parameters in OCD. Originally, it was intended to perform the studies in the same samples of patients and controls, but, as is often the case in science, unforeseen circumstances led to

another research scheme and eventually the studies had to be performed in virtually separated groups of patients.

## Concluding remarks

This research project would have been impossible without the participation of the many patients with OCD that visited the outpatient unit of the Department of Psychiatry. After the nature of the studies was explained to them, almost all eligible patients were more then willing to participate. Most of them expressed their relief that this type of research could provide a kind of window on the obsessive-compulsive brain. They were convinced that they had some kind of malfunction of their brain and often hoped for the identification of a clearly visible defect or some kind of visual marker for OCD. Such visible defects and markers have not been identified in this research project, but hopefully its results will contribute to the further elucidation of the pathophysiology of OCD and the development of more efficient treatments.

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# Summary in Dutch (samenvatting)

De dwangstoornis of obsessieve-compulsieve stoornis (OCS), wordt gekenmerkt door dwanggedachten en dwanghandelingen. Dwanggedachten zijn zich opdringende en aanhoudende beelden of gedachten die door een persoon als misplaatst ervaren worden en die angst of lijden veroorzaken,voorbeelden zijn de gedachte anderen te zullen besmetten of een vreselijk ongeval te hebben veroorzaakt. Patiënten realiseren zich dat deze gedachten het product van de eigen geest zijn en proberen de gedachten te onderdrukken of te neutraliseren. Dwanghandelingen bestaan uit zich overdreven herhalend gedrag, zoals handen wassen of tellen, meestal in reactie op een dwanggedachte, met als doel de spanning te verminderen of de inhoud van de dwanggedachte te neutraliseren.
Zoals beschreven in het inleidende hoofdstuk I werd OCS aanvankelijk beschouwd als een zeldzame aandoening, tegenwoordig wordt OCS echter tot de meest voorkomende psychiatrische aandoeningen gerekend. OCS komt waarschijnlijk bij zo'n 3% van de bevolking op een bepaald moment in het leven voor. Dwangfenomenen waarbij geen sprake van een stoornis is, komen waarschijnlijk voor bij meer dan 10% van de algemene bevolking. Ook is bekend dat voorbijgaande dwangsymptomen kunnen optreden gedurende de normale ontwikkeling van het menselijke brein. Velen zullen zich bijvoorbeeld zoiets herinneren als het moeten tellen van stoeptegels om daarmee iets gevreesd te voorkomen. OCS komt in alle culturen ongeveer even veel voor en waarschijnlijk iets meer bij vrouwen dan bij mannen. Er wordt een variant onderscheiden met een begin op jonge leeftijd, die een grotere erfelijke component en een slechtere prognose heeft, en een variant met een begin van de aandoening op volwassen leeftijd. Bij het merendeel van de patiënten heeft de aandoening onbehandeld een chronisch karakter, waarbij de ernst van de klachten over de loop van de tijd kan fluctueren.
OCS is niet alleen een veel voorkomende medische aandoening, het is tevens een van de meest invaliderende, met aanzienlijke directe en indirecte socio-economische lasten. In 1990 werden de totale kosten van OCS in de Verenigde Staten op 8.4 miljard dollar geschat.
Over het algemeen duurt het verscheidene jaren voordat de diagnose OCS wordt gesteld, onder andere omdat patiënten zich te veel schamen om een dokter te bezoeken. Verder wordt de aandoening door artsen aanvankelijk vaak niet herkend en wordt een aanzienlijk deel van de patiënten, ondanks het bestaan van behandelrichtlijnen, niet op de juiste manier behandeld.
De eerste medische beschrijvingen en definities van OCS dateren uit de negentiende eeuw. In die tijd werd OCS als een hersenaandoening met een erfelijke component beschouwd. Met de opkomst van het psychoanalytisch concept in het begin van de twintigste eeuw raakte dit model op de achtergrond. OCS werd beschouwd als een typisch voorbeeld van een neurose, het resultaat van een verdrongen intrapsychisch conflict, alhoewel de klachten maar zeer beperkt verbeterden met psychoanalytische therapie.
In de tweede helft van de twintigste eeuw leidden diverse ontwikkelingen er toe dat de dwangstoornis, net zoals veel andere psychiatrische aandoeningen, opnieuw primair werd beschouwd als een hersenaandoening. Meer recent hebben beeldvormende onderzoeken van de hersenen (in het engels: neuroimaging studies) in belangrijke mate bijgedragen aan de ontwikkeling van neuronanatomische modellen voor de dwangstoornis. Volgens deze

modellen is bij OCS de informatieverwerking in circuits tussen met name gebieden in de voorhoofdskwabben en dieper gelegen hersenkernen verstoord, mogelijk als gevolg van neurochemische veranderingen. Het verstoorde functioneren van deze circuits zou niet alleen de dwangklachten in stand houden, maar geeft ook aanleiding tot afwijkingen die met behulp van neuropsychologisch onderzoek kunnen worden vastgesteld.
In de onderzoeken beschreven in dit proefschrift werden bepaalde aspecten van het cognitief functioneren en van de neurochemie van de dwangstoornis onderzocht bij zorgvuldig geselecteerde patiënten, waarbij vooral gebruik is gemaakt van twee zogenaamde functionele beeldvormende technieken: functionele Magnetic Resonance Imaging (fMRI) en Single Photon Emission Computer Tomography (SPECT). Functioneel wil hierbij zeggen dat met deze technieken informatie over de activiteit, het metabolisme of de neurochemie van het brein van levende proefpersonen kan worden verkregen. Bij fMRI wordt gebruik gemaakt van de paramagnetische eigenschappen van hemoglobine om de toegenomen bloeddoorstroming van actieve gebieden in de hersenen in kaart te brengen. Bij SPECT wordt gebruik gemaakt van in de bloedbaan ingebrachte radioactieve stoffen waarmee of de bloeddoorstroming of specifieke microstructuren in de hersenen in beeld kunnen worden gebracht. In tegenstelling tot depressie of schizofrenie waren bij OCS functionele beeldvormende technieken nog niet of nauwelijks toepast bij onderzoek naar cognitief functioneren en neurochemie.

# Deel 1
# Cognitief functioneren

## Antisaccade studies

OCS symptomen ontstaan waarschijnlijk in specifieke neuronale circuits die delen van de voorhoofdskwab, de dieper in de hersenen gelegen basale kernen, de thalamus en delen van het limbische systeem verbinden. Disfunctioneren van deze complexe circuits leidt ook tot verstoringen van het zogenaamde executieve functioneren (de cognitieve processen die doelgericht gedrag mogelijk maken). Hiertoe kunnen bijvoorbeeld het vermogen om gedrag te plannen of bewust te onderdrukken (inhibitie) worden gerekend. De kenmerkende symptomen van OCS, de zich opdringende gedachten en de zich herhalende handelingen, hebben geleid tot de hypothese dat een verstoord vermogen tot inhibitie een centrale rol zou spelen bij de aandoening. Deze hypothese wordt ondersteund door studies die hebben laten zien dat patiënten met OCS minder presteren op zogenaamde antisaccade taken. Dit zijn oogbewegingstaken waarbij aan proefpersonen wordt gevraagd om de reflex om direct naar een lichtje te kijken wat in het blikveld verschijnt (de saccade reflex) te inhiberen, en vervolgens een snelle oogbeweging naar precies de tegenovergestelde kant van het blikveld te maken. Onderdelen van de eerder genoemde complexe neuronale circuits zijn ook betrokken bij (anti)saccades. In hoofstuk II worden de resultaten van een tweedelige studie beschreven waarin eerst onderzocht werd hoe patiënten met OCS die nog nooit medicijnen tegen de aandoening hebben gebruikt presteren op een aantal oogbewegingstaken.

Opmerkelijk genoeg bleken deze patiënten de saccade reflex in alle taken net zo goed te kunnen inhiberen als gezonde controlepersonen, hadden ze net zoveel tijd nodig om de reflex uit te voeren als dat wel was toegestaan, maar hadden ze meer tijd nodig als ze moesten inhiberen en vervolgens een beweging naar de andere kant moesten maken (de antisaccade). Dit pleit tegen een centrale rol van inhibitie in het verstoorde cognitieve functioneren bij OCS, en wijst mogelijk eerder op een gestoord vermogen om interne representaties van een gedragsdoel (in dit geval het imaginaire doel van de antisaccade) te gebruiken. In het tweede deel van deze studie bleek het boven beschreven patroon toestandsonafhankelijk; afname van de klachten had geen effect op het patroon. Dit suggereert dat de specifieke afwijkingen op de antisaccadetaak een kenmerk zouden kunnen zijn voor de aanwezigheid van OCS, maar wellicht ook voor een (genetische) kwetsbaarheid voor de aandoening.

## Werkgeheugen

Neuropsychologische studies hebben laten zien dat OCS ook gepaard gaat met een verstoring van het ruimtelijke werkgeheugen, een ander aspect van het executief functioneren. Met werkgeheugen wordt het systeem bedoeld waarmee we tijdelijk informatie 'on-line' kunnen houden, zoals bijvoorbeeld een telefoonnummer of de posities van voorwerpen. Hoofdstuk III beschrijft de eerste studie waarin het ruimtelijke werkgeheugen bij OCS met behulp van beeldvormend onderzoek is onderzocht. Bij deze fMRI studie werd gebruik gemaakt van een in belasting toenemende werkgeheugen taak. Opnieuw namen patiënten deel die voor hun dwangklachten nog nooit medicatie hadden gebruikt. In vergelijking met controle personen presteerden de patiënten slechter op het moeilijkste niveau van de taak. Zij gebruikten tijdens de taak echter dezelfde hersengebieden en op een vergelijkbare wijze als de controlepersonen. Alleen in een gebied centraal in de voorhoofdskwabben (de cingulate cortex) waarvan bekend is dat het betrokken is bij het uitvoeren of monitoren van strategieën, was de activiteit gedurende de hele taak verhoogd. Deze resultaten lijken erop te wijzen dat het spatiele werkgeheugen als zodanig niet tekort schiet, maar dat er mogelijk sprake is van een probleem rond aansturing of strategie. In zeer recente studies bij OCS wordt in toenemende mate aandacht besteed aan een mogelijk afwijkend functioneren van de cingulate cortex op het vlak van strategie en het monitoren van doelgericht gedrag

In een volgende studie, beschreven in hoofdstuk IV, onderzochten we of een duidelijke afname van klachten door behandeling effect had op de prestatie op de taak en op de activiteit in de betrokken gebieden. Een afname van klachten bleek te leiden tot een verbetering van de prestatie en ging gepaard met een globale verandering van het activatiepatroon. De geobserveerde verandering van het activatiepatroon lijk te wijzen op een effectiever gebruik van de betrokken gebieden. In tegenstelling tot wat men echter op grond van de bevindingen uit de eerste studie zou kunnen verwachten, was de verandering van het activatiepatroon echter niet beperkt tot het gebied van de cingulate cortex.

# Deel 2

# Neurochemie

In Deel II wordt onderzoek beschreven naar de betrokkenheid van bepaalde neurotransmittersystemen bij OCS. Neurotransmitters zijn stoffen die zorgen voor de prikkeloverdracht tussen zenuwcellen. Op grond van diverse indirecte bevindingen is verondersteld dat OCS vooral gepaard gaat met afwijkingen in het systeem voor serotonine. Recente bevindingen lijken er echter op te wijzen dat ook andere neurotransmittersystemen, met name het dopaminerge systeem, betrokken kunnen zijn bij het ontstaan of instandhouden van dwangklachten. Met behulp van bepaalde functionele beeldvormende technieken kan men onderdelen van neurotransmittersystemen op direct wijze in de hersenen van levende proefpersonen onderzoeken. Hierbij wordt meestal gebruik gemaakt van een radioactief gelabelde stof die, na in de bloedbaan te zijn ingebracht, selectief aan het te onderzoeken onderdeel bindt. Door het meten van de radioactieve straling kan men onderzoeken in welke hersengebieden het specifieke onderdeel voorkomt en kan men tevens een maat voor de dichtheid van dat onderdeel in een bepaald hersengebied verkrijgen.
In hoofdstuk V werden met behulp van Single Photon Emission Tomography (SPECT), in combinatie met een anatomische MRI scan, de bindingspatronen van een radioactief gelabelde stof ([123I]beta-CIT) onderzocht bij patiënten met OCS die nog nooit medicatie hadden gebruikt en bij een groep zorgvuldig uitgezochte controlepersonen. Beta-CIT bindt aan zowel serotonine als dopamine transporters, maar door bepaalde eigenschappen van de stof kunnen de twee soorten transporters apart in beeld gebracht worden. Transporters zorgen ervoor dat dopamine of serotonine weer in de zenuwcel worden opgenomen nadat het is vrijgekomen bij de prikkeloverdracht. In tegenstelling tot de hypothese die een centrale rol van serotonine veronderstelt, werden wel afwijkingen gevonden in de binding aan dopamine transporters, maar niet in die aan de serotonine transporters.
In hoofdstuk VI werden met dezelfde combinatie van SPECT en anatomische MRI technieken de bindingspatronen onderzocht van een andere radioactief gelabelde stof ([123I] IBZM), die vooral bindt aan de zogenaamde D2 receptor. Een receptor is een eiwit, in dit geval op de buitenkant van een zenuwcel, waaraan een bepaalde neurotransmitter zich kan binden (sleutel-slot principe). Binding van de neurotransmitter zorgt voor een verandering van de structuur van het receptor eiwit, waardoor allerlei andere gebeurtenissen in gang worden gezet, zoals bijvoorbeeld ontlading van de zenuwcel (= signaal). Bij de patiënten met OCS bleek de binding aan de D2 receptor in een onderdeel van de voor OCS belangrijke basale kernen, minder dan bij de controlepersonen.
In hoofdstuk V en VI werd op een directe wijze aangetoond dat er bij OCS afwijkingen in het dopaminerge systeem bestaan. Deze bevindingen kunnen leiden tot een verdere verfijning van de modellen voor OCS en tot nieuwe aangrijpingspunten voor onder andere onderzoek naar de genetica en medicamenteuze behandeling van OCS.

In de verschillende hoofdstukken en in hoofdstuk VII (Summary and general discussion) worden specifieke mogelijke beperkingen van de verrichtte studies besproken en aanbevelingen gedaan voor verder onderzoek. Een aantal opmerkingen is echter op alle

studies van toepassing. Zo werden bijna alle studies uitgevoerd bij streng geselecteerde patiënten met OCS die geen bijkomende psychiatrische aandoening hadden. In de praktijk is echter wel vaak sprake van een bijkomende psychiatrische aandoening, wat de algemene toepasbaarheid van bevindingen in dit proefschrift voor patiënten met OCS beperkt. Een andere algemene beperking is dat er geen rekening is gehouden met het type dwangklachten wat patiënten vertoonden. Inmiddels zijn er steeds meer aanwijzingen dat er aparte clusters van OCS symptomen bestaan, die waarschijnlijk ook een iets andere basis in de hersenen hebben.

Tenslotte moet genoemd worden dat oogbewegingen, werkgeheugen en neurotransmittersystemen bij de OCS hier min of meer apart onderzocht zijn. Studies suggereren echter dat er verbanden bestaan tussen deze onderwerpen. Deze verbanden konden in dit project uiteindelijk niet worden onderzocht, omdat de onderzoeken door omstandigheden bij verschillende groepen patiënten moesten worden verricht.

# Dankwoord

Velen ben ik dank verschuldigd voor hun hulp en steun bij het tot stand komen van dit proefschrift. Allereerst wil ik graag de patiënten noemen die deelnamen aan de verschillende onderzoeken. Zij waren zeer gemotiveerd en stelden vaak alles in het werk om onderzoeken hoe dan ook door te laten gaan en zo betrouwbaar mogelijke gegevens te verkrijgen.

Mijn beide promotoren: René Kahn en Herman Westenberg.
Beste René, ik heb het altijd als een voorrecht beschouwd dat ik bij jouw mijn basisopleiding tot psychiater kon doen. Je gedegen en voortvarende aanpak van opleiding en onderzoek en je visie op het vak spraken me zeer aan. Ik solliciteerde aanvankelijk voor een promotieplaats, maar kwam vervolgens in de opleiding terecht. Promoveren is echter nooit uit beeld geraakt en uiteindelijk is het de omgekeerde volgorde geworden. Ik ben je dankbaar voor het vertrouwen wat ik altijd gevoeld heb. Je hebt een opmerkelijk vermogen om direct tot de essentie te komen en de grote lijnen in de gaten te houden. Indrukwekkend is ook de snelheid waarmee je altijd reageerde op manuscripten en e-mail.
Beste Herman, vanaf het begin af aan was je zeer betrokken bij de verschillende projecten en kon ik profiteren van je indrukwekkende kennis en je vermogen om zeer uiteenlopende onderzoeksterreinen met elkaar te verbinden. Jij initieerde de SPECT studies naar de mogelijke rol van dopamine bij de dwangstoornis. Ik heb goede herinneringen aan het samen bediscussiëren van resultaten en manuscripten. Ik heb veel respect voor je onvermoeibare intellect en enthousiasme.

Mijn copromotor: Harold van Megen.
Beste Harold, ik heb het geluk gehad een groot deel van mijn opleidingstijd onder jouw supervisie te mogen doen en later ook als collega met je te kunnen samenwerken. Zelden heb ik zoveel geleerd over de psychiatrie, mijzelf en het leven in het algemeen. Ook als copromotor was je rol weer van groot belang. Jij startte de behandelstudie waarvoor veel patiënten met dwangklachten naar Utrecht kwamen. Je vermogen om de zaken steeds in een juist perspectief te plaatsen, je goed ontwikkelde gevoel voor humor en een inmiddels legendarische Bourgondische instelling zijn gedurende het promotietraject van grote waarde geweest. Daarnaast was je ook altijd een kritisch lezer van de manuscripten en onderzoeksvoorstellen.

Dr. Nick Ramsey.
Beste Nick, zonder jou intensieve bemoeienis waren de studies niet van de grond gekomen, al was het in het begin wel ‘learning functional MRI the hard way’. Je bijdrage is zonder meer essentieel geweest. Je hebt er veel energie in gestoken om mij tot iets van een neuroimaging onderzoeker om te vormen. Ik zal op deze plaats ook nog excuses maken voor het feit dat ik je tijdens onze eerste gesprek heb gevraagd of jij voor je opleiding ook een bepaalde fMRI cursus ging volgen. Je bleek de cursus te geven… Je beheersing van werkelijk alle aspecten van de neuroimaging, van hardware tot onderzoeksdesign en analyse, is fenomenaal. Ik ben je zeer dankbaar voor de prettige samenwerking.

Ik ben veel mensen uit mijn 'Utrechtse tijd' dank verschuldigd voor hun steun, expertise of kameraadschap. Martijn Jansma, René Mandl , Hans Hoogduin, Magriet Sitskoorn, Geert-Jan Rutten en Arjen van der Schaaf leverden alle drie en speelden een belangrijke rol bij de opzet en uitvoering van verschillende studies. Damiaan Denys was medebehandelaar en medeonderzoeker binnen de Utrechtse OCS behandelstudie en zorgde regelmatig voor een verfrissend perspectief door de zaken vanuit zijn Vlaamse achtergrond te beschouwen.
Mijn stagiair Hans Hardeman was van onschatbare waarde met zijn pragmatische instelling, zijn werklust en zijn correcte manier van omgaan met proefpersonen. Helaas ben je niet voor de psychiatrie behouden gebleven. Henk Stevens en Alice van Dongen van de afdeling Nucleaire Geneeskunde waren onmisbaar voor het SPECT project. Het invliegen van de radioactieve ligand en het ontwikkelen van de juiste markerprocedure was geen sinecure. Mathijs Raemaekers was zo goed te helpen bij het opzetten van de oogbewegingstudies. Femke de Geus en Mirjam Salden ben ik erkentelijk voor hun efficiënte en prettige manier van samenwerken en het delen van hun methodologische kennis. Diverse medewerkers van de structurele en functionele MRI groepen zorgden op de achtergrond voor de computer systemen, het databeheer en de software. Die enkele keer dat het misliep bleek hun onschatbare waarde.
De toenmalige leden van de 'Angstgroep', onder wie Gerrit Glas, Irene van Vliet, Nienke Tenney en Arnold Franken, vormden een onmisbaar klankbord door de referaten en onderzoeksbesprekingen. Jeanette Isopacua, Emmy Drost en Elly Schreurs vormden samen een secretariële rots in de branding. De collegae stafleden en de arts-assistenten in het UMCU bezagen met enige verwondering hoe ik op mijn wekelijkse onderzoeksdagen aan beeldschermen en laptops gekluisterd zat, maar waren altijd geïnteresseerd en zorgden voor de broodnodige klinische afwisseling.
De bewoners van de 'kantoortuin' en 'de beeld(schermen)tuin'; de onderzoekers en stagiaires, namen me als medisch staflid zonder problemen in hun midden op, waardoor ik ook iets van het echte AIO- en onderzoekersgevoel mocht ervaren. Het bekende ruimtegebrek in kantoortuinen leek in dit geval het beste in iedereen naar boven te halen.Veel goede herinneringen heb ik ook aan de 'half twaalf lunchclub'. Ruim voordat de kantine volstroomde met het personeel van de andere afdelingen in het ziekenhuis werd er met een gemêleerd gezelschap uitgebreid gegeten, maar vooral ook uitgebreid gediscussieerd over zaken van maatschappelijk, existentieel en van twijfelachtig wetenschappelijk belang.

De collegae en onderzoekers van de afdeling psychiatrie in het LUMC hebben mij gesteund bij de laatste loodjes en vormen een inspirerend gezelschap. Frans Zitman wil ik bedanken voor het feit dat hij mij in de gelegenheid heeft gesteld op het LUMC mijn proefschrift af te ronden.

De leden van de beoordelingscommissie wil ik bedanken voor het kritisch beoordelen van het proefschrift.

Mijn beide paranimfen Bart van der Worp en Peter van den Borne, en natuurlijk Geert-Jan Itjeshorst. We kennen elkaar al sinds onze studententijd. Het is geruststellend om te merken

hoe weinig we ondanks alle life-events eigenlijk veranderd zijn en hoe gemakkelijk we altijd weer de draad op kunnen pakken.
Door de jaren heen is ook mijn intervisieclub een gezelschap geweest waar ik op een andere manier naar mijn promotie of professionele beslommeringen kon kijken en waar ik gesterkt vandaan kwam. Ik hoop dat de komende jaren net zo verrijkend mogen zijn.

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Lieve Marieke, het is een zeldzaam drukke tijd geweest, al was je zo lief tegen anderen op te merken dat ons intensieve gezinsleven en vele sociale activiteiten er niet onder leden. Hopelijk is er nu weer eens gelegenheid om samen een moment niets te doen.

# Curriculum Vitae

Nic van der Wee werd op 9 maart 1965 geboren in Bergen op Zoom. Hij behaalde daar in 1983 het diploma Atheneum B aan de Roncalli Scholengemeenschap. Van 1983 tot en met 1986 studeerde hij Biologie aan de Rijksuniversiteit Utrecht. In 1985 werd tevens aangevangen met de studie Geneeskunde. Gedurende zijn studie was hij diverse malen studentenassistent, was actief op verschillende studentenverenigingen en sportclubs en was gedurende een jaar lid van de Universiteitsraad. In de wachttijd voor de co-schappen liep hij een primary health care stage aan de University of Calabar, Calabar, Nigeria. Ook een aantal co-schappen werd in het buitenland gevolgd: Psychiatrie en Chirurgie in het Centre Hospitalier Sainte Anne te Parijs, en Gynaecologie in het United Bulawayo Hospital te Bulawayo, Zimbabwe. Het artsexamen werd behaald op 30 oktober 1992. Aansluitend vervulde hij de militaire dienstplicht bij de Sectie Individuele Hulpverlening van de Koninklijke Landmacht. In 1994 startte hij met de basisopleiding tot psychiater op het Academisch Ziekenhuis Utrecht (opleider Prof. dr. R.S. Kahn). De stage sociale psychiatrie werd parttime gevolgd op het Regionaal Psychiatrisch Centrum in Zeist (opleider M. de Pater) in combinatie met een parttime keuzejaar biologisch psychiatrisch onderzoek op het Academisch Ziekenhuis Utrecht. Op 1 maart 1999 volgde de registratie als psychiater. Van maart 1999 tot en met augustus 2002 was hij werkzaam als psychiater en onderzoeker bij de Zorglijn Angst en Dwangstoornissen van de afdeling Psychiatrie van het Universitair Medisch Centrum Utrecht. Gedurende deze periode werd het grootste deel van het in dit proefschrift beschreven onderzoek verricht. Sinds augustus 2002 is hij verantwoordelijk voor de polikliniek Angststoornissen en het beeldvormend onderzoek van de afdeling Psychiatrie van het Leids Universitair Medisch Centrum. Hij is gehuwd met Marieke van Haaren. Zij hebben een tweeling, Bente en Mats.