Cognitive flexibility in obsessive-compulsive disorder and major depression

Functional neuroimaging studies on reversal learning and task switching

Peter Lorin Remijnse

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'…en wee hem die vraagt: Waarom?'
Nescio, *Titaantjes*

Aan Jac. Remijnse (1918-2009)

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Contents

Chapter 1

Introduction and outline of the thesis

Introduction

Obsessive-compulsive disorder

Obsessive-compulsive disorder (OCD) is a psychiatric disorder characterized by recurrent, anxiety-provoking thoughts (i.e. obsessions) and repetitive behaviors or mental acts (i.e. compulsions). Compulsions aim to alleviate the anxiety that is caused by obsessions. Obsessions and compulsions are time-consuming and lead to significant functional impairments (APA, 1994; table 1.1). This debilitating mental illness has an estimated lifetime prevalence of 0.9% in the general population in the Netherlands (van Dorsselaer et al., 2006), and of 2.3% in the United States of America (Ruscio et al., 2010).

Notably, the content of obsessions and compulsions in patients with OCD is heterogeneous. Factor and cluster analytical studies have consistently identified at least four symptom dimensions: 1. symmetry/ordering, 2. harm/checking, 3. contamination/cleaning, and 4. hoarding (Mataix-Cols et al., 2005). These dimensions are temporally (Mataix-Cols et al., 2002) and cross-culturally (Matsunaga et al., 2008) stable, and are associated with specific patterns of comorbidity (Hasler et al., 2005) and treatment response (Mataix-Cols et al., 1999). Moreover, neuroimaging studies have shown that these different symptom dimensions are mediated by partially distinct and overlapping neural substrates, as assessed in resting-state PET studies (Saxena et al., 2004), symptom provocation magnetic resonance imaging designs (Phillips et al., 2000; Mataix-Cols et al., 2004; An et al., 2009) and voxel-based morphometry studies (van den Heuvel et al., 2009).

Major depressive disorder

Major depressive disorder (MDD) is characterized by a period of at least 2 weeks in which there are core symptoms of either lowered mood and/or a loss of interest or pleasure in nearly all activities. In addition, this unipolar mood disorder entails a range of additional symptoms such as inattention, fatigue, self-depreciating or suicidal thoughts, and disturbances of psychomotor activity, sleep, appetite and weight (APA, 1994; table 1.2). MDD occurs frequently, as indicated by an estimated lifetime prevalence of 18.7% in the general Dutch population (de Graaf et al., 2010). For this reason, depression has been designated as 'the epidemic of our time' (Savitz et al., 2009). Importantly, OCD and MDD are frequently co-morbid disorders (Overbeek et al., 2002), with 40.7% of all patients with OCD fulfilling the criteria of a co-morbid MDD (Ruscio et al., 2010).

Cognitive flexibility

Cognitive flexibility can be defined as the ability to rapidly change response strategies upon altering task-relevant information in the environment (Evers et al., 2006; Cools et al., 2006). Over the last decades, the concept of cognitive flexibility has been operationalized in several ways in laboratory settings. Originally, the Wisconsin Card Sorting Test (WCST) was introduced as the prototypical assay of cognitive flexibility (Milner, 1963). However, the WCST was gradually

Table 1.1: Diagnostic criteria for obsessive-compulsive disorder according to DSM-IV (APA, 1994)

A.	Either obsessions or compulsions: Obsessions as defined by (1), (2), (3), and (4): (1) Recurrent and persistent thoughts, impulses or images that are experienced, at some time during the disturbance as intrusive and inappropriate and that cause marked anxiety or distress (2) the thoughts, impulses, or images are not simply excessive worries about real-life problems (3) the person attempts to ignore or suppress such thoughts, impulses, or images, or to neutralize them with some other thought or action (4) the person recognizes that the obsessional thoughts, impulses, or images are a product of his or her own mind (not imposed from without as in thought insertion) Compulsions as defined by (1) and (2): (1) repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly (2) the behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviors or mental acts either are not connected in a realistic way with what they are designed to neutralize or prevent or are clearly excessive
B.	At some point during the course of the disorder, the person has recognized that the obsessions or compulsions are excessive or unreasonable. Note: This does not apply to children.
C.	The obsessions or compulsions cause marked distress, are time consuming (take more than 1 hour a day), or significantly interfere with the person's normal routine, occupational (or academic) functioning, or usual social activities or relationships.
D.	If another Axis I disorder is present, the content of the obsessions or compulsions is not restricted to it (e.g., preoccupation with food in the presence of an Eating Disorder; hair pulling in the presence of Trichotillomania; concern with appearance in the presence of Body Dysmorphic Disorder; preoccupation with drugs in the presence of a Substance Use Disorder; preoccupation with having a serious illness in the presence of Hypochondriasis; preoccupation with sexual urges or fantasies in the presence of a Paraphilia; or guilty ruminations in the presence of Major Depressive Disorder).
E.	The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition

acknowledged a measure too complex to specifically tap neuropsychological functions (Rogers et al., 1998). Therefore, in an attempt to decompose the various neurocognitive processes supposedly involved in the WCST, the CANTAB (Cambridge Neuropsychological Test Automated Battery; see www.camcog.com) intra- and extradimensional (ID/ED) shift learning task was introduced by the research group of professor Trevor Robbins and professor Barbara Sahakian from the department of experimental psychology in Cambridge, UK (e.g. Owen et al., 1991). This ID/ED shift task consisted of different, separate stages, i.e. a compound visual discrimination acquisition stage, an 'ID shift' stage, an 'ED shift' stage and a 'reversal' stage (Rogers et al., 2000; Robbins, 2007). In the compound visual discrimination acquisition stage, subjects learn to respond to a particular stimulus dimension, such as color or shape. In the ID shift stage, subjects are required to transfer the learned rule to a novel set of exemplars of the same stimulus dimension. During the ED shift stage, participants need to shift set to an alternative, previously irrelevant dimension. Finally, in the reversal stage, subjects are required

Table 1.2: Diagnostic criteria for a major depressive episode according to DSM-IV (APA, 1994)

A.	Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure 1) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). Note: In children and adolescents, can be irritable mood. 2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others) 3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gains. 4) insomnia or hypersomnia nearly every day 5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down) 6) fatigue or loss of energy nearly every day 7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick) 8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others) 9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
B.	The symptoms do not meet criteria for a Mixed Episode (i.e. criteria are met for both a manic and a major depressive episode during at least a 1-week period)
C.	The symptoms cause clinically significant distress or impairment in social, occupational, or other \ important areas of functioning
D.	The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism)
E.	The symptoms are not better accounted for by Bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation

to reverse stimulus-reward associations between the same pair of exemplars within a dimension. Traditionally, the ID and ED shifts have been termed 'attentional set shifts' and a reversal shift has been termed 'affective shifting' (Dias et al., 1996). Interestingly, a double dissociation for attentional and affective shifts has been demonstrated in marmoset monkeys: whereas lateral prefrontal lesioned monkeys showed impairments on extra-dimensional ('attentional') shifting but intact reversal ('affective') shifting, the opposite was true for orbitofrontal cortex ablated animals (Dias et al., 1996). These results in monkeys were partly confirmed in humans by Fellows et al. (2003), who reported a single dissociation in that OFC-lesioned patients exhibited deficits on reversal shifting, in contrast to subjects with DLPFC damage. Apart from these dorsal and ventral prefrontal brain areas, intact basal ganglia functioning has also been shown a prerequisite for adequate shifting behavior (e.g. Divac et al., 1967).

A drawback of the outlined ID, ED, and reversal neuropsychological paradigms, however, is that they all conflate switching with feedback-based learning (Robbins, 2007). A switch paradigm

uncontaminated by contingency learning is 'task switching', that was first introduced by Rogers et al. (1995). In such a design, subjects perform task A and – after several trials – switch to task B upon a cue, then after several trials back to A and so on (Monsell, 2003).

OCD, MDD and cognitive flexibility

Both patients with OCD and patients with MDD are characterized by a lack of cognitive flexibility from a phenomenological point of view. Specifically, in patients with OCD, recurrent intrusive thoughts and repetitive invariant motor or mental acts clearly contain elements of cognitive and behavioral rigidity. In MDD, the feature of 'rumination' which is highly characteristic of depressed patients (Gotlib et al., 2010), points to an impairment in cognitive flexibility as well.

In addition to these phenomenological features, neuropsychological studies on cognitive flexibility in OCD and MDD have resulted in numerous reports of deficits on such measures in these patient groups. For instance, patients with OCD have shown impairments on ID set shifting (Veale et al., 1996), ED set shifting (Veale et al., 1996; Watkins et al., 2005; Chamberlain et al., 2006, but see Purcell et al., 1998 and Nielen et al., 2003), and reversal learning (Valerius et al., 2008, but see Chamberlain et al., 2007). Similarly, patients with MDD have shown impairments on ID shifting (Purcell et al., 1997), on ED shifting (Purcell et al., 1997; Beats et al., 1996), and on reversal learning (Murphy et al., 2003). However, findings in MDD have also been equivocal, see for instance Elliott et al. (1996) and Sweeny et al. (2000).

Finally, numerous neuroimaging studies in patients with OCD (for a review see Aouizerate et al., 2004) and patients with MDD (for a review see Savitz et al., 2009) have repeatedly demonstrated dysfunctions in frontal-striatal and frontal-limbic brain circuits. These large-scale neural networks connect prefrontal cortical regions with basal ganglia and limbic areas, respectively, and subserve intact human cognitive and emotional functioning. Indeed, these brain structures also constitute the neural substrate of intact cognitive flexibility, as indicated previously.

Thus, to summarize, several lines of research suggest that cognitive flexibility may be disturbed in OCD and MDD.

Outline of the thesis

In 2002, the current PhD research started as part of a tripartite NWO-funded TOP-project (No. 912-02-050) in collaboration with the University of Maastricht and the Netherlands Institute for Neuroscience. The main objective of this three-centre research was to investigate the role of the orbitofrontal cortex and the involvement of serotonin (5-HT) in cognitive flexibility. To this aim, prefrontal cortex functioning was assessed in healthy volunteers (University of Maastricht, PhD student Lisbeth Evers; PhD thesis 2006), in rats (Netherlands Institute for Neuroscience, PhD student Geoffrey van de Plasse; PhD thesis 2010) and in psychiatric patients (VU University Medical Center Amsterdam, Peter Remijnse; the present PhD thesis). Specifically, our VUmc project aimed to assess the neural correlates of measures of cognitive

flexibility in two groups of psychiatric patients putatively associated with cognitive rigidity, abnormal prefrontal cortex functioning and 5-HT transmission, i.e. patients with OCD and with MDD.

First, we reviewed all published neuroimaging studies in OCD up until around 2004, at the start of the experimental work described in this thesis. This review is presented in **chapter 2.** It contains an overview of different categories of neuroimaging designs in OCD, according to the experimental paradigms used, i.e. structural neuroimaging studies, functional resting-state studies, symptom provocation designs, cognitive activation paradigms, and MRS/ligand studies. Apart from these different experimental paradigms, various techniques have been used in the field of neuroimaging in OCD (e.g. PET, SPECT, functional MRI), each with its own strengths and limitations. Finally, in addition to patients presently suffering from OCD symptoms, remitted subjects with OCD post-treatment have been scanned in follow-up designs, with the aim to assess trait- and state-aspects of aberrant neuroimaging findings in this disorder. Our review concludes with an attempt to integrate the described findings into an emotion processing model (Phillips et al., 2003) that the authors previously had used for major psychiatric disorders such as schizophrenia and depression, but not OCD.
As outlined earlier in this introduction, a specific neuropsychological paradigm targeting the OFC-striatal circuit is reversal learning. Until 2002, four functional neuroimaging studies using reversal learning tasks in healthy volunteers had been published (Rogers et al., 2000; Nagahama et al., 2001; O'Doherty et al., 2001; Cools et al., 2002). However, all of these studies showed methodological problems on important aspects. Specifically, the lower part of the brain (below the AC-PC axis including the OFC) was not scanned (Nagahama et al., 2001), PET was used as a scanning-technique precluding event-related assessment of brain activity (Rogers et al., 2000), the crucial contrast of affective switching was not reported in an event-related fMRI study (O'Doherty et al., 2001), and susceptibility artefacts distorted BOLD signals in OFC in another fMRI study (Cools et al., 2002). Moreover, in none of these paradigms the main effects of reward, punishment and affective switching could be assessed, due to the lack of an affectively neutral baseline. In order to tackle these previous methodological limitations, we developed a novel reversal learning task. In **Chapter 3**, we describe the methodological issues as well as the neural substrate of our newly developed reversal learning task which we used in our experimental work. Importantly, we implemented an optimized EPI sequence sensitive to OFC signal - known to suffer from susceptibility artefacts in regular EPI sequences. Moreover, we added an affectively neutral baseline to our experimental task.
Having addressed these methodological issues and having identified the neural substrate of our reversal learning paradigm in healthy subjects, we subsequently aimed to employ this paradigm in a group of patients with OCD. Since the use of psychotropic medication has been shown to interact with neural activations (Norbury et al., 2007), we recruited a sample of unmedicated patients with OCD. **Chapter 4** describes the behavioral and imaging findings of a group of patients with OCD on our reversal learning task during fMRI.

Next, we aimed to implement the reversal learning task in a sample of unmedicated patients with MDD. The objective of that study was two-fold: first, we wished to assess the neural substrate of reversal learning in another psychiatric disorder presumed to be characterized by cognitive inflexibility and by dysfunctional frontal-striatal activations. Second, we aimed to directly compare patients with MDD and patients with OCD in a single-activation design. Notably, neuroimaging studies directly comparing OCD and depression have thus far been very rare in the literature. Of importance, we partly assembled a new group of patients with OCD - free from co-morbid depression - relative to the described sample in chapter 4. The results of this experiment are presented and discussed in **chapter 5**.

A different neuropsychological task for measuring cognitive flexibility is a task switching paradigm. In such a design, as outlined earlier in the introduction, learning and switching are not conflated measures, in contrast to a reversal learning paradigm. Moreover, this type of cognitive flexibility examines a 'purely' cognitive form of switching outside the context of emotional/motivational factors. This, too, is in contrast to reversal learning. In order to investigate the neural correlates of task switching in both OCD and MDD, we conducted the study described in **chapter 6**.

The previous chapters (4-6) all describe *functional* neuroimaging studies in MDD and OCD. However, little is known concerning the relationship between dysfunctional neuroimaging activations and possible *structural* brain abnormalities in these disorders. To obtain more insight into this relationship with regard to OCD, we employed a structural neuroimaging study using Voxel Based Morphometry (VBM), which is presented in **chapter 7.** In this study, we investigated both grey matter (GM) and white matter (MW) volumes in the brains of a large number of patients with OCD (N = 55) compared with an age-matched sample of healthy volunteers (N = 50). As outlined above in this introduction, OCD is a heterogeneous disorder containing several symptom dimensions. These various symptom dimensions have been associated differentially with dysfunctional neuroimaging activations. (Phillips et al., 2000; Mataix-Cols et al., 2004; An et al., 2009). However, structural neuroimaging studies with sufficient power assessing the neural substrates of these symptom dimensions in unmedicated patients with OCD were lacking thus far. Due to the large number of participants with OCD in our VBM study, and to the fact that all patients were off medication at the time of study, we were additionally able to explore the GM and WM correlates of the major symptom dimensions of OCD.

This thesis ends with **chapter 8,** that contains a summary of the findings presented in the previous chapters, and a general discussion. In this latter section, implications of our results for the neuropathophysiology of OCD and of MDD are discussed. Moreover, implications of our findings for the issue of comorbidity between OCD and MDD are considered. Finally, the strengths and limitations of the studies in this dissertation are discussed, and suggestions for future research presented.

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Chapter 2

Neuroimaging in obsessive-compulsive disorder

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*Both authors contributed equally to this chapter

Abstract

Neurobiological models of OCD have emphasized the mediation of clinical symptoms by aberrant frontal-striatal circuits in addition to dysfunctional neurotransmitter interactions, i.e. serotonergic-dopaminergic and glutamatergic-serotonergic. These models were mainly based on preclinical animal and laboratory reports as well as lesion studies and early imaging paradigms. Recently, a neurobiological model for normal human emotion perception has been described, proposing distinct ventral and dorsal processing systems corresponding with differential levels of emotion perception. This construct appears relevant for elucidating the pathophysiology of OCD, as OCD is classified as an anxiety disorder.

In the present paper we present a comprehensive review of the neuroimaging literature in OCD with the aim of critically appraising the support provided for current pathophysiological models, as well as relating these findings to constructs of normal emotion perception. Traditionally, neuroimaging designs in OCD included structural studies in search of morphological abnormalities, resting state measurements of cerebral blood flow and metabolism, and symptom provocation designs. Over the last few years, sophisticated functional neuroimaging paradigms have been introduced using cognitive and/or emotional paradigms; also, radioligands have become available to assess receptor distribution and affinity. These recent study designs are more hypothesis-driven and better respect the heterogeneity of OCD, increasing their sensitivity and specificity for elucidating the pathophysiological substrate of this disorder.

Results of imaging studies point to the need for adjustments in current models with respect to the involvement of frontal-striatal circuits in OCD. In line with recent insights into the neurobiology of emotion processing, a ventral-dorsal dissociation may be distinguished. Moreover, data from pediatric OCD patient samples have commenced to shed light on developmental characteristics of OCD. Furthermore, longitudinal designs from early into later life, in combination with pre-post treatment comparisons, are of great value for assessing the state-trait duality. Finally, the use of multimodal study designs holds great promise for the near future.

Introduction

Obsessive-compulsive disorder (OCD) is a neuropsychiatric condition that is characterized by intrusive anxiety-provoking thoughts (obsessions) and subsequent repetitive behaviors (compulsions)[1]. Lifetime prevalence rates of this often debilitating disorder as found in recent epidemiological studies range from 0.5%[2] to 2.9%[3] in the general population.

The role of neurobiological factors in the etiology of OCD was first suggested by descriptions of obsessive-compulsive behavior in patients with subcortical disorders, e.g. Huntington's disease[4], Sydenham's chorea[5], and pallidal lesions[6], and in patients with frontal lobe lesions[7]. Based on such observations, as well as on more recent functional neuroimaging data, several neurobiological models for OCD have been proposed[8-10]. Although differing on details, all these models emphasize the mediation of OCD symptoms by hyperactivity of frontal-striatal circuitry. In brief, cortical regions, mainly the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC), and striatal structures are presumed to be captured in a hyperfunctional, self-perpetuating loop[9]. In this hyperactive circuit, the prefrontal regions putatively subserve enhanced 'error detection', corresponding to the patients' characteristic sense that 'something is wrong'. The striatum is supposedly engaged in abnormal 'gating', relating to the selection and generation of aberrant behavioral patterns on the basis of erroneous information from cortical areas. Moreover, the dysfunctional striatum may allow the emergence of repetitive behavioral patterns that have a reinforcing function in alleviating distress caused by obsessional thoughts. Possibly, the striatum exerts this pathological function due to overactive dopaminergic projections to this structure[8;10]. Other neurotransmitters hypothesized to be involved in the pathophysiology of OCD are serotonin through its inhibitory interactions with dopamine, and glutamate by means of its excitatory role in frontal-striatal connections and its interactions with serotonin[11].

Although these models stress the involvement of para-limbic regions such as OFC and ACC in the pathophysiology of OCD, they do not attribute a role to key limbic structures, i.e. the insula and amygdala. This is surprising given the fact that OCD is considered an anxiety disorder and the amygdala is assumed to be the central component of fear processing[12]. A recent neurobiological model for human emotion processing[13;14] proposed several levels of emotion perception with corresponding neuronal correlates: first, the identification of the emotional significance of a stimulus and, subsequently, the production of an affective state. These subprocesses were assumed to be associated with a *ventral* neuronal system consisting of the amygdala, insula, ventral striatum and ventral regions of the prefrontal and cingulate cortices. Second, the regulation of the affective state was hypothesized to be represented by a *dorsal* neuronal pathway, i.e. hippocampus and dorsal regions of prefrontal and cingulate cortices. The authors used this model to describe affective symptoms in four main psychiatric disorders[14]. However, OCD was not among these disorders, leaving a lacuna to be filled.

In this article, we intend to contribute to the existing literature on the pathophysiology of OCD by reviewing all available neuroimaging papers in OCD, categorized according to the applied

technique or paradigm. First, we summarize the results of structural studies, after which we discuss resting state functional imaging studies. Next, symptom provocation designs are discussed followed by cognitive paradigms and, finally, ligand and magnetic resonance spectroscopy (MRS) studies. In each paragraph, we aim to not only review the results but also critically appraise methodological issues, and discuss the possibilities and limitations of the imaging technique or paradigm at stake for unraveling the neurobiology of OCD. A final discussion will integrate the findings, discuss the implications for the above-mentioned emotion processing model[13] and neurobiological models of OCD, and provide some directions for future research.

Structural imaging studies

Findings of structural imaging studies in OCD are summarized in Table 2.1. The first studies suggesting brain abnormalities in OCD were based on either *qualitative* evaluation of computed tomography (CT) scans, or measurements of whole brain volume and ventricle-to-brain ratios VBR[15;16]. Some years later, Luxenberg et al.[17] used CT for measurements of the striatum in a small sample of early-onset male OCD patients and healthy controls, reporting decreased bilateral caudate volumes in OCD. Subsequent volumetric studies in OCD, which were mainly based on magnetic resonance imaging (MRI) data, restricted their data analysis to the striatum. Variability of neuroanatomical criteria for delineation of regions of interest (ROIs), used in most of these studies[18-26], may partly explain inconsistent results obtained in these studies. Whereas results of Robinson et al.[21] supported the finding of decreased striatal volumes, also normal[18;20;22-26] or even increased[19;27] striatal volumes have been reported.

More recent MRI studies expanded the number of ROIs or performed whole brain data acquisition and analysis. These studies, however, revealed similarly inconclusive results. Concerning the ventral regions of the prefrontal cortex, including the ACC, increased[26;28;29] as well as decreased[27;30;31] volumes have been reported. Thalamic volumes were increased in medication-naïve pediatric OCD patients, normalizing after paroxetine treatment[32], as well as in adult OCD[29]. Both enlarged and diminished volumes were also found for temporal lobe structures such as the amygdala and hippocampus[28;30;33;34].

An alternative method of volumetric analysis of MR images is voxel-based morphometry (VBM)[35]. In VBM, structural images are segmented on a voxel-by-voxel basis and subsequently warped to anatomical standard space, so that individual volumetric differences will appear as differences in gray matter density. Potential confounds in VBM include differences in white matter/gray matter contrast between groups, and misclassification of voxels due to partial volume effects[36]. On the other hand, time-consuming drawing of ROIs, with its often low interrater reliability, can be avoided; moreover, VBM is a useful technique to assess subtle differences in gray matter concentrations at a microstructural level. So far, only 2 studies have used VBM in OCD[29;37]. Comparing 25 OCD patients with 25 healthy control subjects, Kim et al.[29] found increased gray matter densities in left OFC, left thalamus and bilateral hypothalamus in OCD patients. Gilbert et al.[37] investigated the relationship between age

Table 2.1: Structural imaging studies in OCD

Authors (publication date)	Technique	Subjects	Main findings	Methodological comments
Gilbert et al. (2004)[37]	MRI	21 pediatric OCD vs 15 co	Negative correlation between age and gray matter concentration in DLPFC in controls, not in OCD.	VBM
Pujol et al. (2004)[27]	Whole brain MRI	72 OCD vs 72 co	Decreased volume of medial PFC, OFC and L insulo-opercular region, increased volume bilateral ventral striatum and anterior cerebellum.	
Szeszko et al. (2004)[26]	MRI	23 pediatric OCD vs 27 co	Decreased volume L pallidum and increased gray matter volume of bilateral ACC.	ROI method (caudate, putamen, pallidum, ACC), comorbid diagnoses
Szeszko et al. (2004)[33]	Whole brain MRI	11 pediatric OCD vs 11 co (before vs after paroxetine)	At baseline (drug-naive): asymmetry of amygdala (L>R) in OCD, not in co. Post vs pre-treatment: decreased volume of L amygdala, correlation with paroxetine dosage.	Limited sample size
Choi et al. (2004)[31]	MRI	34 OCD vs 34 co	Decreased volume L anterior OFC, correlated with decreased performance on Rey-Osterrieth Complex Figure test.	ROI method (OFC), educational bias
Kwon et al. (2003)[34]	MRI	22 OCD vs 22 co vs 22 schizophrenia	Decreased volume bilateral hippocampus (in both OCD and schizophrenia), increased volume L amygdala (only in OCD).	ROI (hippocampus, amygdala, thalamus) instead of whole brain
Kim et al. (2001)[29]	MRI	25 OCD vs 25 co	Increased gray matter density in L OFC, L thalamus and bilateral hypothalamus, decreased in L cerebellum and cuneus.	VBM
Gilbert et al. (2000)[32]	MRI	21 pediatric OCD vs 21 co (before vs after paroxetine)	At baseline: increased thalamic volume. After paroxetine treatment: normalization of thalamic volume, correlated with reduction in symptom severity.	ROI (thalamus), treatment effect based on limited sample size (N=10)
Szeszko et al. (1999)[30]	MRI	26 OCD vs 26 co	Decreased volumes of bilateral OFC and amygdala in OCD; hemispheric asymmetry of hippocampal-amygdalar complex in co, not in OCD.	ROIs instead of whole brain.
Rosenberg et al. (1998)[28]	MRI	21 pediatric OCD vs 21 co	Increased volume ACC, normal volumes DLPFC, posterior cingulate, amygdala, hippocampus and temporal cortex. Negative correlation (trend) between age and ACC volume in controls, not present in OCD.	ROI method (OFC, DLPFC, ACC, post. cingulate, temporal cortex, hippocampus, amygdala)

Table 2.1: Continued

Authors (publication date)	Technique	Subjects	Main findings	Methodological comments
Bartha et al. (1998)[25]	MRI / MRS	13 OCD vs 13 co	Normal striatal volumes, but decreased levels of N-acetylaspartate in L striatum.	Limited sample size, ROI method (striatum)
Stein et al. (1997)[24]	MRI	13 OCD vs 12 co vs 17 trichotillomania	Normal striatal volumes, but positive correlation between striatal volume and performance on neuropsychological tests (Rey-Osterrieth Complex Figure test and Stroop test).	Limited sample size, ROI method (striatum)
Rosenberg et al. (1997)[23]	MRI	19 treatment-naïve pediatric OCD vs 19 co	Decreased volumes of putamen, normal caudate volumes, larger third ventricles, inverse correlation between volume of putamen and OCD symptom severity.	ROIs (striatum, PFC, ventricles)
Jenike et al. (1996)[38]	MRI	10 female OCD vs 10 female co	Decreased total white matter, but increased total cortex and operculum volumes.	Limited sample size
Aylward et al. (1996)[22]	MRI	24 OCD vs 21 co	Normal caudate volume.	ROI method (striatum)
Robinson et al. (1995)[21]	MRI	26 OCD vs 26 co	Decreased bilateral caudate volumes.	ROIs (striatum, PFC, ventricles)
Stein et al. (1993)[20]	CT	8 OCD(+HSS) vs 8 OCD(+LSS) vs 8 co	Increased ventricular volumes in OCD(+HSS) compared to OCD(+LSS) and controls. Normal caudate volumes.	ROIs (striatum, ventricles)
Scarone et al. (1992)[19]	MRI	20 OCD vs 16 co	Increased volume of R caudate nucleus.	ROI method (striatum), medicated patients.
Kellner et al. (1991)[18]	MRI	12 OCD vs 12 co	Normal caudate volume.	Limited sample size, ROIs (striatum, ACC, corpus callosum region), medicated patients
Garber et al. (1989)[144]	MRI	32 OCD vs 14 co	Prolonged T1 relaxation time in right frontal cortex, R>L asymmetry of OFC	Medicated patients
Luxenberg et al. (1988)[17]	CT	10 male early-onset OCD vs 10 male co	Decreased bilateral caudate volumes.	ROI method (striatum, ventricles), limited sample size, age biased.
Behar et al. (1984)[16]	CT	17 adolescent OCD vs 16 co	Ventricular enlargement.	VBR, Comorbid major depression
Insel et al. (1983)[15]	CT	10 OCD vs 10 co	Normal VBR, normal R-L asymmetry, no cortical atrophy.	VBR

and gray matter concentrations in 21 children with OCD and 15 control subjects. A negative correlation was found in the dorsolateral prefrontal cortex (DLPFC) in controls, reflecting a physiological age-related decrease in gray matter density. This correlation was absent in OCD patients, suggesting a neurodevelopmental abnormality.
During normal development of the brain neurons, dendrites, axons and synapses are first produced in excess, after which some are maintained while others are eliminated. This process of normally programmed cell death during brain development yields a decreasing ratio of gray to white matter. Increased gray matter density in specific regions of the frontal-striatal circuits in OCD patients compared with healthy control subjects may reflect a failure in synaptic proliferation or a defect in pruning processes. In 1996, Jenike and colleagues[38] were the first to report that cortex-to-white matter ratio was larger in OCD compared with controls. In addition to the search for subtle gray matter abnormalities, VBM might be used to detect white matter changes in the frontal-striatal pathways[39]. The investigation of normal and abnormal brain maturation in very young children with and without OCD may contribute to a better understanding of the role of neurodevelopmental processes in the pathophysiology of OCD. Longitudinal follow-up of these children into adolescence and adulthood enables visualization of natural history as well as the evaluation of long-term effects of treatment strategies.

To conclude, so far results of structural imaging studies in OCD have shown that morphological abnormalities, if present, are subtle. More refined analysis of whole brain images, including measurements of gray as well as white matter densities, is needed in homogeneous large samples. Accumulating evidence suggests that structural changes in OCD occur early in life, necessitating longitudinal follow-up of pediatric cohorts. Moreover, to understand the functional implications of structural changes, multi-modal imaging investigations are warranted. For instance, altered morphology may be related to an imbalance of interacting neurotransmitter systems[28]. Study designs combining MRS and VBM in pediatric OCD appear promising to investigate this issue. In addition, neuropsychological dysfunction and altered responsiveness of frontal-striatal circuits during functional MRI paradigms might be explained, at least partly, by subtle gray and/or white matter changes in frontal-striatal pathways. Therefore, results of functional imaging studies need to be corrected for possible morphological differences. Moreover, comparisons between OCD patients, their first-degree relatives and non-related control subjects may elucidate an underlying genetic predisposition. Finally, morphological characteristics, suggestive for neurodevelopmental abnormalities, may be used as endophenotypes for subsequent genetic investigations.

Resting-state studies

Resting-state studies aim to acquire data of basal brain metabolism or regional cerebral blood flow (rCBF) in patients while being in a neutral state. Resting-state studies have mainly been performed with the use of 18F-fluorodeoxyglucose (FDG) positron emission tomography

(PET) or Technetium-99m hexamethyl propyleneamine-oxime (99mTc-HMPAO) single photon emission computed tomography (SPECT), or inhalation of xenon-133 (133Xe) during SPECT. Results of these studies in OCD are summarized in Table 2.2.

Compared with healthy controls, these studies have frequently shown increased metabolism or rCBF for OCD patients in the OFC, either bilaterally[40-42], left-lateralized[43;44] or right-lateralized[45;46], and in bilateral[47;48] or left[44] ACC, left frontotemporal cortex[42], left insula[45] and right dorsal parietal cortex[41]. Also, elevated metabolism and rCBF have often been found in subcortical structures, such as bilateral[46;48-50] or right[42;44] thalamus, bilateral[40;43] or right[50] head of caudate nucleus, and bilateral putamen/pallidum[48;51]. These findings point toward hyperactive frontal-striatal circuitry in mediating OCD symptoms. This assumption is supported by frequently observed positive correlations between these metabolic alterations and symptom severity in OCD patients[41;45;46;52]. Also in line with this hypothesis is that functional correlations between these areas tend to diminish after successful treatment, as has been repeatedly demonstrated[53-55].

Conflicting findings have also been reported: *decreased* metabolism and rCBF have been found in the above mentioned structures as well, for the right OFC[52;56], left ACC[52], left lateral temporal cortex[56], left parietal cortex[45;56], bilateral[41] or right[56-58] caudate nucleus, bilateral putamen[57] and right[56] thalamus. Some of these functional abnormalities in this opposite direction were also correlated with clinical OCD rating scores[52;56]. However, metabolism and rCBF have been consistently found to be decreased in the bilateral dorsolateral/superior prefrontal cortex[56;58;59].

Differences between these studies with respect to the identified structures and to the direction of aberrant activity in OCD subjects may be due to several methodological issues, concerning both patient characteristics and technical (imaging) aspects. With regard to the former, the inclusion of OCD patients that used antiobsessional medication in some studies may have presented a confound[43;56;57;59]. Notably, in a recent pre-treatment to post-treatment functional neuroimaging study in OCD, the use of medication itself was found to induce brain metabolic alterations over time[60]. This implies that the concomitant use of medication in the above mentioned early resting-state studies might have confounded the results on cerebral metabolism or rCBF. Indeed, in several of these studies additional analyses were performed excluding medicated patients, which sometimes led to (slightly) different outcomes.

Another confounder in differentiating OCD and healthy subjects may have been the use of patient samples with concurrent major depression[43;50]. The exclusion of major depression in OCD for the comparison with controls is important, as depression rating scores in OCD patients have been found to be strongly correlated with decreased metabolism in right caudate, bilateral thalamus, bilateral amygdala and left hippocampus[49]. In support of this finding, Busatto et al.[52] demonstrated that diminished rCBF in right lateral OFC in OCD subjects relative to controls disappeared after excluding patients with concomitant major depression.

A final factor with regard to patient characteristics that may have skewed findings between patients and controls across resting-state studies is the inclusion of OCD groups differing

Table 2.2: Resting-state imaging studies in OCD

Authors (publication date)	Technique	Subjects	Main findings	Methodological comments
Saxena et al. (2004)[50]	FDG PET	12 hoarding OCD vs 33 non-hoarding OCD vs 17 co	Increased metabolism in bil thalamus and R caudate in non-hoarding vs hoarding OCD and controls. In hoarding OCD: decreased metabolism in post cingulate vs normals, decreased metabolism in bil dorsal ACC vs non-hoarders.	ROI and voxel-by-voxel. Comorbid depression in boarding and non-boarding OCD groups
Lacerda et al. (2003)[46]	HMPAO SPECT	16 OCD vs 17 co	Increased rCBF in R sup and R inf PFC and bil thalamus. Positive correlation CGI and R inf PFC	ROI
Nakatani et al. (2003)[51]	Xe-CT	31 OCD (before and after CBT) vs 31 co	Increased rCBF in bil putamen/pallidum. After successful CBT: decrease in rCBF in R caudate nucleus, correlated with functional improvement (GAF score).	ROI.No rescanning o control group
Kang et al. (2003)[67]	FDG PET	10 OCD (before vs after SSRI)	Follow-up of Kwon et al. (2003). Decreased rCBF in bil OFC, R hippocampus and R putamen, increased rCBF in post (parietal-occipital) regions.	Voxel-by-voxel rescanning of control group
Kwon et al. (2003)[45]	FDG PET	14 OCD vs 14 co	Increased metabolism in R OFC and L insula, decreased metabolism in parietal-occipital cortex. Positive correlation metabolism in L putamen, R hippocampus and R parietal cortex with Y-BOCS scores.	Voxel-by-voxel
Saxena et al. (2002)[60]	FDG PET	25 OCD vs 25 MDD vs 16 OCD+MDD (before vs after paroxetine) vs 16 co	Follow-up of Saxena et al. (2001). In OCD responders: decreased metabolism in R caudateand R putamen. In OCD (responders+non-responders): decreased metabolism in R VLPFC, bil OFC and thalamus.	ROI and voxel-by-voxel

Table 2.2: Continued

Authors (publication date)	Technique	Subjects	Main findings	Methodological comments
Saxena et al. (2001)[49]	FDG-PET	27 OCD vs 27 MDD vs 17 OCD+MDD vs 17 co	In OCD+MDD: decreased metabolism in L hippocampus. In OCD: increased metabolism in bil thalamus. In all OCD patients: negative correlation between depression scores and activity in subcortical structures.	ROI and voxel-by-voxel
Hoehn-Saric et al. (2001)[66]	HMPAO SPECT	16 OCD+MDD (before vs after sertraline or desipramine)	At baseline: increased rCBF in PFC, ACC and basal ganglia in eventual responders vs. non-responders. Decreased rCBF after treatment diffusely in PFC in responders, not in non-responders.	Voxel-by-voxel.No control group,, changes in rCBF activity not controlled for improvement severity0
Alptekin et al. (2001)[42]	HMPAO SPECT	9 OCD vs 6 co	Increased rCBF in bil OFC, R thalamus and L fronto-temporal cortex.	ROI. Limited sample sizes
Busatto et al. (2000)[52]	ECD SPECT	26 OCD vs 22 co	Decreased rCBF in R lateral OFC and L dorsal ACC. Y-BOCS scores positively correlated with L lat OFC and R med OFC activity.	Voxel-by-voxel. Eight OCD subjects with concomitant MDD
Saxena et al. (1999)[65]	FDG PET	20 OCD (before vs after paroxetine)	Decreased metabolism in R anterolateral OFC and R caudate in responders vs. non-responders. Lower pretreatment metabolism in L+R OFC predicted greater improvement in OCD severity with treatment.	ROI
Brody et al. (1998)[70]	FDG PET	27 OCD in prediction study; 18 treated with BT, 9 with fluoxetine	Higher pretreatment metabolism in L OFC associated with greater clinical improvement in BT group, yet worse outcome in medication group.	ROI. Small N in medication group, no random assignment to treatment groups
Lucey et al. (1997)[58]	HMPAO SPECT	15 OCD vs 15 PD+A vs 16 PTSD vs 15 controls	Extension of Lucey et al. (1995). Reduced rCBF in bil sup frontal cortices and R caudate for OCD and PTSD compared to PD and controls. BDI scores (highest in PTSD and OCD) correlated negatively with caudate metabolism.	ROI. RDI ratings not excluded as possible confounder for caudate hypometabolism

Table 2.2: Continued

Authors (publication date)	Technique	Subjects	Main findings	Methodological comments
Schwartz et al. (1996)[54]	FDG PET	9 OCD (also combined with 9 OCD from Baxter et al., 1992) after CBT	Replication from Baxter et al. (1992): decrease in L+ R caudate after successful BT, correlated with improved Y-BOCS scores on left side. Before treatment: significant correlations between OFC/Cd/thalamus on the right side.	ROI. No control group
Lucey et al. (1995)[56]	HMPAO SPECT	30 OCD vs 30 controls	Lower rCBF in R inf frontal cortex (including some of the OFC), R+L sup frontal cortex (including DLPFC), R caudate, L lat temp, L parietal and R thalamus. Lower rCBF in R inf frontal cortex correlated with Y-BOCS scores.	ROI. Small number of patients medicated (N=8)
Perani et al. (1995)[48]	FDG PET	11 OCD (9 of whom rescanned after SSRIs) vs 15 controls	Pretreatment: increased activity in cingulate, putamen and thalamus. Pre- to post-treatment: decrease in cingulate metabolism, correlated with improved Y-BOCS scores.	ROI. No rescanning of controls
Rubin et al. (1995)[55]	Xe inhalation and HMPAO SPECT	8 OCD pre- and post-treatment (clomipramine) vs 8 co	Follow-up of Rubin et al. (1992): For HMPAO pre- to post-treatment: decline in R dorsal parietal, L postero-frontal, bil OFC activity, persistent decrease in bil caudate	ROI. No rescanning of controls, confoudning medication effect not excluded
Edmonstone et al. (1994)[57]	Tc-exemetazime SPECT	12 OCD vs 12 MDD vs 12 controls	Decreased uptake in bil putamen and R caudate in OCD vs other groups. Inverse relationship between anxiety ratings and reduced basal ganglia uptake.	ROI. Medicated subjects
Baxter et al. (1992)[53]	FDG PET	9 OCD before and after fluoxetine or BT vs 9 co	Significant decrease in R caudate metabolism in responders to fluoxetine and BT, correlated with decrease in Y-BOCS scores for medication group.	ROI. Limited sample size, no direct comparisons between patients and controls

Table 2.2: Continued

Authors (publication date)	Technique	Subjects	Main findings	Methodological comments
Swedo et al. (1992)[64]	FDG PET	13 OCD after drug treatment	Follow-up of Swedo et al. (1989). Decreased metabolism in R+L OFC after therapy. Lower caudate metabolism at baseline predicted better long-term outcome. Change in R OFC correlated with improved OCD symptom scores.	ROI. No control group rescanned
Rubin et al. (1992)[41]	Xe inhalation and HMPAO SPECT	10 OCD vs 10 co	Increased uptake of HMPAO in R dorsal parietal, bil OFC and L postero-frontal. Decreased uptake in bil caudate. Positive correlation between rCBF and symptom severity.	ROI. No rating of depressive symptoms in patients
Hoehn-Saric et al. (1991)[68]	HMPAO SPECT	6 OCD after therapy with fluoxetine	Extension of Machlin et al. (1991). Decrease in relative medial frontal uptake after successful therapy, accompanied by a significant decrease in OCD symptoms.	ROI. Control group not rescanned, depressive symptoms not rated
Machlin et al. (1991)[47]	HMPAO SPECT	10 OCD vs 8 co	Increased rCBF in relative medial frontal uptake (including PFC regions and ACC), negatively correlated with Hamilton Anxiety scores. No difference for OFC.	ROI. Only prefrontal areas assessed
Benkelfat et al. (1990)[63]	FDG PET	8 OCD before and during clomipramine while performing CPT	Follow-up of Nordahl et al (1989). Decreased metabolism in R OFC and L caudate during successful treatment, correlated with improved OCD severity ratings.	ROI. No rescanning of control group
Martinot et al. (1990)[59]	FDG PET	16 OCD vs 10 co	Decreased absolute metabolism in whole brain, OFC, DLPFC, medial frontal PFC, temp cortex, striatum, thalamus. Decreased relative metabolism in DLPFC.	ROI. Partly medicated patient sample
Baxter et al. (1989)[145]	FDG PET	14 OCD vs 10 MDD vs 10 OCD+MDD vs10 BD vs 6 mania vs 12co	OCD=controls > MDD=BD in L + R DLPFC activity. OCD+MDD < OCD in L DLPFC activity.	ROI. Only DLPFC assessed

Table 2.2: Continued

Authors (publication date)	Technique	Subjects	Main findings	Methodological comments
Swedo et al. (1989)[44]	FDG PET	18 OCD vs 18 co	Increased absolute metabolism L+ R prefrontal, L orbital frontal, L premotor, R inf temp, R thalamus, L+R ACC. Increased relative metabolism in R prefrontal and L ACC.	ROI. No anatomie specification of 'prefrontal' regions
Baxter et al. (1988)[40]	FDG PET	10 OCD vs 10 co	Increased metabolism in bil hemispheres, bil heads of caudate, bil orbital gyri, bil orbital/hem ratio.	Except for OPC, only absolute metabolic rates reported
Baxter et al. (1987)[43]	FDG PET	14 OCD (10 restudied after treatment with trazodone) vs 14 MD vs 14 co	Increased absolute uptake in bil heads of caudate nuclei, bil orbital gyri, and increased relative uptake in L orbital gyrus, in OCD vs controls. After successful treatment: further increase in R caudate/hem ratio in OCD.	Comorbid MD in OCD group

on clinical subdimensions. These subdimensions are likely to be associated with distinct neurophysiological correlates[50;61;62]. However, most resting-state studies do not provide information on the composition of their patient samples in this respect, so that differences in patients' symptom dimensions across studies may have accounted for discrepant findings.

Next to patient inclusion factors, imaging methodologies differ across resting-state studies and thus may also explain divergent findings. Such differences are the reporting of absolute versus relative metabolic or rCBF rates, the use of ROIs versus voxel-by-voxel analysis, the various ways of outlining neuroanatomical structures, and the determination of sites, sizes and shapes of the applied ROIs. A clear example of how such factors may influence comparability of results between studies has been provided by Aylward and colleagues[22]. These authors investigated if previously reported differences between OCD and healthy subjects in caudate metabolism[40;43;48;59] merely reflected the use of absolute versus relative metabolic rates. They concluded that differences between OCD and normal subjects disappeared after correcting caudate metabolic rates for differences in whole brain glucose uptake.

Changes in activity after treatment

Apart from cross-sectional designs, resting-state studies have been conducted longitudinally in OCD patients, i.e. at baseline and following treatment, either with antidepressant medication or cognitive behavioral therapy (CBT). These studies point towards a decrease in baseline-elevated metabolism or rCBF in the OFC[55;60;63-67], ACC[48;66;68], caudate nuclei[51;53;54;60;63;65;67], putamen[60;67] and thalamus[60]. These changes were found both after medication and CBT. Importantly, these neuronal differences at follow-up were significantly greater in responders compared with non-responders[60;65;66] and/or were associated with decreases in OCD symptom severity[48;53-55;63;64;68] or in general functioning[51]. However, discrepant findings with regard to post-treatment metabolic rates in OCD patients have also been reported, such as a further increase in pretreatment elevated right caudate metabolism after trazodone[43], an increase in right putamen metabolism[63] and a decrease in bilateral caudate glucose uptake[55] both before and after clomipramine treatment.

Despite these few discordant findings, the overall impression is that improvement of OCD symptoms is accompanied by a normalization of frontal-striatal circuit activity. Two methodological issues need to be pointed out, however. First, except for two studies[53;60], in these longitudinal designs the control group was not rescanned, so that treatment effects were potentially confounded with time (order) effects. However, session to session variability for metabolic or rCBF alterations is likely to be small, as shown for HMPAO SPECT[69] and FDG PET[53] in healthy subjects. Second, in some of these longitudinal studies, the use of medication[55;67] or the improvement in comorbid depression[66] cannot be excluded as a confounder for post-treatment brain activity alterations.

Finally, resting-state studies have been used to predict treatment response. Swedo et al.[64] found that lower pre-treatment metabolism in right OFC and right ACC predicted better short-term outcome on clomipramine (2 months later), whereas lower left caudate activity

predicted better long-term response outcome (over 1 year). Based on analyses from previously published data[53;54], Brody and colleagues[70] demonstrated that higher pre-treatment activity in left OFC was associated with more improvement in the CBT group, yet less improvement in the fluoxetine-treated group. Similarly, Saxena et al.[65] found bilateral lower OFC pretreatment metabolism to be a good predictor for paroxetine response. Thus, remarkably consistent findings show that decreased activity in OCD-associated brain regions at baseline is related to a better outcome after medication treatment, whereas the opposite (i.e. increased activity at baseline) may be true for CBT. An exception is the study of Hoehn-Saric and colleagues[66] in which higher pre-treatment rCBF in OFC, basal ganglia and cingulate areas was associated with better clinical outcome after medication. This discrepant finding may be attributed to the use of an OCD patient sample with comorbid depression.

In summary, resting-state studies have indicated that OCD pathophysiology is mediated by hyperactivity in frontal-striatal circuits, involving the OFC, caudate nucleus, putamen and thalamus. Interestingly, a recent meta-analysis that weighed effect sizes for regional CBF and metabolism differences between OCD and control groups across resting-state functional studies, showed that significant hyperactivity in OCD was actually limited to the orbital gyrus and the head of the caudate nucleus[71]. Although the importance of such quantitative assessments of functional abnormalities in OCD cannot be underestimated, the very nature of such analyses restricts the inclusion to comparable paradigms, thereby leaving out a substantial number of valid yet incompatible studies. The functional abnormalities described in the current review appear to be state-related, as brain activity in these structures tends to normalize upon successful treatment with medication or CBT. The finding of elevated resting-state activity in various brain regions in OCD may have implications for other functional neuroimaging designs in this disorder, in particular symptom provocation or cognitive activation paradigms. In such designs, brain activity during a baseline condition is often subtracted from an experimental condition, and these differences are subsequently compared between OCD and control groups. However, if baseline activity differs between groups as indicated by resting-state studies, these interaction effects are more difficult to interpret.

A related issue when considering these resting-state imaging data, is what constitutes the actual nature of 'rest' in OCD. It may be incorrect to regard this state as an asymptomatic one, since OCD is characterized by *tonic* rather than *phasic* symptomatology, as opposed to other anxiety disorders, e.g. panic disorder. If indeed 'resting-state' is not equivalent to 'symptom-free' in OCD, again this has implications for the interpretation of abnormalities found in other functional imaging paradigms (e.g. symptom provocation or cognitive activation), as determining the exact nature of 'mind states' in each of these paradigms is currently impossible.

Symptom provocation studies

Another strategy to differentiate between state and trait aspects of OCD is represented by symptom provocation designs. By alternating rest and symptom states within a session, the role of time (order) effects, as discussed in the previous paragraph, can be ruled out. However, studies using symptom provocation in OCD have yielded mixed results, as summarized in Table 2.3. Overall, the most consistent finding is provocation-induced increased activation of various frontal-striatal regions, such as the OFC[61;72-79], ACC[73;75], striatum[72-74;78;79], and thalamus[72;78;79]. In contrast to the *increased* activation in *ventral* prefrontal regions, OCD patients showed *decreased dorsal* prefrontal activation during the symptomatic state[72;80]. In addition to the frontal-striatal involvement, activation of middle temporal lobe structures, such as the amygdala, also has been demonstrated during the provoked state[72;74;75;80]. Moreover, OCD patients with predominant contamination fear showed increased activation in the insular cortex, implicated in disgust perception[61;74;77].

Inconsistencies in results may again be explained by methodological issues, concerning technical aspects of imaging (e.g. imaging modality, ROIs versus whole brain data acquisition and analyses, correction for motion artifacts), patient selection (i.e. medication status, comorbidity, disorder sub-dimensions and sample size), and stimulus paradigms (i.e. randomized versus off-on design, tactile versus visual, and idiosyncratic versus standardized stimuli). Many provocation studies used tactile stimuli ('dirty' vs. 'clean'), which necessitated ritual behavior (i.e. hand washing), interrupting the scan sessions. Since in these studies subjects, once provoked, remained symptomatic for up to several hours, a balanced order paradigm (intended to control for order effects) was precluded[73-76;81].

In contrast to most OCD symptom provocation studies investigating contamination fear in *'washers'*, Cottraux and colleagues[82] included OCD patients with prominent *checking* rituals. OCD patients as well as controls showed increased orbitofrontal perfusion during the provoked compared with the neutral state. In addition, provocation-induced rCBF in the basal ganglia was higher in controls compared with OCD patients. Our own results, based on a comparison between eleven medication-free contamination-feared OCD patients and ten healthy control subjects, also showed decreased caudate activation in OCD patients compared with controls, during provocation of contamination fear[80]. Since most studies, which report increased provocation-induced caudate activation, lack a healthy control group[72;73;79], it cannot be excluded that activation of the basal ganglia reflects normal processing of emotional information or ritualistic behavior, also present in healthy volunteers. Moreover, in OCD patients, the recruitment of the frontal-striatal circuit seems to be even sub-optimal compared with controls[80;82]. Therefore, it seems likely that the failure of the frontal-striatal circuit in OCD patients to control the processing of negative disease related stimuli results in an inadequate fear response.

This fear response involves limbic activation, which was reflected by the activation of the

Table 2.3: Symptom provocation studies in OCD

Authors (publication date)	Technique/stimulus paradigm	Subjects	Main findings	Methodological comments
van den Heuvel et al. (2004)[80]	H215O PET, visual stimuli (contamination vs neutral)	11 OCD (washers) vs 10 co	Increased activation in L amygdala and bil. extrastriate cortex, sensitization effect in R amygdala. In controls: increased activation in L DLPFC, OFC, L anterior temporal cortex, R caudate nucleus and bil. extrastriate cortex.	
Chen et al. (2004)[79]	MRI (PWI), idiosyncratic tactile stimuli (contamination vs neutral)	10 female OCD (washers)	Increased rCBF in bilateral OFC, R caudate nucleus and R thalamus.	No healthy control group, ROI method (OFC, caudate, thalamus)
Mataix-Cols et al. (2004)[78]	fMRI, visual stimuli (general aversive vs washing-related vs checking-related vs hoarding-related vs neutral)	16 OCD (mixed) vs 17 co	Increased activation in bil. ventromedial PFC and R caudate nucleus (washing-related stimuli), putamen, pallidum, thalamus and dorsal cortical regions (checking-related), L precentral gyrus and R OFC (hoarding-related), L occipito-temporal cortex (general aversive).	Comorbid diagnoses, medicated subjects
Shapira et al. (2003)[77]	fMRI, visual stimuli (general threat vs disgust vs neutral)	8 OCD (washers) vs 8 co	During disgust provocation increased activation in R insula, bil. inf. frontal gyrus, L parahippocampal gyrus, L post. cingulate cortex and L inf. occipital gyrus. No differences between OCD and controls during general threat provocation.	Limited sample size
Hendler et al. (2003)[97]	SPECT, idiosyncratic stimuli	26 OCD (mixed, 13 resp. vs 13 non-resp.) before and after sertraline treatment	Before treatment: responders show less activation in R ACC than non-responders. In responders increased activation in L ant. temporal cortex after (compared to pre-) treatment.	Comorbid depression

Table 2.3: Continued

Authors (publication date)	Technique/stimulus paradigm	Subjects	Main findings	Methodological comments
Rauch et al. (2002)[76]	H215O PET, idiosyncratic tactile stimuli	9 OCD (washers) before vs after fluvoxamine treatment	Increased activation in R OFC during provocation. Lower bil. OFC and higher bil. post. cingulate activation predicted better treatment response, independent of symptomatic state at the time of PET data acquisition.	Limited sample size, off-on design
Adler et al. (2000)[75]	fMRI, idiosyncratic stimuli	7 OCD (mixed)	Increased activation in bil. OFC, ant./lat. temporal cortex, R ACC and R med. temporal cortex (including hippocampus and amygdala).	Limited sample size, ROIs (OFC, ACC, basal ganglia, temporal regions), no control group, off-on design
Simpson et al. (2000)[81]	EEG, tactile stimuli (live vs imaginary exposure)	6 OCD (washers)	Increased activation of anterior relative to posterior brain regions during live exposure.	Limited sample size, medicated subjects, no control group, off-on design
Phillips et al. (2000)[61]	fMRI, visual stimuli (general disgust vs washing-related vs neutral)	14 OCD (7 washers vs 7 checkers) vs 14 co	In all subjects: increased activation in visual regions and insula during general disgust stimuli. During washing-related stimuli, increased activation in visual regions, insula and PFC in washers, and frontal-striatal regions in checkers and controls.	Medicated subjects
Breiter et al. (1996)[74]	fMRI, idiosyncratic tactile stimuli	10 OCD (mixed) vs 5 co	Increased activation in frontal-striatal regions, L insula and bilateral amygdala.	Medicated subjects, off-on design
Cottraux et al. (1996)[82]	H215O PET, idiosyncratic auditory stimuli (obsession vs neutral vs rest)	10 OCD (checkers) vs 10 co	No group x condition interaction effects reported. At rest: increased rCBF in superior temporal cortex in OCD. During provocation: increased rCBF in caudate nuclei in controls.	ROI method (prefrontal regions, caudate, putamen, thalamus, temporal cortex)
Rauch et al. (1994)[73]	H215O PET, idiosyncratic tactile stimuli	8 OCD (mostly washers)	Increased activation in bil. OFC, L ACC and R caudate nucleus.	Limited sample size, no healthy control group, off-on design
McGuire et al. (1994)[72]	H215O PET, idiosyncratic tactile stimuli (of hierarchic intensity)	4 OCD (washers)	Increased activation in R OFC, posterior cingulate, basal ganglia, thalamus and L hippocampus; decreased activation in R dorsal PFC and parietal-temporal region.	Limited sample size, no healthy control group

amygdala in our study[80]. Whereas we found that left amygdala activation was stable over time during the provoked states, right amygdala showed a sensitization effect, positively correlated with scores of subjective distress and obsessionality (figure 2.1). In contrast to our PET results, many provocation experiments in OCD have observed amygdala involvement only in small subgroups and/or at lower statistical thresholds[74;75], or not at all[61;73;77-79;82]. This inconsistency may be explained partly by the use of ROIs excluding the amygdala[79;82], limited statistical power of small sample off-on designs[73;74], use of medication[61;78], and differences in stimulus paradigm. Although the amygdala receives multimodal sensory information, projections from visual processing areas are particularly prominent[83]. Therefore, salient visual stimuli may give rise to amygdala activation more easily than tactile or auditory stimuli. The use of antidepressants is likely to suppress amygdala function[84]. Amygdala involvement in OCD during the symptomatic state is in agreement with studies using fear paradigms in normal controls[85-90], supporting the role of the amygdala as a key structure in evaluating the behavioral significance of external stimuli and fear responses[91]. Since amygdala activation has also been found during symptom provocation in patients with posttraumatic stress disorder[92] as well as during CCK challenge in healthy volunteers[93], activation of limbic structures during symptom provocation in OCD may reflect an inadequate, but nonspecific, fear response. As mentioned before, this fear response seems to be secondary to a failure of the frontal-striatal circuit to control the processing of negative (e.g. contamination-related) stimuli.

OCD is a clinically heterogeneous disorder. Factor-analytic studies have consistently identified

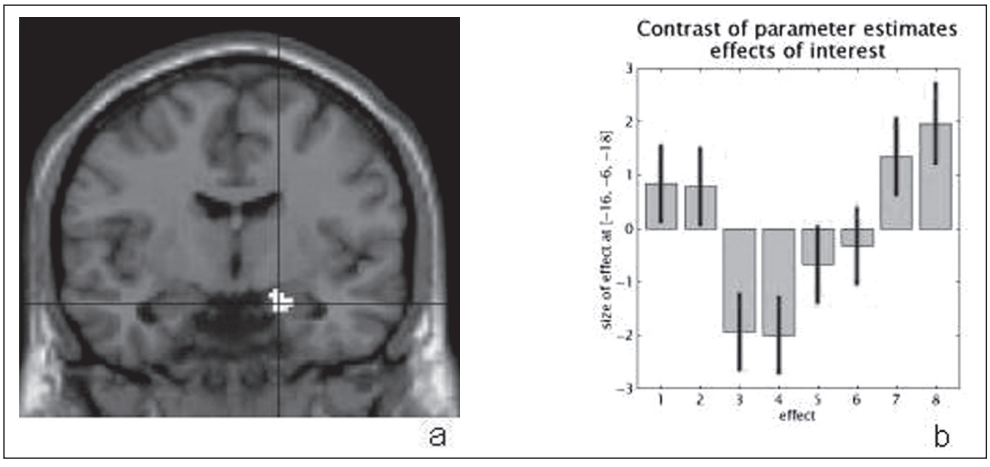

Figure 2.1: van den Heuvel et al. (2004), a. PET symptom provocation, time-by-condition ('dirty' vs 'clean') contrast images for 11 OCD patients displayed on mean T1-weighted MRI show activation in right amygdala (Talairach coordinates x, y, z = 16, -6, -18). b. Plot of effect size (y-axis) in right amygdala for time by condition analysis in 11 OCD patients. Plot shows decreasing effect size over time during subsequent resting conditions (x-axis 1, 2, 3, 4) and increasing effect size over time during subsequent provoked conditions (x-axis 5, 6, 7, 8).

at least 4 stable symptom dimensions: contamination/washing, aggressive/checking, hoarding, and symmetry/ordering[94;95]. As mentioned in the previous paragraph, different neuronal mechanisms may underlie the heterogeneous symptoms of the various OCD dimensions. In two symptom provocation studies, differentiation between OCD subcategories has been investigated[61;78]. Phillips and colleagues[61] compared 'checkers' and 'washers' using standardized visual stimuli. Similar to the results of Cottraux et al.[82], 'checkers' as well as normal control subjects showed increased activation of the frontal-striatal regions during the provoked versus neutral state. In contrast, insular activity was observed in 'washers'. A methodological drawback of this study, restricting the between-subtype comparison, is the fact that only washing-relevant, no checking-relevant stimuli, were presented during the provocation.
Recently, Mataix-Cols and colleagues[78] also investigated the neuronal differentiation between OCD dimensions, using general aversive, washing-related, checking-related, hoarding-related, and neutral visual stimuli in a heterogeneous group of OCD patients. In contrast to Phillips et al.[61] who allocated their *patients* to mutually exclusive subgroups, Mataix-Cols and colleagues compared different *stimulus* sub-types within one heterogeneous group of OCD patients. Whereas ventral regions of the frontal-striatal circuits were activated during washing-related provocation, checking-related stimuli induced recruitment of dorsal regions of these circuits. Unfortunately, no symptom subtype by stimulus subtype interaction analysis was described. In future research, it would be interesting to combine the two strategies, thus comparing both patient symptom dimensions (e.g. using the Padua Inventory-Revised[96]) and stimulus sub-type within the same study design.

Two studies have been performed to investigate the correlation between pre-treatment response during symptom provocation and the efficacy of treatment with selective serotonin reuptake inhibitors (SSRIs). Rauch and colleagues[76] found in a small sample of contamination-feared OCD patients lower bilateral orbitofrontal and higher bilateral posterior cingulate activation to be predictive of a better response to fluvoxamine. Hendler et al.[97], using SPECT, investigated a larger group of OCD patients with mixed symptoms. Before treatment, responders showed less provocation-induced activation in the dorsal ACC than non-responders, although these results might have been biased by differences in comorbid depressive symptoms. An additional post-hoc ROI analysis showed that prospective responders also had significantly more pre-treatment provocation-induced activation in the right caudate nucleus than non-responders. Following 6 months of sertraline treatment, symptom provocation led to increased activation in left anterior temporal cortex in responders, but not in non-responders. Whether the results reflect biological subtypes of the disorder with differential sensitivity to SSRIs, or just differences in pre-treatment symptom severity or comorbid depressive symptomatology awaits further investigation. In addition, since no placebo control group was included, it cannot be excluded that these neurophysiological changes reflect spontaneous improvement. Moreover, it would be interesting to know, if a therapeutic response to CBT may also be predicted by pre-treatment neuronal responses to symptom provocation.

Taken together, symptom provocation studies have implicated a number of regions in the pathophysiology of OCD. The results so far have provided evidence that frontal-striatal involvement reflects ritualistic behavior, even in normal subjects, whereas increased medial temporal activity (including the amygdala) has been associated with (pathological) anxiety. Provocation-induced anxiety may be associated with non-specific rCBF changes due to increases in vigilance and/or arousal that obscure the functional circuitry changes specific to the disease. For this reason, symptom induction in a scanning environment needs to be refined by the use of standardized, symptom- and dimension-specific stimuli, controlling for general emotional effects by including a generally aversive control condition. Although some evidence exists that different neuronal correlates underlie different OCD symptom dimensions, more research is warranted to further address the issue of heterogeneity, including analyses of covariance with scores of dimensional symptom subscales. In addition, to better understand the temporal order of neuronal effects during symptom provocation, region-specific changes in time have to be investigated, for example by simultaneous fMRI/EEG registration. Moreover, longitudinal designs and pre-post treatment measurements may provide more insight in the trait-state question. Finally, to enable correction for differences in morphology and resting state metabolism, combined data acquisition within the same subjects is needed.

Cognitive activation paradigms

The use of cognitive probes during functional neuroimaging is a highly promising tool for the study of neuropsychiatric disorders. These paradigms are sensitive and specific for unraveling their neuronal correlates, in that they allow the induction of hypothesis-driven and disorder-associated functional brain states of interest. OCD is associated with a number of cognitive deficits, as indicated by neuropsychological studies. Although results are far from consistent, impairments appear to stand out in the field of executive functioning and (nonverbal) memory, especially in the context of the need to apply organizational strategies to effectively complete such tasks[98;99].

So far, cognitive paradigms during functional neuroimaging in OCD have been relatively sparse and have been used to investigate different, often unrelated cognitive domains (see Table 2.4). In one of the first of such designs, Rauch and colleagues[100], using $H_2{}^{15}O$ PET, showed a lack of bilateral striatal activation during successful *implicit* learning in OCD patients, in contrast to healthy subjects. Instead, patients recruited (para)hippocampal regions that normally serve the processing of *explicit* learning and memory. This finding was replicated in a small (N=6) OCD sample during fMRI instead of PET scanning[101]. It was argued that (para)hippocampal brain areas are engaged during task performance in OCD to compensate for frontal-striatal dysfunction. This hypothesis was confirmed in a neuropsychological study that showed a failure of implicit learning in OCD when subjects had to simultaneously perform an explicit memory task[102]. However, the reported differential activations between OCD subjects and controls by Rauch et al.[100;101] were only partly replicated in a recent, similar experiment during fMRI scanning[103].

Employing a verbal fluency paradigm, Pujol and colleagues[104] investigated left DLPFC function during fMRI. They noticed increased activation in this region for OCD subjects while performing the task, as well as elevated residual activation during a subsequent resting period. According to the authors, these functional alterations indicated enhanced responsiveness to cognitive challenge in the DLPFC, and diminished ability to suppress activation during rest in the same area. Differential activations in the DLPFC between OCD and healthy controls was also found in a recent study on planning capacity using the Tower of London task, conducted in our laboratory. In this experiment, we demonstrated that dorsal frontal-striatal circuitry was recruited to a lesser extent in OCD patients compared with controls[105]. Instead, patients activated the ACC, VLPFC, parahippocampal gyrus and dorsal brain stem. Results appear to reflect an inadequacy to appropriately engage the dorsal frontal-striatal circuit for planning in OCD, together with compensatory engagement of structures involved in maintenance of task rules in working memory (VLPFC), performance monitoring (ACC), intermediate-term memory capacity (parahippocampal gyrus) and arousal/effort (dorsal brain stem) (figure 2.2). The hypothesis of a compensatory increased effort in OCD patients compared with normal controls during task performance has received additional support from another recent cognitive activation study by our group [106]. Using a classical Stroop task, we found that posterior regions (fusiform area, parahippocampal gyrus, insula, brain stem, precuneus and parietal cortex) were increasingly activated in patients during cognitive interference (i.e. incongruent vs. congruent color naming). Moreover, in an emotional variant of this task, processing of OCD related versus neutral words during color naming was associated with enhanced activation of VLPFC, dorsal ACC, putamen and amygdala in OCD compared with controls. In comparison with other anxiety patients suffering from hypochondriasis and panic disorder, OCD subjects were unique in two ways. First, they exhibited neuronal effects during emotional interference (i.e. emotional versus neutral words) only for OCD related words, whereas hypochondriasis and PD patients reacted on both OCD- and panic related words. Second, patients with

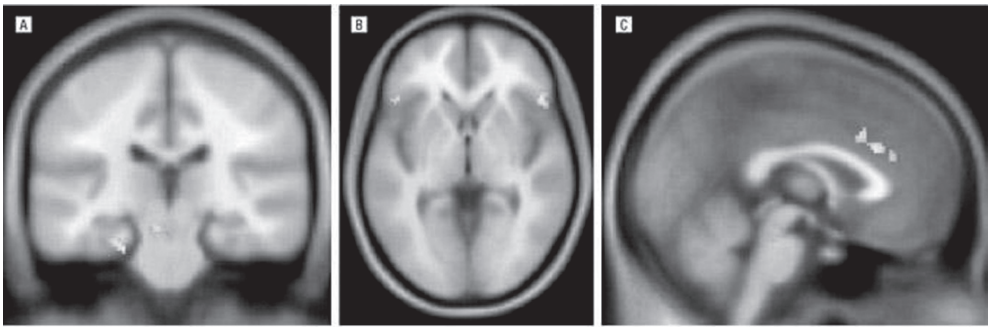

Figure 2.2: Van den Heuvel et al. (2005), fMRI study using Tower of London task, showing increased blood oxygenation level–dependent signal correlating with task load, in patients with obsessive-compulsive disorder compared with control subjects. A, In parahippocampal gyrus and brainstem. B, In bilateral ventrolateral prefrontal cortex. C, In cingulate cortex.

Table 2.4: Cognitive activation paradigms in OCD

Authors (publication date)	Technique/Paradigm	Subjects	Main findings	Methodological comments
van den Heuvel et al. (2005a)[106]	fMRI, cognitive and emotional Stroop task (attentional bias)	16 OCD vs 15 PD vs 13 hypochondriasis vs 19 co	Increased recruitment of posterior regions during cognitive interference; during OCD-related emotional interference: increased activation of VLPFC, dorsal ACC, putamen and amygdala activation vs controls.	Patients and controls not matched for age and gender, no hypochondriasis-related word stimuli
van den Heuvel et al. (2005b)[105]	fMRI, Tower of London task (planning)	22 OCD vs 22 co	Decreased frontal-striatal functioning, i.e. diminished activations in DLPFC, caudate nucleus and putamen; increased activitiy in ACC, VLPFC, parahippocampal.	Patients and controls not matched for educational level
van der Wee et al. (2003)[107]	fMRI, n-back task (working memory)	11 OCD vs 11 co	Increased activation in ACC at all levels of task difficulty in OCD, and normal involvement of DLPFC, premotor regions and parietal cortex	Both samples only women
Ursu et al. (2003)[108]	fMRI, Continuous Performance task (response conflict)	11 OCD vs 13 co	Increased activation in ACC during high-conflict trials and error trials in OCD that correlated positively with symptom severity (trend).	Comorbid anxiety disorders, medicated subjects, ROI analysis
Pujol et al. (1999)[104]	fMRI, Word Generation task	20 OCD vs 20 co	Increased task-related activation of L lateral PFC and impaired suppression of this activation during the following rest condition. Inverse correlations for 'activation signal' and positive correlations for 'remaining activation' with total Y-BOCS score.	No controlled task performance, ROI (L lateral PFC) instead of whole brain analysis
Rauch et al. (1997)[100]	H215O PET, Serial Response Time task (implicit learning)	9 OCD vs 9 co	Implicit learning without recruitment of bil striatum (present in controls), yet activation of bil (para)hippocampal regions (absent in controls).	Limited sample size, both samples only women, interaction analysis only for striatum

Table 2.1, 2.2, 2.3 and 2.4: All main findings reported for obsessive-compulsive disorder (OCD) versus controls, unless indicated otherwise
Abbreviations: ACC = anterior cingulate cortex, BD = bipolar disorder, BDI = Beck Depression Inventory, bil = bilateral, BT = behavioral therapy, CBT = cognitive behavioral therapy, CPT = continuous performance task, CT = computed tomography, CGI = Clinical Global Impression scale, co = controls, DLPFC = dorsolateral prefrontal cortex, ECD = ethyl-cisteinate-dimer, FDG = fluorodeoxyglucose, GAF = Global Assessment of Functioning, HMPAO = hexamethyl propyleneamine-oxime, IFG = inferior frontal gyrus, inf = inferior, L = left, lat = lateral, MDD = major depressive disorder, med = medial, OCD = obsessive compulsive disorder, OCD(+HSS) = OCD patients with high soft signs scores, OCD(+LSS) = OCD patients with low soft signs scores, OFC = orbitofrontal cortex, PD+A = panic disorder with agoraphobia, PET = positron emission tomography, PFC = prefrontal cortex, post = posterior, PTSD = posttraumatic stress disorder, R = right, rCBF = regional cerebral blood flow, ROI = regions-of-interest, SPECT = single-photon emission computed tomography, SSRIs = selective serotonin reuptake inhibitors, sup = superior, Tc-exametazime = Technetium-exametazine, temp = temporal, VBM = Voxel based morphometry, VBR = ventricle-to-brain ratio, VLPFC = ventrolateral prefrontal cortex, vs = versus, Xe = xenon, Y-BOCS = Yale-Brown Obsessive Compulsive Scale

OCD recruited a predominantly *ventral* neuronal system for processing this disease-specific emotional material, as opposed to the other patient groups that also used a *dorsal* system for processing emotional cues. As noted in the introduction, these two activation pathways, i.e. a ventral and dorsal one, have recently been distinguished in human emotion processing. The former corresponds to amygdala, insula and ventral regions of the striatum, ACC and OFC, whereas the latter is composed of the hippocampus and dorsal regions of the ACC and PFC[13]. In a spatial working memory paradigm using the n-back task, van der Wee et al.[107] found diminished performance at the highest task load level although activity in regions normally found in spatial working memory, i.e. bilateral DLPFC and parietal cortex, was similar to control subjects in OCD at all load levels. However, in OCD subjects, the ACC was engaged to a greater extent at all load levels. The authors concluded that spatial working memory capacity is normal in OCD, but performance is impaired at the highest load level due to an interfering abnormal process originating in the ACC. Increased ACC activity, not related to performance is in line with the results of Ursu et al.[108], who used a response conflict (continuous performance) task in OCD and normal subjects during fMRI. They found increased ACC activity both during errors and during correct trials encompassing high-conflict situations. Previously, increased *error-related* ACC activity had been found as heightened and prolonged error-negativity responses during false trials in an ERP paradigm, using a variant of the Stroop task[109]. However, the results of van der Wee et al.[107] and Ursu et al.[108] extend these findings by showing that increased ACC activity is also present during correct responses, across task paradigms. This may reflect an enhanced and dysfunctional action monitoring in OCD subjects, regardless of actual task performance. It may represent the neuronal substrate of the subjective feelings of doubt despite correct task performance that are so characteristic of this disorder.

In summary, the number of cognitive paradigms during functional neuroimaging in OCD up to this date is small. It can be expected, however, to increase rapidly over the next few years due to the opportunities these paradigms provide for elucidating the neuronal substrate of this disorder. The few experiments conducted so far have begun to shed light on various neurophysiological mechanisms involved in OCD. First, during cognitive challenge (both explicit and implicit), dorsal frontal-striatal responsiveness appears to be diminished in OCD, which is presumably compensated for by recruitment of posterior (e.g. medial temporal) brain regions. Second, OCD related emotional material may be processed primarily by ventral but not dorsal prefrontal pathways. This may indicate a lack of effortful regulation of affective states in OCD[13]. Third, increased and performance-unrelated ACC activity appears to be present across cognitive paradigms, putatively corresponding to enhanced, inadequate action monitoring in OCD. Further research is needed to investigate the neuronal substrate of cognitive deficits in OCD and the interactions between emotional and cognitive processing systems in OCD, i.e. between the limbic and dorsal frontal-striatal systems. In the selection of cognitive tasks, it is important that specific abnormalities in OCD as identified in recent or ongoing neuropsychological research be respected. For the interpretation of results from

such designs, it is important to take into account findings from related imaging paradigms; for instance, the increased resting-state activity in brain regions such as the striatum in OCD may be responsible for a failure to recruit these areas with cognitive probes, i.e. may cause a 'ceiling effect'.

MRS and ligand studies

MRS enables direct and non-invasive measurements of brain chemistry in vivo, and therefore this tool is specifically useful for child- en adolescent psychiatric research and longitudinal follow-up by repeated measurements without the possible risks involved when using ionizing radiation. Most MRS studies in OCD have been performed by Rosenberg and coworkers, investigating early-onset OCD in children and adolescents [110-117]. Compounds that can be measured by ^{1}H MRS include myoinositol (mI), choline (Cho), (phospho)creatine (Cr), glutamatergic compounds (Glx), and N-acetyl-aspartate (NAA). Increased Cho signal reflects increased levels of choline-containing compounds, such as acetylcholine. Changed Glx activity has been found to parallel altered brain glutamatergic excitatory neurotransmission[118]. NAA is a marker for neuronal viability[119] and declines in neuronal tissue before neuronal loss is detectable by conventional MRI methods[120].

So far, MRS results concerning neurochemical changes in OCD have been inconsistent (see Table 2.5). An important methodological limitation of MRS is that data acquisition in most studies is limited to a single voxel or small volume in the striatum, thalamus or prefrontal cortex, restricting comparisons between studies. Decreased NAA signal in left[25] and right striatum[121] has been found in adult OCD, whereas striatal volumes were unchanged. This finding supports the idea that MRS enables early detection of decreasing cell density. In contrast to these studies, the results of Ohara and colleagues[122], based on medicated OCD patients, suggested normal viability of the neuronal cells in the putamen and pallidum. The caudate nucleus, however, was not included in the analysis. Differences in medication status cannot explain this inconsistency since Rosenberg and colleagues also found normal thalamic[113] and striatal NAA signal[111] in their medication-naive pediatric OCD patients. In addition, even increased NAA concentrations have been found in the DLPFC[114] of children with OCD. Moreover, absolute measures of the compounds showed that the reported reductions in right and left medial thalamic NAA/(Cho+Cr) and NAA/Cho ratios in pediatric OCD actually reflected an increase in Cho levels[110] rather than a decrease in NAA[113]. Therefore, the possible role of cholinergic dysfunction in the pathophysiology of OCD needs further elaboration.

Dysfunctional glutamatergic neurotransmission and altered serotonergic modulation of glutamatergic transmission at the level of the caudate nucleus may also be involved in the pathogenesis and maintenance of OCD symptoms[28;123]. Glutamate is the primary excitatory neurotransmitter in the frontal-striatal circuits and increased glutamatergic neurotransmission in specific regions of these circuits may contribute to obsessive-compulsive symptoms[123]. Glutamate receptor antagonists have been shown to reduce OCD-like behavior in mice[124].

Table 2.5: Ligand and MRS studies in OCD

Authors (publication date)	Ligand/Technique	Subjects	Main findings	Methodological comments
Denys et al. (2004)[138]	[^{123}I] IBZM SPECT (D_2 receptor)	10 OCD vs 10 co	Decreased D2 binding ratios in and reduced volume of L caudate nucleus.	SPECT-results not corrected for structural differences
Stengler-Wenzke et al. (2004)[137]	[^{123}I] β-CIT SPECT (SERT)	10 OCD vs 7 co	Reduced β-CIT binding in midbrain and upper brain stem (SERT).	Nonspecific binding β-CIT
Pogarell et al. (2003)[135]	[^{123}I] β-CIT SPECT (SERT and DAT)	9 OCD vs 10 co	Increased β-CIT binding in midbrain/pons (SERT), normal β-CIT binding in striatum (DAT), highest SERT availability in patients with early-onset OCD, negative correlation with depression scores, no correlation with OCD severity.	Nonspecific binding β-CIT, gender and age bias, no MRI co-registration
Blair Simpson et al. (2003)[136]	[^{11}C] McN 5652 PET (SERT)	11 OCD vs 11 co	Normal SERT availability in subcortical and limbic regions.	Nonspecific binding McN 5652
Kim et al. (2003)[140]	[^{123}I] IPT SPECT (DAT)	15 OCD vs 19 co	Increased IPT binding in R basal ganglia (trend for L basal ganglia)	
Rosenberg et al. (2004)[117]	^{1}H MRS (NAA, Cr, Cho, Glx)	20 pediatric OCD vs 14 pediatric MDD vs 14 co NAA, Cho and Cr.	Reduced Glx concentrations in ACC in pediatric OCD as well as in pediatric MDD compared to control children. Normal	OCD group significantly younger than MDD group and controls, measurements limited to ACC.
Russell et al. (2003)[114]	^{1}H MRS (NAA, Cr, Cho)	15 pediatric OCD vs 15 co	Increased NAA concentrations in L DLPFC, normal Cr and Cho concentrations.	
Smith et al. (2003)[115]	^{1}H MRS (Cho)	27 pediatric OCD vs 18 pediatric MDD vs 18 co	Increased Cho concentrations in bilateral medial thalamus in pediatric patients with OCD compared to controls and pediatric patients with MDD.	Measurements limited to bilateral medial and lateral thalamus.
Benazon et al. (2003)[116]	^{1}H MRS (NAA, Cr, Cho, Glx, mI)	21 pediatric OCD (before vs after CBT)	No significant pre-posttreatment change of Glx in L caudate nucleus.	Measurements limited to single voxel in L caudate nucleus.
Rosenberg et al. (2001)[113]	1H MRS (NAA, Cr, Cho)	11 pediatric OCD vs 11 co	Increased Cho in bilateral medial thalamus, normal Cr and NAA.	

Table 2.5: Continued

Authors (publication date)	Ligand/Technique	Subjects	Main findings	Methodological comments
Rosenberg et al. (2000)[111]	^{1}H MRS/MRI (NAA, Cr, Cho, Glx, mI)	11 pediatric OCD (before vs after paroxetine) vs 11 co	Increased Glx in L caudate nucleus in pediatric OCD compared to controls, normalizing after paroxetine treatment, positive correlation with reduction in OCD symptom severity scores.	Measurements limited to single voxel in L caudate nucleus, not placebo controlled.
Fitzgerald et al. (2000)[110]	^{1}H MRS (NAA, Cr, Cho)	11 pediatric OCD vs 11 co	Decreased NAA/(Cho+Cr) and NAA/Cho ratios in bilateral medial (not in lateral) thalamus.	Measurements limited to bilateral medial and lateral thalamus.
Ohara et al. (1999)[122]	^{1}H MRS (NAA, Cr, Cho)	12 OCD vs 12 co	Normal levels of NAA, Cho, and Cr in lenticular nucleus.	Medicated patients.
Bartha et al. (1998)[25]	^{1}H MRS/MRI (NAA, Cr, Cho, Glx)	13 OCD vs 13 co	Decreased NAA in L striatum and normal striatal volumes.	Analyses limited to small volume in L striatum.
Ebert et al. (1997)[121]	^{1}H MRS (NAA, Cr, Cho, Glx)	12 OCD vs 6 co	Decreased NAA in R striatum and ACC	Measurements limited to R striatum, ACC, occipital and parietal cortex..

All main findings reported for obsessive-compulsive disorder (OCD) versus controls (co), unless indicated otherwise.
IBZM = iodobenzamide, β-CIT = 2β-carbomethoxy-3β-(4-iodophenyl)tropane , McN 5652 = trans-1,2,3,5,6,10 β-hexahydro-6-[4-9methylthio)phenyl] pyrrolo-[2,1-a]-isoquinoline, IPT = N-(3-iodopropen-2-yl)-2β-carbomethoxy-3β-94-chlorophenyl) tropane, DAT = dopamine transporter, SERT = serotonin transporter, Cho = choline, Glx = glutamatergic compounds, NAA = N-acetyl-aspartate

Moreover, in a family-based association study, variants of the glutamate subunit receptor gene were associated with the susceptibility to develop OCD[125]. MRS results have provided additional evidence for a dysfunctional glutamatergic neurotransmission in OCD. Comparing 11 medication-naive pediatric OCD patients to 11 healthy control children, Rosenberg et al.[111] reported increased left caudate Glx concentrations in OCD. After 12 weeks of paroxetine treatment, Glx levels had normalized. Interestingly, adequate cognitive behavioral therapy did not induce a reduction in striatal Glx[116]. The disease-specificity of glutamatergic dysfunction in OCD still has to be addressed, since altered Glx concentrations in the ACC were found in OCD as well as in MDD[117].

In contrast to MRS studies, PET and SPECT ligand designs require radiolabeled high-affinity ligands to detect neurochemical differences between experimental groups. These techniques enable in vivo measurements of global and regional receptor density and affinity of the various interacting neurotransmitter systems. Although only a small number of ligand studies have been performed in OCD so far, future use of these techniques is promising. However, some important methodological issues have to be considered. First, the radiation risk limits its use in child and adolescent research, and in longitudinal follow-up designs. Second, since the spatial resolution of PET and SPECT is moderate at best, MRI co-registration is necessary for precise anatomical localization and correction for volumetric differences between groups. Third, the functional mechanisms underlying decreased or increased ligand binding are not yet fully understood. Altered ligand binding can be explained by a number of factors, including 1) changes in endogenous neurotransmitter concentrations, 2) genetic modification of the receptor proteins, 3) morphological changes of specific brain regions and 4) altered receptor density due to up or down-regulation of the postsynaptic receptors. Moreover, changes in one neurotransmitter might be secondary to primary changes in another neurotransmitter system.

So far, ligand studies in OCD have mainly focused on 5-HT and DA. A possible role of dysfunctional brain serotonergic and dopaminergic neurotransmitter systems in the pathophysiology of OCD has been suggested a long time ago. The hypothesis that OCD involves a disturbance in 5-HT transmission was initially based on the clinical observation that the tricyclic antidepressant clomipramine is an effective psychopharmacological agent in OCD[126-128]. Since other tricyclic antidepressants are ineffective in OCD, it has been concluded that the efficacy of clomipramine is due to its potent serotonin reuptake inhibiting properties, similar to SSRIs. However, a substantial fraction of patients with OCD show no significant improvement in response to SSRIs alone, suggesting that an isolated disturbance in 5-HT function cannot fully account for the pathophysiology of OCD[129]. Clinical studies showed that the combination of a SSRI with an antipsychotic drug, antagonizing the DA receptor, is successful in a considerable amount of these SSRI-refractory cases[130;131].

Concerning the role of the monoaminergic systems in OCD, recent ligand SPECT and PET studies have given additional support for the hypothesis that both DA and 5-HT are involved in the modulation of obsessive-compulsive symptoms. Iodine-labeled [^{123}I]-2β-

carbomethoxy-3β-(4-iodophenyl)tropane ([^{123}I] β-CIT) is a SPECT radiotracer with high affinity to monoamine transporters[132] and thus can be used to visualize the human central dopamine (DAT) and serotonin transporters (SERT) in vivo[133]. Although β-CIT lacks specificity within the monoamine transporter family, distinct brain regions were found to be related to DA and 5-HT binding: whereas striatal β-CIT uptake mainly reflects binding to DAT, in the other regions comprising the hypothalamus, thalamus, midbrain and pons, β-CIT uptake has been predominantly associated with SERT availability[134]. Alternative radiotracers used to visualize DAT and SERT are the SPECT-ligand iodine-labeled N-(3-iodopropen-2-yl)-2β-carbomethoxy-3β-(4-chlorophenyl)tropane ([^{123}I] IPT) and the PET-ligand C-11 labeled trans-1,2,3,5,6,10 β-hexahydro-6-[4-9methylthio)phenyl]pyrrolo-[2,1-a]-isoquioline ([^{11}C] McN 5652), respectively.

So far, ligand studies focusing on SERT and DAT in OCD have produced conflicting results (see Table 2.5), probably due to methodological issues concerning differences in age, gender, medication history, comorbidity and/or genetic predisposition. Moreover, the sample sizes of these studies were limited. Pogarell et al.[135], using [^{123}I] β-CIT SPECT, found increased β-CIT binding in the midbrain and pons of medication-naive OCD patients, reflecting increased SERT availability. Midbrain β-CIT binding was highest in patients with childhood or adolescence onset of symptomatology, suggesting a more pronounced serotonergic dysfunction in early compared with late-onset OCD. In contrast to Pogarell et al.[135], other studies reported unchanged[136] or reduced[137] SERT availability, using [^{11}C] McN5652 PET and [^{123}I] β-CIT SPECT, respectively. Since SSRI treatment may lead to long-term decreases in SERT availability, inconsistencies may be explained by the fact that most OCD patients in the study of Pogarell et al. were medication-naive, in contrast to the patients in other studies.

Very recently, Denys and colleagues[138] performed a radiolabeled iodobenzamide ([^{123}I] IBZM) SPECT study, investigating D_2 receptor binding in 10 OCD patients and 10 healthy control subjects. Decreased D_2 receptor binding in the left caudate nucleus and a reduced left compared with right caudate volume was found in OCD. Decreased [^{123}I] IBZM binding might be explained by several underlying mechanisms. First, structural changes of striatal cells due to developmental abnormalities or degeneration processes might be present. Since left caudate volume was smaller in OCD patients compared with control subjects, this explanation cannot be ruled out. Second, reduced dopamine D_2 densities in OCD could also be the result of genetic variability, although this seems a less likely explanation for the observed hemispheric asymmetry. The authors suggested that the decreased [^{123}I] IBZM binding reflects postsynaptic dopamine D_2 receptor down-regulation by competition with high concentrations of endogenous dopamine. This third explanation is in agreement with the hypothesis of an imbalance between the direct and indirect pathways of the frontal-striatal circuits in OCD, due to increased inhibition of the indirect pathway by dopamine D_2[139]. Increased secretion and higher synaptic concentrations of endogenous dopamine may result from decreased inhibition of dopamine due to serotonergic dysfunction. The presence of increased endogenous dopamine concentrations in the striatum is supported by the [^{123}I] IPT SPECT results of Kim et al.[140], who

found an increased DAT binding in the right basal ganglia and a tendency toward an increased DAT binding in the left basal ganglia. In contrast, Pogarell et al.[135] reported normal striatal ß-CIT binding in a smaller sample of mostly medication-naive OCD patients.
Future ligand studies in OCD should attempt to distinguish between changes in endogenous ligand concentrations and altered receptor density and/or affinity, for example by using double infusion protocols with high and low specific activity radiotracers. In addition, dopaminergic reactivity in OCD could be investigated with the aid of amphetamine pretreatment, similar to studies in schizophrenia[141].

In conclusion, results from MRS and ligand studies have revealed some evidence for changes in various interacting neurotransmitter systems in OCD, including serotonin, dopamine, glutamate and acetylcholine. The exact mechanism of the neurochemical imbalance and the interactions between different neurotransmitters needs further elaboration. The use of MRS in the follow-up of early-onset OCD patients to investigate glutamatergic and cholinergic changes, in combination with ligand serotonin and dopamine measurements in their later life, is likely to contribute to a better understanding of dysfunctions at a neurochemical level in OCD.

Summary and conclusions

In the present paper, we intended to critically review the neuroimaging literature in OCD. The most consistent finding emanating from various imaging modalities and paradigms is the role of frontal-striatal and limbic circuits in the pathogenesis and maintenance of the disorder. However, the functional meaning of altered activation patterns in these circuits remains uncertain. The term 'frontal-striatal' appears to be too broad to capture the subtle alterations of brain functioning in OCD during the various emotional and/or cognitive paradigms investigated thus far. In addition, although OCD is classified in the DSM-IV as an anxiety disorder, the role of limbic regions such as the amygdala in the pathophysiology of OCD has received little attention in the neuroimaging literature. Moreover, the interactions between frontal-striatal and anterior medial temporal regions are still poorly understood.
A second general finding emerging from the data is the functional differentiation, which appears to be present between ventral and dorsal frontal-striatal regions. Resting state in OCD patients is associated with increased activity of the ventral parts of frontal-striatal circuitry - probably reflecting ongoing emotional and cognitive processing due to tonic symptomatology. During symptom provocation, activation of limbic structures (mainly the amygdala) and additional recruitment of ventral frontal-striatal regions may reflect the processing of salient information together with emotional responding. Furthermore, exaggerated responses (anxiety and/or distress) may, at least in part, be the result of insufficient suppression or top-down control by the dorsal frontal-striatal circuit. These neuroimaging results can now be related to the model of Phillips et al.[13]. As discussed in the introduction section, this model distinguishes three

levels of emotion perception, relying on different parts of ventral and dorsal (prefrontal and temporal) regions: 1) the identification of the emotional significance of an external stimulus, 2) the generation of an affective state in response to the stimulus, and 3) the regulation of the affective state. At present it is insufficiently clear which processing subsystem is dysfunctional, or how abnormalities at these distinct levels interact in OCD; do these patients attribute exaggerated affective significance to disease related stimuli in the environment (level 1) or do they identify these cues appropriately, but subsequently develop a disproportional fear response due to a hypersensitive limbic system (level 2)? Or, alternatively, do these patients lack an adequate modulation of this initial fear response as a result of a dorsal dysfunction (level 3)? These questions will need to be addressed in future neurobiological research in OCD. Dysfunction of dorsal frontal-striatal circuitry might be secondary to abnormal maturation of gray and white matter during early childhood. Moreover, glutamatergic, serotonergic and/or dopaminergic dysfunction, resulting in an altered balance between these various neurotransmitter systems, are likely to interact with cerebral maturation processes. Therefore, more insight in normal brain maturation and its role in the characteristic, temporary compulsive-like behaviors in normal young children might contribute to OCD research[142]. Investigation of normal development might also provide an answer to the question whether OCD symptomatology primarily results from a cortical abnormality or primarily emanates from a subcortical dysfunction. The decreased responsiveness of the dorsal frontal-striatal circuit not only modulates emotional processing, but also has implications for cognitive, mainly executive, functioning. OCD patients show impaired performance on executive tasks, correlated with decreased dorsal frontal-striatal responsiveness and increased activation of posterior cortical and subcortical regions reflecting both compensatory mechanisms (e.g. effort) and heightened arousal. Cognitive function in OCD patients is also characterized by enhanced performance monitoring, associated with increased ACC recruitment.
Although the OFC and VLPFC have been implicated in decision making[143], so far no imaging studies using such a paradigm (e.g. a gambling task) have been performed in OCD. Moreover, fMRI paradigms might be useful to further investigate emotion-cognition interactions.

So far, almost all neuroimaging results in OCD have been based on comparisons between OCD patients and healthy control subjects. Concerning the issue of disorder-specificity, two questions arise: 1) is a neurophysiological differentiation possible between OCD subcategories, and 2) are the frontal-striatal and limbic activation patterns observed in functional imaging studies specific for OCD or is there an overlap with other anxiety disorders, mood disorders or even psychotic disorders? To answer these questions, two opposite approaches are needed: 'splitting', i.e. contrasting subcategories within OCD, and 'lumping', or grouping together of OCD patients with patients suffering from other neuropsychiatric disorders, by changing the focus to functional dimensions instead of DSM-categories.

Over the last two decades, imaging techniques have proven to be very useful in elucidating underlying neurophysiological and neurochemical mechanisms in a number of psychiatric disorders, including OCD, and the ongoing progress in technology makes these techniques even more promising in the near future. However, several issues related to important general methodological aspects in functional imaging, have to be considered. Probably the most urgent questions in this respect that still need to be addressed are: in which state is the patient at the moment of data acquisition and to what extent do researchers succeed in inducing and maintaining the intended emotional and/or cognitive state in subjects within an experimental setting? Functional MRI is blind to baseline differences, which may confound group-by-task comparisons, although a few studies have attempted to control for this problem by the use of parametric designs. In general, it is questionable whether customary subtraction designs really succeed in isolating only the neuropsychological function of interest, even with a carefully matched baseline condition (e.g. for stimulus complexity and motor demands). Moreover, assessment of task related effects in patient groups, as well as group-by-task interaction effects, may be problematic due to aspecific factors, such as increased arousal or distress. Next to these issues that are to be resolved, future designs will need to optimize methodological aspects such as sufficiently large sample sizes, adequate matching between patients and controls (for age, gender, education level, among others), and homogeneous patient groups with regard to medication history, illness duration and severity, and comorbid diagnoses.

Even in the ideal situation of no methodological drawbacks, the *interpretation* of data still remains a challenge as well. We need to reconsider the functional significance of hypoperfusion or hyperactivation in a specific brain region and what it tells us about the underlying neuronal response. Altered state-related oxygenation levels might be secondary to structural and/or neurochemical abnormalities and the specificity of the findings for OCD is yet to be assessed. There is an obvious need for designs adopting an integrated approach, for example by comparing multiple tasks within the same subject sample and using multimodal imaging. Also, most imaging studies in OCD published to date have been cross-sectional. For that reason, longitudinal designs, combing structural, functional and biochemical (PET or MRS) imaging techniques in sufficiently large, homogeneous cohorts are likely to hold the greatest promise for unraveling the pathogenesis of psychiatric disorders such as OCD.

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Chapter 3

Neural correlates of a reversal learning task with an affectively neutral baseline: an event-related fMRI study

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Abstract

Reversal learning may conceptually be dissected into acquiring stimulus-reinforcement associations and subsequently altering behaviour by switching to new associations as stimulus-reinforcement contingencies reverse (i.e. affective switching). Previous imaging studies have found regions of the ventrolateral and orbitofrontal cortex (OFC) to be involved in both subprocesses. However, these studies did not contain an affectively neutral baseline, which precluded adequate assessment of main effects of reward, punishment, and affective switching. We aimed to determine the neural substrate of these main effects, and of common and dissociable regions for reward and punishment. Furthermore, we aimed to discriminate between stimulus-punishment association and affective switching, i.e. to assess affective switching proper. To this end, we implemented a reversal learning task with an affectively neutral baseline condition that matched the experimental task in visual complexity and motor demands. Interestingly, we found dorsolateral prefrontal cortex (DLPFC) and anterior PFC to be engaged in affective switching, a finding that has not been reported before to our knowledge. Enhanced responses in these areas may represent their involvement in cognitive set-shifting *per se* unrelated to the affective context in a reversal learning design. In addition, OFC, insular and medial prefrontal cortex regions were involved in affective switching. Right medial and lateral OFC were shown to be common areas for feedback processing, whereas right ventral striatum and right lateral OFC were specifically activated by reward and punishment, respectively. These results extend our understanding of the neural substrate of reversal learning in humans.

Introduction

Reversal learning can be defined as the ability to alter behaviour when reinforcement contingencies change and is believed to play an important role in social behaviour (Rolls, 1999). It can be conceptually dissected into (i) learning associations between neutral stimuli and their rewarding or punishing value and (ii) switching to new associations, i.e. 'affective switching', that implies inhibiting the selection of the previously rewarded stimulus and seeking the newly rewarded stimulus after contingencies have reversed.

With regard to the former, it is believed that stimulus-reinforcer association learning is mainly subserved by the orbitofrontal cortex (OFC) (Rolls, 2000). Evidence for this was originally based on data derived from electrophysiological studies in nonhuman primates during which pleasant and unpleasant stimuli in different sensory modalities were presented (Thorpe et al., 1983; Critchley et al., 1996). More recently, the role of the OFC in this form of learning has been confirmed by neuroimaging studies in humans being presented rewarding and punishing stimuli either from a sensory, i.e. olfactory, gustatory, visual and tactile quality (Zald et al., 1997; Zald et al., 1998; Francis et al., 1999; Gottfried et al., 2002; O'Doherty et al., 2003b) or from an abstract (monetary) nature (Thut et al., 1997; Elliott et al., 2000a; O'Doherty et al., 2001; Breiter et al., 2001; Knutson et al., 2001; Elliott et al., 2003; Akitsuki et al., 2003). In addition to the OFC, other structures were found to be involved in reward as well, such as the ventral and dorsal striatum (Elliott et al., 2000a; Delgado et al., 2000; Koepp et al., 1998; Akitsuki et al., 2003), midbrain and thalamus (Thut et al., 1997; Elliott et al., 2000a), dorsolateral prefrontal cortex (DLPFC) (Thut et al., 1997) and amygdala (Elliott et al., 2003). In punishment, the amygdala (Zald et al., 1997; Zald et al., 1998) and hippocampus (Elliott et al., 2000a) were also detected apart from the OFC.

With regard to the latter aspect of reversal learning, i.e. making an affective switch after reinforcement contingencies have changed, lesion studies in nonhuman primates and in humans have shown that the ventral striatum (Divac et al., 1967) and the OFC (Iversen et al., 1970; Dias et al., 1996; Rolls et al., 1994; Fellows et al., 2003) are involved in the inhibition of responding to the previously rewarded stimulus and seeking the newly rewarded stimulus.

In view of these results, both above-described subprocesses of reversal learning appear to be at least partly localized in the OFC. Surprisingly, until recently functional neuroimaging studies employing reversal learning tasks to verify OFC engagement in reversal learning have been sparse. In a PET study by Rogers et al. (2000), no involvement of the OFC was found during reversal learning, and activity in the ventral caudate nucleus was revealed only at a low statistical threshold. An event-related functional magnetic resonance imaging (fMRI) study using a reversal learning task showed the activation of distinct OFC areas in response to the receipt of monetary gains and losses, but did not assess the neural substrate of affective switching (O'Doherty et al., 2001). A subsequent event-related fMRI reversal learning study demonstrated a dissociation of the neural correlates of stimulus-punishment association and of

affective switching (Cools et al., 2002). Using a region of interest (ROI) analysis, these authors reported that right ventrolateral prefrontal cortex (PFC) was specifically involved in affective switching, uncontaminated by negative feedback. However, due to susceptibility artefacts in this study, no signal was found in the OFC. Moreover, it did not contain an affectively neutral baseline, thereby precluding adequate assessment of the main effects of reward, punishment and affective switching.

The aim of this study was to further elucidate the neural substrate of reversal learning. To this end, we used a reversal learning task during fMRI which included an affectively neutral baseline condition that matched the experimental task in visual complexity and motor demands. This allowed us to determine the neural correlates of main effects of reward, punishment and affective switching as well as to assess differences between punishment and affective switching. Moreover, the present design enabled us to investigate dissociable and common brain areas with respect to feedback valence by computing, respectively, interaction and conjunction analyses for reward and punishment against baseline. The task was performed during functional MR imaging applying a sequence sensitive to OFC signal (Deichmann et al., 2003). Similar to O'Doherty et al. (2001), we used monetary incentives as reinforcement contingencies, because this form of feedback has been found to activate brain structures to a greater extent than mere appraisal (Thut et al., 1997). With the aim of optimizing the statistical power of our study, we included a large number of subjects compared to previous imaging studies on reversal learning.

Based on earlier findings, we hypothesized the OFC to be engaged in both subprocesses of reversal learning, together with additional areas such as the striatum in reward and the ventrolateral PFC in affective switching. Moreover, we expected that differential subregions of the OFC would be involved in these distinct subprocesses, in view of previous reports of a dissociation between punishment and affective switching, and of separate OFC subareas for processing reward and punishment.

Materials and Methods

Subjects

Twenty-seven healthy volunteers (19 females, 8 males) with a mean age of 32 years (range 22-53) participated in this study. In a pre-assessment, subjects with current or past psychiatric and neurological diseases as well as substance abuse were excluded. Further exclusion criteria were the use of psychiatric or neurological medication, the presence of metal objects precluding MR investigation, and (possible) pregnancy. All participants gave informed consent and the study was approved by the local research ethics committee of the VU University Medical Center.

Reversal learning task and experimental procedure

We used a modified reversal learning task, based on O'Doherty et al. (2001) and Cools et al. (2002), and graphically outlined in figure 3.1. This task served to assess the main factors

of reward, punishment and affective switching. In a pilot study, several versions of this task were implemented differing in various aspects such as the number of trials after which a reversal occurred, the range and magnitude of feedback amounts, interstimulus intervals and probabilistic reinforcement schedules. Based on these data, the version that yielded the largest number of reversal events was used for the present study. At most within two weeks before the scanning session, subjects performed a brief practice version of this task on a computer screen that only differed from the experimental task in that it did not contain reversal stages and that it ended after 30 trials. Moreover, feedback was given in the form of centrally presented words ''goed" and ''fout" (Dutch for ''right" and ''wrong") instead of points.

The experimental task consisted of two stimuli (the cartoon of a bus and a tie) that were serially presented on a white background in the left and right visual fields with randomized locations. A correct response (CR) was given positive or negative feedback on the basis of the ratio 80:20. Positive and negative feedback consisted of, respectively, gaining or losing a random amount of 80-250 points (representing 8-25 eurocents) and was presented, respectively, in blue and red coloured numbers. A CR that was given negative feedback was defined as a ''probabilistic error" (PE) and could either lead to a shift in the choice of stimulus (probabilistic error with shift: PES) or not lead to such a shift (probabilistic error, no shift: PENS). The chance of a second, consecutive PE was 1:10 after a first PE. False responses, ''spontaneous errors" (SE), were always given negative feedback. The last CR before reversal was never given negative feedback and neither was the first CR after reversal. Reversal occurred after 6-10 CR's (randomized) and this was unknown to the subject. Immediately after reversal, a false response (according to the new criterion) that did not lead to a shift to the new correct stimulus was called a ''preceding reversal error (PRE)" and the last false response prior to a shift was called a ''final reversal error (FRE)". On each individual trial, stimuli were presented for 3000 ms within which the response had to be made. After each response, the number of points won or lost and the total amount of accumulated points were presented for 2000 ms, followed by a fixation cross for 1000 ms, after which the next trial was presented.

An affectively neutral baseline (BL) task consisted of two novel, equivalent stimuli (the cartoon of a car and a pair of trousers) that were presented in-between experimental trials for 3000 ms as well. Neutral feedback was given in the form of the words ''choice made" during 2000 ms after which a fixation star was presented for 1000 ms. BL trials were randomly presented throughout the task with an average frequency of every 7 experimental trials and at least once within maximally 15 experimental trials. BL trials were never presented more than once consecutively. The scanning session ended after 400 trials (reversal learning task and BL task together) and lasted roughly 25 minutes.

Subjects were instructed beforehand to select either stimulus from the reversal task by pressing one of two keys on a keyboard corresponding with the left and the right side of the computer screen. They were required to strive to obtain positive feedback as often as possible. Moreover, they were instructed in advance which of the two BL stimuli to select (half of the participants were instructed to select the car, the other half the pair of trousers). These instructions appeared written on the screen and were repeated orally by the experimenter.

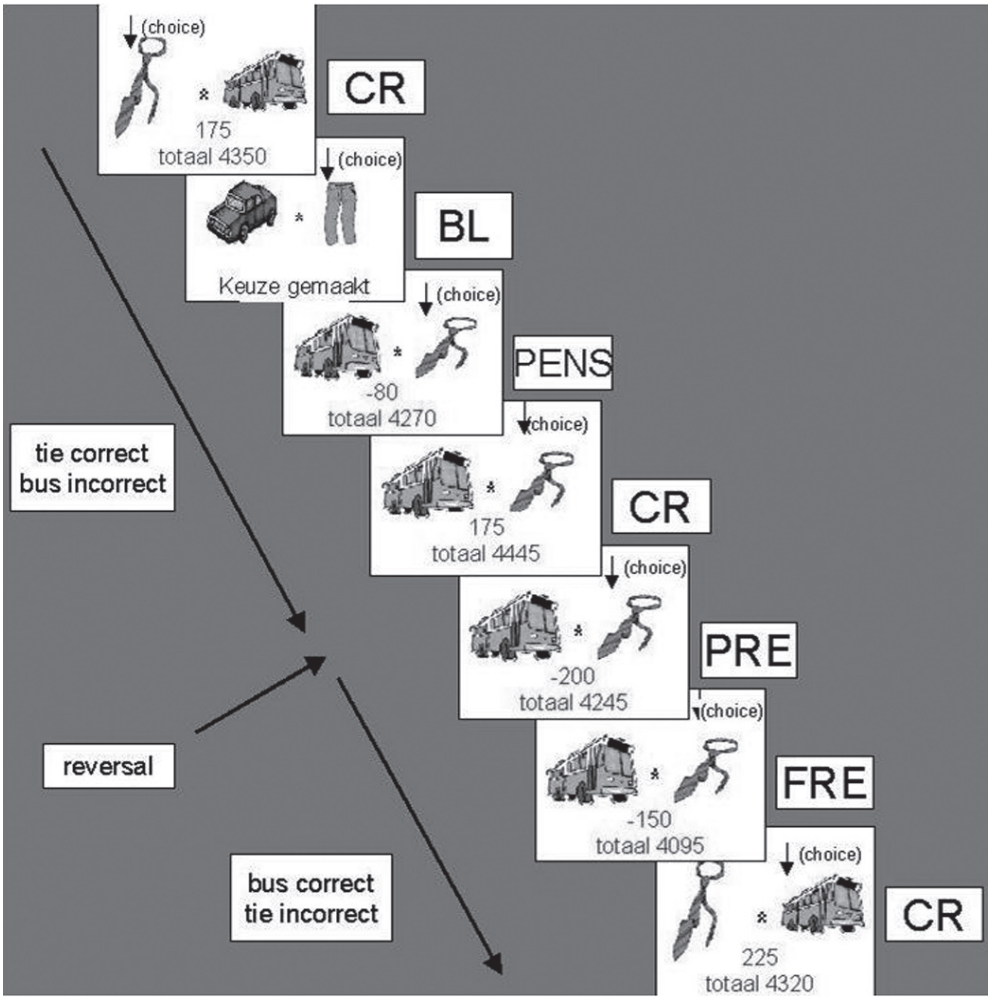

Figure 3.1. The reversal learning task. In this example (consecutive trials are running from top-left to bottom-right) all events of interest are displayed. Subjects are presented two stimuli on each trial, i.e. the cartoon of a bus and a tie in experimental trials and the cartoon of a car and a pair of trousers on baseline trials. In experimental trials, either one stimulus is correct and positive or negative feedback is given in the form of points immediately after a subjects choice, as well as the total amount of points accumulated up to that trial. In baseline trials, subjects were instructed in advance which of the two stimuli to select and neutral feedback is given after a subject's choice ('choice made'). After 6-10 correct responses, a reversal occurs unknown to the subject.
CR = correct response, BL = baseline trial, PENS = probabilistic error, no shift, PRE = preceding reversal error, FRE = final reversal error

Finally, participants were told that after the study they would receive any positive amount of accumulated points in euros divided by 1000, but would not lose any negative amount. After the scanning session, all subjects received the total amount of accumulated points during the task divided by 1000 in euros, if over 10,000 points in total. If under 10,000 points, they received 10 euros.

Thus, this reversal learning and BL task allowed us to determine the neural correlates of reward, punishment and affective switching by comparing, respectively, CR with BL events, PENS + PRE with BL events, and FRE with BL events.

Imaging procedure

Imaging data were collected using a 1.5-T Sonata MR system (Siemens, Erlangen, Germany) with a standard circularly polarized head coil. Task stimuli were generated by a Pentium PC and projected on a screen behind the subject's head at the end of the scanner table. The screen was visible for the subject through a mirror mounted above the subject's head. Two magnet-compatible response boxes were used to record the subject's responses. In order to reduce motion artefacts, the subject's head was immobilized using foam pads.

T2*-weighted echo-planar images (EPI's) with blood oxygenation level-dependent contrast (BOLD) were acquired in each session. An optimized EPI sequence sensitive to OFC signal was used (Deichmann et al., 2003) in which the acquisition plane was tilted parallel to the air/tissue interface of the OFC for each subject (between 0 and 15 degrees from the anterior-posterior commissure line in our subject group). Furthermore, a preparation pulse was applied with a duration of 1 ms and an amplitude of –1.3 milliTesla per meter in the slice direction. Using this sequence with a TR of 2.18 s. and a TE of 45 ms., 35 slices (3 x 3 mm in-plane resolution; 2.5 mm slice thickness; matrix size 64 x 64) per image were acquired. The first two images in each session were automatically discarded by the scanner before the task started. Scanning was manually finished after the task had ended.

A whole-brain EPI-image for each subject was also acquired using the same sequence (40-43 slices per image, 3 images in total) as well as a structural image using a 3D coronal T1-weighted sequence (voxel size 1 x 1 x 1.5 mm, 160 sections).

Data analysis

Imaging analysis was performed using SPM2 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, London, UK). Images were reoriented, slice-timed and realigned to the first volume. The mean image was co-registered with the whole-brain volume, and images were normalized to a SPM T2* template and spatially smoothed using a 6 mm full-width-half-maximum (FWHM) Gaussian kernel.

Statistical analysis was carried out in the context of the general linear model, in which each event was modelled using a delta function convolved with the canonical hemodynamic response function (HRF). Each event was modelled to the onset of the feedback presentation, as defined previously: (1) baseline events (BL), (2) correct responses (CR), (3) probabilistic

errors, no shift (PENS), (4) final reversal errors (FRE), and (5) preceding reversal errors (PRE). In addition, two events were modelled as events of no interest: (6) spontaneous errors (SE), and (7) probabilistic errors with shift (PES). Finally, movement parameters were included in the model as regressors of no interest.

The following contrasts were computed: (1) CR minus BL to assess the main effect of reward, (2) PENS + PRE + FRE minus BL to assess the main effect of all punishment events including those that led to a shift in stimulus choice, (3) PENS + PRE minus BL to assess the main effect of punishment excluding those events immediately prior to a shift (4) FRE minus BL to assess the main effect of affective switching events, (5) FRE minus PENS + PRE to discriminate between stimulus-punishment association and affective switching, i.e. to assess affective switching proper. Contrasts were performed at single subject level. These were then entered into a second level (random effects) analysis by calculating one-sample t-tests on each individual's contrast images for contrasts 1 to 5. One-way ANOVA analyses were used to assess conjunction and interaction analyses for reward and punishment. Interaction analyses were performed by contrasting main effects of reward and punishment masked with the relevant main effect at $p = 0.05$. In order to perform a conjunction analysis for reward and punishment that would not involve the use of a common baseline, new single subject-models were computed that involved two different sub-baselines. The latter were created by randomly assigning baseline events to either sub-baseline. Reward and punishment were each compared to a different sub-baseline and these contrasts were subsequently entered into a second-level analysis in order to perform a conjunction analysis. All results are reported at $P < 0.05$ FDR corrected ('false discovery rate'; Genovese et al., 2002) for multiple comparisons unless indicated otherwise.
Localization of group results was expressed in MNI (Montreal Neurological Institute) coordinates (Brett et al., 2002).

Results

Behavioural data

During the task, subjects were presented a mean of 47 BL trials (SD 3.5). On average, subjects made 224 (SD 17.0) correct responses, 19 (SD 7.7) 'PENS' errors, 16 (SD 9.4) 'PRE' errors and 17 (SD 5.8) 'FRE' errors. The average number of accumulated points by the end of the task was 15524 (range 1580-25859).

Imaging data

Reward

Contrasting correct responses (CR) with baseline events (contrast 1; see Materials and Methods) resulted in a significantly increased BOLD signal in right medial OFC, right lateral OFC and striatum, i.e. bilaterally in the head of the caudate nucleus and in the borderzone of

Table 3.1: Main effect of reward (CR > BL). All results at P<0.05 FDR-corrected

Regions	L/R	MNI coordinates			z-value
		x	y	z	
Medial OFC	R	15	36	-15	4.69
Lateral OFC	R	30	51	-15	4.56
Dorsolateral PFC	R	39	39	15	3.80
Gyrus frontalis inferior	R	45	3	27	3.65
Parietal cortex (superior)	R	30	-60	48	4.20
Parietal cortex (inferior)	R	51	-39	51	3.76
Occipital cortex	R	27	-93	-12	5.63
	L	-30	-96	-12	4.34
Caudate nucleus	R	6	15	3	4.90
	L	-6	18	6	3.73
Ventral pallidum/ Nucleus accumbens	L	-12	6	-9	3.92

left ventral pallidum anteriorly and left nucleus accumbens posteriorly. Moreover, this contrast was associated with increased activity in right dorsolateral prefrontal cortex, the posterior part of the right inferior frontal gyrus, bilateral occipital cortex and right superior and inferior parietal cortex. Imaging results for the main effect of reward are listed in table 3.1 and shown in figure 3.2.

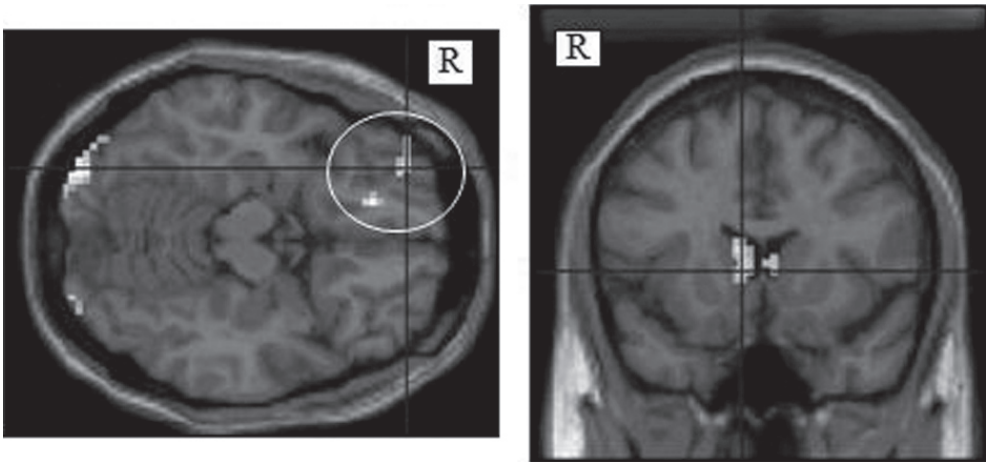

Figure 3.2: BOLD signal increases for reward vs. baseline across subjects. *Left:* right medial and lateral OFC responses (encircled), maximal activations at x = 15, y = 36, z = -15 for medial OFC and x = 30, y = 51, z = -15 for lateral OFC. *Right:* bilateral head of caudate nucleus, maximal activations at x = -6, y = 15, z = 3 for left side and x = 6, y = 18, z = 6 for right side. All localizations expressed in MNI coordinates

Table 3.2: Main effect of punishment with (PENS+PRE+FRE > BL) and without (PENS+PRE > BL) reversal events. All results at P < 0.05 FDR-corrected unless indicated otherwise

Regions	L/R	PENS+PRE+FRE > BL MNI coordinates			z-value	PENS+PRE > BL MNI coordinates			z-value
		x	y	z		x	y	z	
Medial OFC	R	18	42	-15	3.94	18	42	-15	3.97*
Lateral OFC	R	33	54	-12	4.83	42	45	-18	3.84*
Insular cortex	R	27	24	-9	4.48	27	24	-6	3.44*
Occipital cortex	R	24	-96	-15	5.11	24	-96	-15	4.92

* p < 0.001 uncorrected

Punishment

When contrasting all punishment events with baseline (PENS + PRE + FRE with BL, i.e. contrast 2), increased activity was found in right medial OFC, right lateral OFC, right insular cortex and right occipital cortex. However, as this assessment of punishment includes reversal events, we also computed the contrast that showed the main effect of punishment without reversal events, i.e. contrast 3: PENS+PRE minus BL. This confirmed the involvement of the orbitofrontal and insular areas, although at a slightly lower statistical threshold (p < 0.001 uncorrected). Results for punishment contrasts are summarized in table 3.2 and shown in figure 3.3.

Conjunction and interaction analyses for reward and punishment

In order to investigate the specificity of the above-mentioned feedback regions with regard to valence, we performed conjunction and interaction analyses for reward and punishment (see table 3.3). A conjunction of reward and punishment, both contrasted against two different

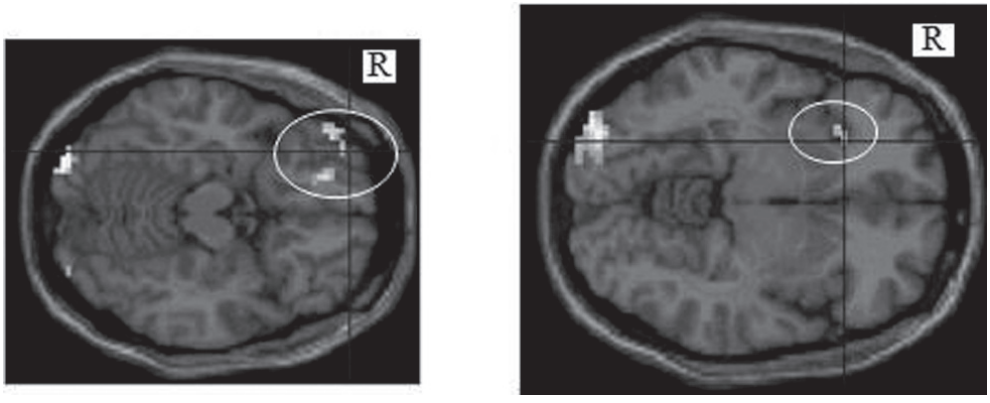

Figure 3.3: BOLD signal increases for punishment vs. baseline (without reversal events, i.e. PENS+PRE minus baseline) across subjects. *Left*: right medial and lateral OFC responses (encircled), maximal activations at x = 18, y = 42, z = -15 for medial OFC and x = 42, y = 45, z = -18 for lateral OFC. *Right*: right insular cortex (encircled), maximal activation at x = 27, y = 24, z = -6. All localizations expressed in MNI coordinates

Table 3.3: Conjunction and Interaction analyses for reward (CR > BL) and Punishment (PENS+PRE > BL). All results at P < 0.05 FDR corrected unless indicated otherwise

Regions	L/R	MNI coordinates			z-value
		x	y	z	
Conjunction of reward and punishment#					
Medial OFC	R	18	39	-15	4.92
Lateral OFC	R	36	54	-12	6.82
Occipital cortex	R	27	-93	-12	7.68
Interaction: Reward > punishment					
Ventral striatum	R	6	12	-6	4.34
Interaction: Punishment > reward					
Lateral OFC	R	42	45	-18	3.10*

#p < 0.001 FDR-corrected, *p < 0.001 uncorrected

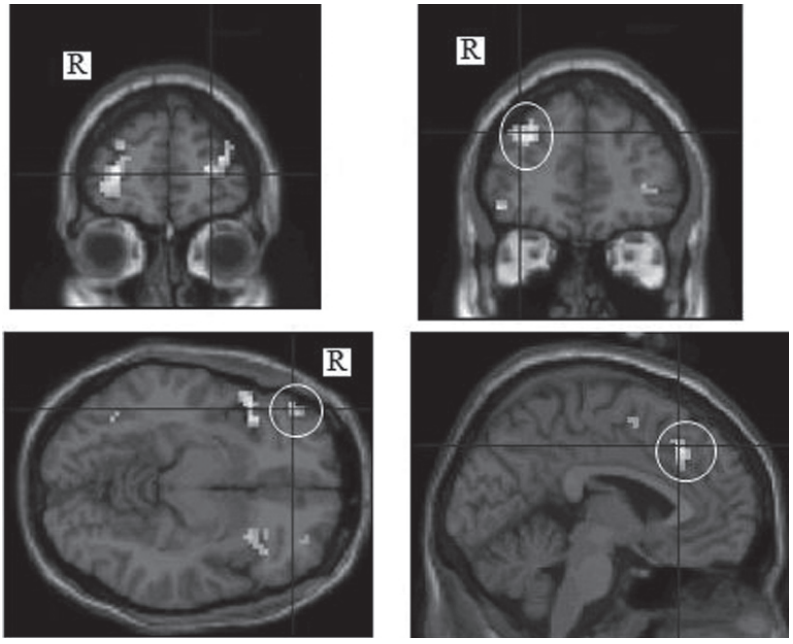

Figure 3.4: BOLD signal increases for affective switching proper (i.e. FRE> PENS+PRE) across subjects. *Top left*: bilateral anterior PFC, maximal activations at x = -27, y = 57, z = 6 for left side and x = 30, y = 51, z = -3 for right side. *Top right*: right dorsolateral PFC (encircled), maximal activation at x = 33, y = 45, z = 33. *Bottom left:* bilateral insula, maximal activations at x = -33, y = 18, z = 6 for left side and x = 33, y = 21, z = 9 for right side, and right lateral OFC (encircled) with maximal activation at x = 45, y = 42, z = -9. *Bottom right:* right dorsomedial PFC (encircled), maximal activation at x = 3, y = 27, z = 42. All localizations expressed in MNI coordinates

Table 3.4: Brain regions that reflect main effect of affective switching (FRE > BL) and the dissociation of stimulus-punishment association and affective switching, i.e. affective switching proper (FRE > PENS+PRE). All results at P<0.05 FDR-corrected

Regions	L/R	FRE > BL MNI coordinates			z-value	FRE > PENS+PRE MNI coordinates			z-value
		x	y	z		x	y	z	
Anterior PFC	R	36	51	9	4.36	27	57	6	4.63
	L					-27	57	6	4.34
	L					-30	51	-3	3.81
Lateral OFC	R	30	51	-15	5.46	45	42	-9	4.24
Posterior OFC	L					-18	15	-18	3.58
Gyrus front. inf.	R	48	18	6	4.49				
	R	48	6	24	4.11	48	3	18	3.94
	L					-60	9	33	4.28
	L					-57	15	12	3.64
Insular cortex	R	30	24	-12	4.53	33	18	6	5.40
	L	-30	18	-9	4.18	-33	21	9	4.70
DLPFC	R	48	33	33	3.80	33	45	33	4.63
	R	33	51	30	3.91				
	R	36	51	9	4.36	36	51	9	5.52
	L					-42	33	42	4.61
Dorsomedial PFC	R	3	30	48	4.54				
	R	3	33	33	3.83				
	R					3	27	42	4.74
Ant. Cingulate	R					0	30	30	3.58
Temporal sup.	R					57	-42	27	3.65
Temporal transv.	R					33	-24	12	4.07
Temporal inf.	R					48	-63	-6	3.43
SMA	R					6	3	54	3.47
Precuneus	L					-15	-66	51	4.52
Parietal inf.	L					-48	-36	39	3.24
Occipital	R	27	-90	-9	4.79				
Cerebellum	R					15	-48	-24	3.99

sub-baselines, revealed highly significant effects in medial and lateral OFC, thereby confirming that these areas were both activated with regard to valence of outcome.

Next, dissociable areas of activity were assessed for reward and punishment by contrasting their main effects in an interaction analysis. This showed right ventral striatum activity for reward minus punishment and right lateral OFC activity for punishment minus reward.

Thus, although the lateral OFC is a common area for processing feedback, it is more strongly activated by punishment as compared to reward.

Affective switching

To assess the main effect of affective switching (contrast 4), we compared the final reversal errors (FRE) with baseline. This resulted in responses in right lateral OFC (the same area as found in the conjunction of reward and punishment) extending into right DLPFC, bilateral insula, dorsomedial PFC, right inferior frontal gyrus and occipital cortex.

Next, we assessed the dissociation of stimulus-punishment association and affective switching, i.e. the assessment of affective switching proper. This was computed by contrasting final reversal errors with punishment events (FRE with PENS and PRE; i.e. contrast 5). This dissociation showed effects in right lateral OFC (more posterolateral than the right lateral OFC region found in the conjunction of reward and punishment and in the main effect of affective switching), left posterior OFC, right dorsomedial PFC/dorsal anterior cingulate, bilateral insula, bilateral anterior PFC, the posterior part of right inferior frontal gyrus and bilateral DLPFC. Moreover, areas in superior and inferior right temporal gyrus were detected as well as areas in right SMA, left precuneus, left inferior parietal cortex and right cerebellum. Imaging results for the main effect of affective switching and for the dissociation of stimulus-punishment association and affective switching are listed in table 3.4 and shown in figure 3.4.

Discussion

The present study on the neural substrate of reversal learning in humans aimed to extend previous findings by introducing an affectively neutral baseline condition in a reversal learning task during fMRI. Based on previous literature, the orbitofrontal cortex (OFC) was expected to play an important role in the process of reversal learning. For this reason, we applied a scanning sequence specifically sensitive to OFC signal (Deichmann et al., 2003).

Behavioural data from the current study showed that all subjects succeeded in accumulating a positive amount of points, which demonstrates that they had understood the requirements of the task. Moreover, the number of correct responses and errors for each subject was sufficient to obtain reliable parameter estimates during first-level (individual) analyses of imaging data.

Our imaging results show a novel finding in that the right dorsolateral PFC (DLPFC) and anterior PFC were involved in affective switching vs. baseline and that these areas were bilaterally engaged in affective switching proper (i.e., vs. punishment). In addition, we demonstrated the activation of OFC, insular and medial prefrontal cortex regions in affective switching, as well as the involvement of OFC subregions in mediating reward and punishment feedback.

Affective switching refers to the process of inhibiting the selection of a previously rewarded but now punished stimulus and seeking the newly rewarded stimulus. A neural dissociation between affective switching and punishment processing has been first demonstrated by Cools et al. (2002). In order to replicate these findings, we used the same contrast, except for the

fact that we did not use a ROI analysis as Cools et al. (2002) did. Two recent fMRI studies also used a similar contrast although in slightly different reversal learning paradigms (O'Doherty et al., 2003; Kringelbach et al., 2003). In the first study, events of punishment feedback followed by a switch in stimulus choice were compared to punishment events not prior to a switch (O'Doherty et al., 2003). The second study used a simple model of social interaction within a reversal learning paradigm. These authors compared a main reversal condition with a face expression control task and a control reversal task, thereby isolating affective switching from punishment (i.e. angry face expression) as well (Kringelbach et al., 2003).

Remarkably, none of these studies reported the involvement of DLPFC or anterior PFC regions in the context of affective switching. In fact, these neuroimaging data were seen as evidence for the validity of previous findings in nonhuman and human lesion studies that had demonstrated a dissociation of brain regions engaged in reversal learning. Specifically, these studies showed that reversal learning performance was affected by OFC/ventromedial damage but not by DLPFC lesions (Dias et al., 1996; Fellows et al., 2003).

Previous fMRI literature has shown the DLPFC and anterior PFC to be involved in cognitive or 'executive' demands; the DLPFC has been associated with working memory (e.g. Belger et al., 1998), reasoning (Prabhakaran et al, 1997) and processing 'relational information', as exemplified by integrating currently known information with hypotheses on likely outcomes in decisional processes (Krawczyk, 2002). The anterior PFC has been related to integrating multiple separate cognitive operations in the pursuit of a higher behavioural goal (Ramnani et al. 2004) and to processing self-generated information (Christoff et al., 2003). Therefore, it might be argued that the DLPFC and anterior PFC activity observed in the present study reflects similar higher-order cognitive processes, for example ongoing strategy considerations in order to 'solve' the task. However, our finding that DLPFC and anterior PFC activity was present only during switching events is difficult to reconcile with this hypothesis. Consequently, we propose that enhanced responses in these areas may represent the involvement of DLPFC and anterior PFC in switching a cognitive set *per se* unrelated to the affective context in a reversal learning design. Support for this reasoning can be found in literature on 'pure' switching tasks in which instructions regarding the current or upcoming set are explicitly provided throughout the task. Such paradigms enable the isolation of the neural substrate of cognitive set-switching by comparing shifting events with repeating events. Using such tasks, DLPFC involvement in this form of 'pure' switching has been found repeatedly (Dove et al., 2000; DiGirolamo et al., 2001), also when accounting for working memory load as a potential confound (Smith et al., 2004). Also, the right anterior prefrontal cortex has been associated with task switching in a recent study in which mixed-task blocks (encompassing switch and repeat trials) were compared to single-task blocks (solely repeat trials) (Braver et al., 2003).

In addition to switching per se, DLPFC activation may reflect its engagement in inhibitory control as found in Go/NoGo tasks (Liddle et al., 2001; Garavan et al., 1999; Garavan et al., 2002). It has been suggested earlier that the ability to inhibit responding to the previously rewarded stimulus is a component in reversal learning (Robbins, 2000) that can be measured with the use of Go/NoGo task (Bechara et al., 2000).

To our knowledge, the current study is the first imaging study to demonstrate that DLPFC and anterior PFC are involved in affective switching within a reversal learning task paradigm. We believe two explanations can be put forward for the fact that this finding has not been reported previously in human imaging studies. First, differences in data analysis and reporting may account for discrepant observations; in particular, both O'Doherty et al. (2003a) and Cools et al. (2002) restricted the assessment of affective switching to a priori regions of interest and consequently were unable to detect neural activity in dorsal brain regions. Second, compared to Kringelbach et al. (2003), our reversal study included probabilistic errors whereas the need for a reversal was cued by face expression in their study. This may have possibly increased 'switch load' in our experiment and hence the need to recruit dorsal prefrontal brain regions. In line with this hypothesis are observations that increasing task load is related to anterior PFC and DLPFC activity in a planning task (van den Heuvel et al., 2003) and in working memory tasks (Pochon et al., 2002; Veltman et al., 2003). A similar explanation may be put forward to account for the intact performance in DLPFC-damaged groups on reversal learning in previous human and nonhuman lesion studies (Dias et al., 1996; Fellows et al., 2003).

Apart from these dorsolateral and anterior prefrontal regions, we also found OFC, insular and medial prefrontal responses during affective switching. These observations are in accordance with previous imaging studies on reversal learning. The enhanced responses in left insula found in our study are similar to the region designated as 'ventrolateral PFC' reported by Cools et al. (2002). The 'response switching' contrast performed by O'Doherty et al. (2003a) showed enhanced signal in the region of right anterior insula-caudolateral OFC which is in very close proximity to the ventral part of the cluster activity in left insular cortex reported here (with MNI coordinates -36, 24, -6, $Z = 3.64$, $p < 0.05$ FDR-corrected, not shown in table 3.4).

The insula is part of a paralimbic circuit encompassing, among other areas, posterior orbitofrontal, temporopolar and cingulate cortices (Augustine et al., 1996; Mesulam, 2000). The activity we observed in insula, left posterior OFC and right dorsomedial PFC/dorsal anterior cingulate during affective switching may reflect their involvement in linking cognition with visceral states and emotion (Mesulam, 2000). Posterior OFC was also found to be associated with reversal learning impairment in a recent study of subjects with ventromedial brain lesions (Fellows et al., 2003). Although this area was also left-sided, as in the present study, no definite conclusions can be drawn with regard to laterality here because there were too few subjects with right ventromedial damage included in the Fellows et al. study. The involvement of right dorsomedial PFC/dorsal anterior cingulate during affective switching in the current study is consistent with findings by O'Doherty et al. (2003a) and by Kringelbach et al. (2003). The importance of the dorsal anterior cingulate region in affective switching is compatible with its role in response selection and monitoring (Badgaiyan et al., 1998; Duncan et al., 2000) and in reward-based decision making (Bush et al., 2002). Alternatively, it may reflect the involvement of dorsal anterior cingulate in autonomic control of cardiovascular arousal that has been shown during effortful cognitive tasks (Critchley et al., 2000; 2003).

Finally, Kringelbach et al. (2003) reported bilateral inferior prefrontal cortex (BA 44/45)

activity during affective switching, when performing a conjunction analysis of a main reversal and a control reversal task (controlling for face expression (angry) as a cue for reversal). We also observed enhanced signal in inferior frontal gyrus (right lateralized) during affective switching, and our finding therefore is in agreement with the hypothesis that this cortical region is involved in inhibiting inappropriate behavioural strategies (Kringelbach et al., 2003).

The second goal of this study was to assess regions involved in reward and punishment. The main effects of reward and punishment were both associated with regional brain activity in right medial and right lateral OFC as was confirmed by a conjunction analysis. These findings support and extend previous data from imaging studies with regard to the key role of the OFC in mediating monetary reward and punishment processing in humans (Thut et al., 1997; Elliott et al., 2000a; O'Doherty et al., 2001; Breiter et al., 2001; Knutson et al., 2001; Elliott et al., 2003; O'Doherty et al., 2003a; Rogers et al., 2004; May et al., 2004; Kringelbach et al., 2004). An interaction analysis subtracting reward from punishment showed residual activity in right lateral OFC. This implies that right lateral OFC, in contrast to right medial OFC, represents a specific area for punishment processing. Conversely, contrasting reward with punishment demonstrated no unique OFC activity for reward but did identify the right ventral striatum as a dissociable area for reward processing compared to punishment.
The fact that negative, but not positive reinforcement has a dissociable representation in the OFC, suggests a specific biological significance that is uniquely associated with the former but not the latter. Indeed, this may very well be the potential behavioural consequence that follows the receipt of negative feedback, i.e. switching in the choice of stimulus in the current paradigm, which will require additional cognitive modulation. This hypothesis appears to be in accordance with a proposed role for the lateral OFC of suppressing responses to previously rewarded stimuli (Elliott et al., 2000b), as it may be assumed that such behavioural sequelae will only follow after the delivery of negative feedback. Evidence for this speculation is also borne out in the present study as a subregion of right lateral OFC activity, adjacent to the region uniquely involved in punishment, was identified in affective switching, suggesting a close functional relationship between the two.
Finally, the reward-related activity we found in dorsal and ventral striatal structures is also in agreement with previously observed relationships between reward processing and the striatum in animal (Apicella et al., 1991; Salinas et al., 1998; Robbins et al., 1992) and human neuroimaging studies for dorsal (Delgado et al., 2000; Koepp et al., 1998; Delgado et al., 2003) and ventral striatum (Elliott et al., 2000a; Delgado et al., 2000; Koepp et al., 1998; Delgado et al., 2003; McClure et al., 2004).

To conclude, the present study extends our understanding of the neural substrate of reversal learning that conceptually can be dissected into (i) the acquisition of stimulus-reinforcement associations and (ii) affective switching. In a reversal learning study using an affectively neutral baseline condition, we present a novel finding by demonstrating that dorsolateral and anterior

prefrontal regions are involved in affective switching next to OFC, insular and medial prefrontal cortex areas. Furthermore, right ventral striatum and right lateral OFC were found to function as dissociable areas for the processing of, respectively, reward and punishment. Finally, right medial and lateral OFC were shown to be common areas for feedback processing regardless of valence. In future research, it will be of interest to investigate whether the involvement of dorsal brain regions in affective switching indeed reflects cognitive set-shifting and 'switch load'. This will enhance our insight into the interplay of emotion and cognition in reversal learning.

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4

Reduced orbitofrontal-stratial activity on a reversal learning task in obsessive-compulsive disorder

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Abstract

The orbitofrontal cortex (OFC)–striatal circuit, which is important for motivational behavior, is assumed to be involved in the pathophysiology of obsessive-compulsive disorder (OCD) according to current neurobiological models of this disorder. However, the engagement of this neural loop in OCD has not been tested directly in a cognitive activation imaging paradigm so far. We conducted the present experiment to determine whether the OFC and the ventral striatum show abnormal neural activity in OCD during cognitive challenge. To this aim, a reversal learning task was employed in 20 patients with OCD who were not receiving medication and 27 healthy controls during an event-related functional magnetic resonance imaging experiment using a scanning sequence sensitive to OFC signal. This design allowed investigation of the neural correlates of reward and punishment receipt as well as of "affective switching," ie, altering behavior on reversing reinforcement contingencies. Results showed that patients with OCD exhibited an impaired task end result reflected by a reduced number of correct responses relative to control subjects but showed adequate behavior on receipt of punishment and with regard to affective switching. On reward outcome, patients showed decreased responsiveness in right medial and lateral OFC as well as in the right caudate nucleus (border zone ventral striatum) when compared with controls. During affective switching, patients recruited the left posterior OFC, bilateral insular cortex, bilateral dorsolateral, and bilateral anterior prefrontal cortex to a lesser extent than control subjects. No areas were found for which patients exhibited increased activity relative to controls, and no differential activations were observed for punishment in a direct group comparison. In conclusion, these data show behavioral impairments accompanied by aberrant OFC-striatal and dorsal prefrontal activity in OCD on a reversal learning task that addresses this circuit's function. These findings not only confirm previous reports of dorsal prefrontal dysfunction in OCD but also provide evidence for the involvement of the OFC-striatal loop in the pathophysiology of OCD.

Introduction

The orbitofrontal cortex (OFC) and the ventral striatum constitute the main components of 1 of a series of parallel, segregated neural loops, which were first described by Alexander et al. (1986; 1990). The functional roles of these areas have been investigated extensively in both nonhuman primates and humans. Electrophysiological studies in monkeys have demonstrated that OFC neurons code the context-dependent positive or negative reinforcement value of sensory stimuli (Thorpe et al., 1983; Critchley et al., 1996; Tremblay et al., 1999; Rolls, 2000) and register the rapid reversal of such stimulus-reinforcement associations (Thorpe et al., 1983; Rolls et al., 1996), which is important for motivational behavior (Rolls, 2000). Orbitofrontal involvement in reversal learning (also termed affective switching) had previously been shown in OFC-ablated macaques, who exhibited perseverant responding to the previously relevant stimulus on an object discrimination reversal task (Iversen et al., 1970; Jones et al., 1972). In a subsequent experiment, a double dissociation in the prefrontal cortex was observed: deficits on affective switching but intact performance on attentional (extradimensional) switching were found in OFC-lesioned marmosets, whereas the opposite was true for dorsolateral prefrontal cortex (DLPFC)–ablated animals (Dias et al., 1996). In humans, research on the function of the OFC has focused primarily on reversal learning and decision-making (Clark et al., 2004). Human lesion studies have corroborated animal experiments with respect to the disruption of reversal learning in OFC-damaged patients (Rolls et al., 1994) and found a dissociation in affective switching for patients with OFC damage and those with DLPFC damage (Fellows et al., 2003; Hornak et al., 2004). In addition, neuroimaging studies in healthy subjects have repeatedly shown the involvement of the OFC in the processing of reward and punishment stimuli, either from a sensory quality (Zald et al., 1998; Francis et al., 1999) or from an abstract (monetary) nature (O'Doherty et al., 2001; Elliott et al., 2003). Moreover, neuroimaging studies using reversal learning paradigms have reported OFC activity during affective switching (O'Doherty et al., 2003; Kringelbach et al., 2003). As stated earlier, the OFC is connected with the ventral sector of the caudate nucleus and these structures conjointly form a frontal-striatal circuit (Alexander et al., 1986; 1990; Rolls, 2000). Indeed, neuroimaging studies have also demonstrated the ventral striatum to be engaged in reward processing (Delgado et al., 2000; Koepp et al., 1998) and in affective switching (Divac et al., 1967; Rogers et al., 2000; Cools et al., 2002). Thus, the OFC and the ventral part of the striatum are presumed to be crucial in an organism's processing of reward and punishment and in the ability to alter behavior on changing stimulus-reinforcement contingencies, ie, in affective switching.

Recent neurobiological models of obsessive-compulsive disorder (OCD) have stressed the role of dysfunctional OFC-striatal circuitry in the pathogenesis of this disorder (Saxena et al., 1998; Schwartz, 1999; Baxter et al., 2001; Aouizerate et al., 2004) based on several observations. First, from a phenomenological point of view, reward and punishment perception appear to be abnormal in OCD; ie, patients with OCD give the impressions of having an ongoing error sensation ("something is wrong") when experiencing obsessions (Schwartz, 1999) and of

feeling insufficiently relieved by compulsive behavior that serves a rewarding goal (Schwartz, 1999; Aouizerate et al., 2004). Moreover, the rigid behavior exhibited by patients with OCD that appears insensitive to reinforcing signals can be thought of as reflecting an inability to perform affective switching. Second, neuropsychological tasks that specifically address OFC function have shown impaired performance in patients with OCD compared with healthy controls (Abbruzzese et al., 1997; Cavedini et al., 2002) (but see other resources, e.g. Hermesh et al., 1999; Nielen et al., 2002). Third, structural and functional neuroimaging studies have repeatedly shown abnormalities associated with these brain areas in OCD, although these findings have not been uniform: ie, increased (Kim et al., 2001) or decreased (Pujol et al., 2004) OFC volumes and enlarged (Pujol et al., 2004), normal (Aylward et al., 1996), or diminished (Robinson et al., 1995) striatal volumes in morphometric studies in addition to either increased (Baxter et al., 1988; Lacerda et al., 2003) or decreased (Busatto et al., 2000) activity in the OFC and hypoactivity (Rubin et al., 1992) or hyperactivity (Baxter et al., 1988; Saxena et al., 2004) in the caudate nucleus during resting-state imaging. Similarly, symptom provocation studies in OCD have demonstrated increased OFC activity (Breiter et al., 1996) next to both increased (Breiter et al., 1996; Rauch et al., 1994) and decreased (van den Heuvel et al., 2004) caudate activity. Finally, selective serotonin reuptake inhibitors and dopamine antagonists appear to be efficacious in OCD (Zohar et al., 2000; McDougle et al., 2000), and intact transmission of serotonin (5-hydroxytryptamine) and dopamine has been associated with normal OFC functioning (Rogers et al., 1999) and reward processing in the ventral striatum (Schultz, 1998), respectively.

Thus, several lines of research have indicated that OFC-striatal dysfunction is a key factor in the pathogenesis of OCD and may be the neural substrate of abnormal reward, punishment, and affective switching processing in OCD. Although other parts of frontal-striatal circuitry, in particular anterior cingulate cortex, have been targeted before using cognitive neuroimaging paradigms in OCD (Ursu et al., 2003; Maltby et al., 2005; Fitzgerald et al., 2005), the OFC-striatal loop has not been challenged directly so far. In the present study, we addressed this issue by employing a reversal learning task in an event-related, functional magnetic resonance imaging experiment. This paradigm enabled assessment of reward and punishment processing as well as affective switching and was shown to recruit OFC and striatal regions in healthy controls (Remijnse et al., 2005), data of which were also used in the present study. Since functional magnetic resonance imaging of the OFC is notoriously difficult because of signal dropout (Cools et al., 2002; Kringelbach et al., 2004), we applied a scanning sequence specifically sensitive to OFC signal (Deichmann et al., 2003). Based on the previously reviewed data on OFC-striatal function together with its proposed role in the pathophysiology of OCD, we hypothesized that patients would show impaired performance during the reversal learning task compared with control subjects. Moreover, we expected that this would be accompanied by abnormal OFC-striatal activity during processing of reward, punishment, and affective switching.

Materials and Methods

Subjects

Twenty patients with OCD (14 women; mean age, 34 years; range, 19-54 years) and 27 healthy controls (19 women; mean age, 32 years; range, 22-53 years) participated in this study. Patients were recruited from the outpatient clinic for anxiety disorders and by advertisements on the internet. Diagnoses were established by experienced clinicians with the Structured Clinical Interview for *DSM-IV* Axis I disorders (First et al., 1996). Exclusion criteria were the presence of alcohol or substance abuse and major internal or neurological disorders. The following comorbid disorders were diagnosed with the Structured Clinical Interview for *DSM-IV* Axis I disorders: major depressive disorder (n = 7), dysthymia (n = 4), social phobia (n = 3), generalized anxiety disorder (n = 3), panic disorder (n = 2), agoraphobia (n = 1), and posttraumatic stress disorder (n = 1). Moreover, comorbid Tourette disorder was clinically diagnosed in 2 patients, whereas 5 patients were diagnosed with "pure" OCD. At the time of the study, all patients and control subjects were free of psychotropic medication for at least 2 weeks and, in case of fluoxetine or antipsychotic medication, for at least 1 month. Moreover, no patients were currently involved in a cognitive behavioral therapy program. All participants gave written informed consent and the study was approved by the ethical review board of the VU University Medical Center (Amsterdam, the Netherlands).

To assess symptom characteristics and severity scores, the Yale-Brown Obsessive Compulsive Scale (Goodman et al., 1989) was administered (patients only), whereas the Padua Inventory–Revised (Sanavio, 1988; van Oppen et al., 1995) was used to measure participants' obsessive-compulsive characteristics (both groups). One patient with OCD had obsessions only and 1 had compulsions only, and symptoms were mainly related to the obsessions/checking (n = 15) and symmetry/ordering (n = 5) dimensions (Mataix-Cols et al., 2005). To rate the presence and severity of depressive symptoms in both groups, we used the Beck Depression Inventory (Beck et al., 1961), the 21-item Hamilton Depression Rating Scale (Hamilton, 1967), and the 10-item Montgomery-Asberg Depression Rating Scale (Montgomery et al., 1979). Because of logistic problems, 3 patients failed to be interviewed with the Hamilton Depression Rating Scale and Montgomery-Asberg Depression Rating Scale, and 2 patients did not complete the Beck Depression Inventory and Padua Inventory–Revised.

Reversal learning task and experimental procedure

We used a self-paced, probabilistic reversal learning task with an affectively neutral baseline (Figure 4.1) that has been described in detail elsewhere (Remijnse et al., 2005). In brief, each trial in the experimental task consisted of 2 stimuli, ie, cartoons of a bus and a tie, which were presented at either side of a screen with randomized locations for 3000 milliseconds maximally. Subjects selected either stimulus by pressing the left or right button on a button box. On a correct response, either positive or negative feedback was given based on an 80:20 ratio, consisting of gaining or losing a random amount of 80 to 250 points. A correct response

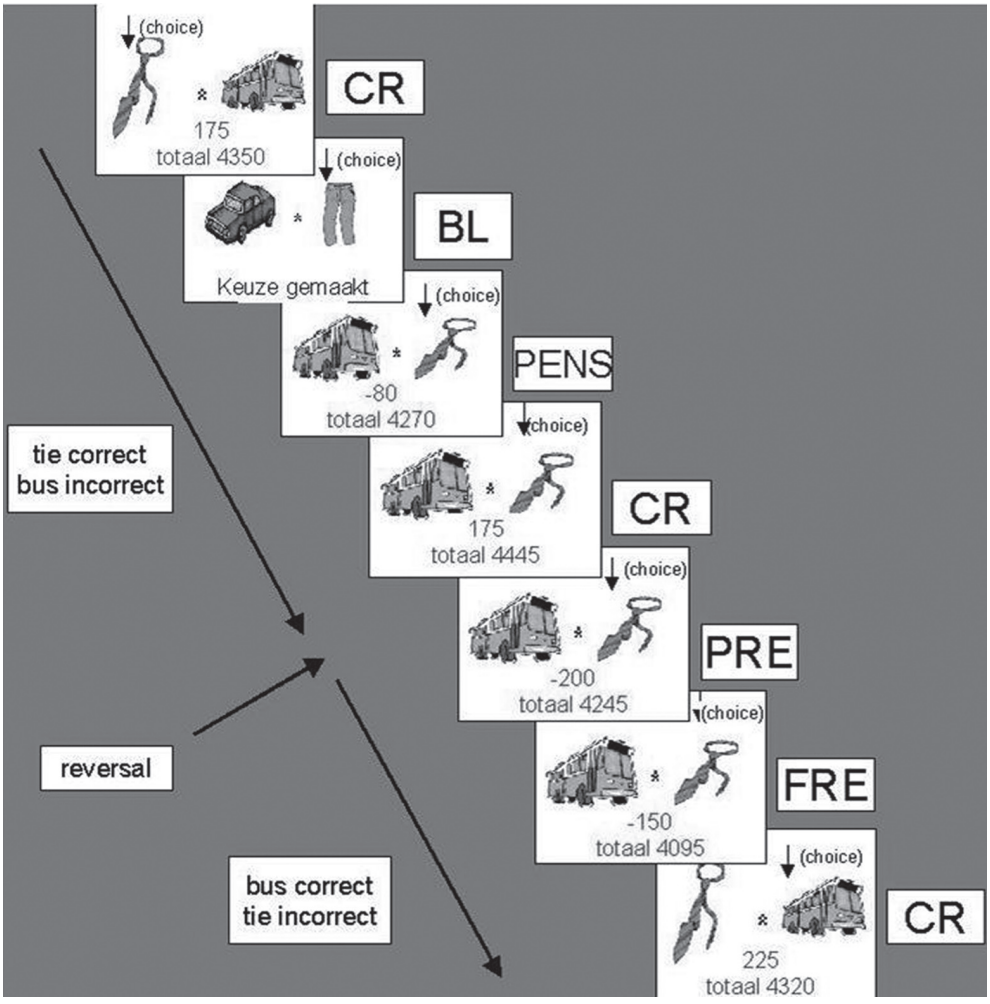

Figure 4.1: The reversal learning task. This example (consecutive trials are running from top left to bottom right) shows all events of interest. Two stimuli are presented to subjects on each trial, ie, cartoons of a bus and a tie in experimental trials and cartoons of a car and a pair of trousers on baseline trials. In experimental trials, either stimulus is correct and positive or negative feedback is given in the form of points immediately after a subject's choice as well as the total number of points accumulated up to that trial. In baseline trials, subjects were instructed in advance which of the 2 stimuli to select and neutral feedback is given after a subject's choice (Choice Made). After 6 to 10 correct responses, a reversal occurs without the subject's knowledge. CR indicates correct response; BL, baseline trial; PENS, probabilistic error with no shift; PRE, preceding reversal error; FRE, final reversal error.

with a reward outcome was defined as a correct response (CR). A correct response that was probabilistically given negative feedback could either lead to a shift in stimulus selection (probabilistic error with shift [PES]) or not lead to such a shift (probabilistic error with no shift [PENS]). False responses (spontaneous errors [SEs]) were always given negative feedback. Criterion for reversal was reached after 6 to 10 correct responses (randomized). Immediately after reversal (unknown to the subject), a false response (according to the new criterion) not leading to a shift to the new correct stimulus was designated a preceding reversal error (PRE), and the last false response prior to a shift a final reversal error (FRE). Each trial ended with a 2000-millisecond display of both the number of points won or lost in that trial and the number of accumulated points in the task up to that trial followed by a fixation cross for 1000 milliseconds. The main task instruction was to strive to obtain a maximum number of points; subjects were not encouraged to respond as quickly as possible. After the scanning session, participants received a payment in euros equal to the total number of accumulated points during the task divided by 1000.

An affectively neutral baseline (BL) task consisting of 2 different equivalent stimuli (cartoons of a car and a pair of trousers) was presented in between experimental trials, and responses in this task were given neutral feedback. Subjects were instructed in advance which of the 2 BL stimuli to select. The scanning session ended after 400 trials (including the BL task) and lasted approximately 25 minutes.

Immediately after the scanning procedure, a 5-item OC questionnaire was administered in the patient group to assess the degree and severity of OC symptoms during the task. This questionnaire consisted of 3 items related to obsessions (assessing their time-consuming, task-interfering, and anxiety-provocative properties) and 2 items related to compulsions (assessing the time spent on mental compulsions and the urge to perform compulsive behavior), all of which were rated on a 5-point scale. To familiarize participants with the concept of probabilistic errors, subjects performed a brief version of the reversal learning task that did not contain reversal stages prior to scanning.

Imaging procedure

Imaging data were collected using a 1.5-T Sonata magnetic resonance system (Siemens, Erlangen, Germany) with a standard circularly polarized head coil. Task stimuli were generated by a Pentium PC and projected on a screen behind the subject's head at the end of the scanner table. This screen was visible for the subject through a mirror mounted above the subject's head. Two magnet-compatible response boxes were used to record the subject's responses. To reduce motion artifacts, the subject's head was immobilized using foam pads. T2*-weighted echo-planar images (EPI) with blood oxygenation level–dependent (BOLD) contrast were acquired. A customized EPI sequence sensitive to OFC signal was used (Deichmann et al., 2003). This sequence included an additional gradient pulse that was applied between excitation and readout, with a duration of 1 millisecond and amplitude of –1.3 mT/m in the slice direction. This gradient pulse resulted in enhanced signal intensity in the OFC at the expense of a slight

decrease in signal intensity acquired in other brain regions characterized by a homogeneous magnetic field. The acquisition plane was tilted parallel to the air/tissue interface of the OFC for each subject (between 0° and 15° from the anterior-posterior commissure line in our subject groups). Using this sequence with a repetition time of 2.18 seconds and an echo time of 45 milliseconds, we obtained 35 slices (3 x 3–mm in-plane resolution; 2.5-mm slice thickness; matrix size, 64 x 64). The scanner automatically discarded the first 2 measurements in each session before the task started. Scanning was manually halted after the task had ended. Furthermore, a whole-brain EPI scan for each subject was acquired using the same sequence (40-43 slices per scan, 3 measurements in total) as well as a structural scan using a 3D coronal T1-weighted sequence (voxel size, 1 x 1 x 1.5 mm; 160 sections).

Data analysis

Demographic and behavioral data were analyzed using SPSS software (version 11.5 for Windows; SPSS Inc, Chicago, Ill). For our behavioral analysis, the following outcome variables were assessed in both groups: the average number of CR, PENS, FRE, PRE, PES, and SE events and the average number of points accumulated by the end of the task. A 1-way analysis of variance with group (OCD vs controls) as the between-subject factor and event type as the within-subject factor was performed to assess performance differences between groups. Imaging analysis was done using SPM2 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, London, United Kingdom). Images were reoriented, slice-timed, and realigned to the first volume. The mean image was coregistered with the whole-brain EPI volume, and images were normalized to a SPM T2* template (using 12 linear parameters and a set of nonlinear cosine basis functions). Spatial smoothing was performed using a 6-mm full-width-at-half-maximum gaussian kernel with the aim of increasing sensitivity for small activation foci, particularly in the OFC, even though larger filters may be more efficient for noise reduction. Statistical analysis was carried out in the context of the general linear model, in which each event was modeled using a δ-function convolved with the canonical hemodynamic response function. The following events were modeled to the onset of the feedback presentation, as defined previously: (1) baseline events (BLs), (2) correct responses with a reward outcome (CRs), (3) probabilistic errors with no following shift (PENSs), (4) preceding reversal errors, ie, false responses after reversal not leading to a shift (PREs), and (5) final reversal errors, ie, the last false response after reversal prior to a shift (FREs). Two events were modeled as events of no interest: (6) spontaneous errors (SEs), and (7) probabilistic errors with a following shift (PESs). Movement parameters were also included in the model as regressors of no interest.

The following contrasts were computed: (1) CRs minus BLs to assess the main effect of reward, (2) (PENSs plus PREs plus FREs) minus BLs to assess the main effect of all punishment events, and (3) FREs minus (PENSs plus PREs) to subtract punishment events not leading to a shift from punishment events prior to a shift, ie, to isolate affective switching.

Contrasts were first performed at single subject level. These were then entered into a second level (random effects) analysis by calculating 1-sample *t* tests on each individual's contrast images for

contrasts 1 through 3. Group main effects for each contrast were analyzed with 1-way analysis of variance. We performed conjunction analyses for our events of interest to identify regions showing consistent activations across groups and group interaction effects by using a statistical parametric map of the minimum *t* statistic over the relevant orthogonal contrasts (Friston et al., 1999). The *P* values of the ensuing regional effects were adjusted for the whole-brain search volume using the false discovery rate method implemented in SPM2 (Genovese et al., 2002). A significant effect ($P<.05$) suggests that one or both contrasts were significant at a corrected level against the null hypothesis of no effect in either contrast. After statistical testing, inclusive masking was used to ensure that both contrasts contributed substantially to the overall effect (Friston et al., 2005). In the patient group, additional correlation analyses were performed between BOLD responses on reward, punishment, and affective switching and OC and depression severity scores. Results for main effects and correlation analyses are similarly reported at $P<.05$ and are false discovery rate–corrected unless indicated otherwise. Localization of group results was expressed in MNI (Montreal Neurological Institute) coordinates (Brett et al., 2002).

Results

Data

Table 4.1 summarizes demographic and clinical characteristics for both groups. The OCD

Table 4.1: Demographic and clinical characteristics of OCD and control group

	OCD (N=20) Mean (SD)	Controls (N=27) Mean (SD)	P-value
Sex (Female/Male)	14 / 6	19 / 8	.97*
Age	34 (10.8)	32 (7.7)	.58**
Handedness (R/L)	16/4	23/4	.64 *
Education (range 1-10)‡	7.8 (2.3)	8.6 (1.4)	.28***
Duration of illness (years)	20.8 (14.1)		
No. of medication naïve patients	7		
No. of patients with previous CBT	10		
Total Y-BOCS severity score	20.8 (5.4), ranging 11-29		
Padua-IR	56.8 (26.6)	11.5 (10.4) †	< .001**
BDI	17.0 (8.5)	1.7 (2.6) †	< .001**
HDRS-21	11.7 (4.3)	0.4 (1.0) ‡	< .001**
MADRS	13.6 (8.0)	0.6 (0.9) ‡	< .001**
5-item post-scan OC-questionnaire (range 0-20)	3.0 (3.4)		

†assessed in 18 OCD patients ‡ assessed in 17 OCD patients
‡ 1 denotes primary school unfinished, 10 denotes university graduated
* Chi-square test
** Independent samples t-test
*** Mann-Whitney U test
Abbreviations: BDI = Beck Depression Inventory, CBT = Cognitive Behavioural Therapy, HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery Asberg Depression Rating Scale, OCD = Obsessive-Compulsive Disorder, Padua-IR = Padua Inventory Revised, Y-BOCS = Yale-Brown Obsessive-Compulsive Scale

Table 4.2: Behavioural data on the reversal learning task: average numbers for each event type in OCD and control groups

Event Type	OCD (N=20) Mean (SD)	Controls (N=27) Mean (SD)	Group X Event Type ANOVA F-value df = 1,45	P-value
BL	47 (3.0)	47 (3.5)	0.36	.55
CR	209 (26)	224 (17)	5.96	< .02
PENS	22 (7.8)	19 (7.7)	1.36	.25
FRE	15 (7.3)	17 (5.8)	1.44	.24
PRE	17 (11.2)	16 (9.4)	0.02	.89
SE	74 (41.5)	55 (23.1)	3.95	.05
PES	19.3 (7.9)	21.4 (8.2)	0.78	.38
Number of accumulated points by end of task	10073 (9709)	15524 (5998)	5.63	< .03
Number of acquired scans over RLT	707.2 (36.0)	679.1 (25.8)	9.7	< .004

Abbreviations: BL = Baseline, CR = Correct Responses, FRE = Final Reversal Errors, OCD = Obsessive-Compulsive Disorder, PENS = Probabilistic Errors with No Shift, PES = Probabilistic Errors with Shift, PRE = Preceding Reversal Errors, SE = Spontaneous Errors, RLT = Reversal Learning task

group displayed significantly higher OCD severity scores in addition to significantly increased depressive symptom ratings compared with the control group. Table 4.2 lists behavioral data from the reversal learning task. Patients with OCD were found to have a significantly lower average number of points accumulated by the end of the task as well as a significantly reduced number of CRs and an increased number of SEs that was borderline significant. In the patient

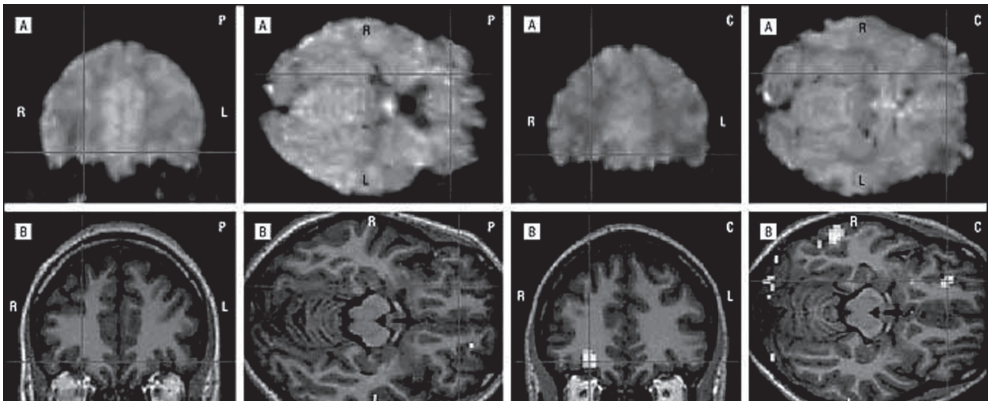

Figure 4.2: Examples of mean echo-planar images (coronal and axial slices) acquired with the orbitofrontal cortex (OFC)–sensitive sequence (A) in a 27-year-old female patient (P) and a 28-year-old female control subject (C) and of their main effects for reward (correct responses – baseline trials) superimposed on each subject's individual normalized structural magnetic resonance imaging scan (B). All slices were at the same level of the OFC; crosshairs were at x = 24, y = 42, z = –15. L indicates left; R, right.

group, no significant correlations were found between the average number of points obtained and the number of CRs on the one hand and depression severity measures (P>.30 for all), OCD severity ratings (P>.10 for all), or scores from the 5-item postscan OC questionnaire (P>.16 for both) on the other. Imaging results for main effects of reward, punishment, and affective switching in both groups as well as conjunction analyses are listed in Table 4.3.

Reward

In controls, reward processing (CRs – BLs) was associated with increased activity in the right medial and lateral OFC, right DLPFC, right superior parietal cortex, bilateral occipital cortex, bilateral caudate nucleus, and left ventral pallidum/nucleus accumbens. Patients with OCD did not show activations at our a priori significance level. However, at P<.001 uncorrected, increased BOLD responses were found in the right DLPFC, right inferior parietal cortex, and bilateral occipital cortex (see Figure 4.2 for an example of individual results at the level of

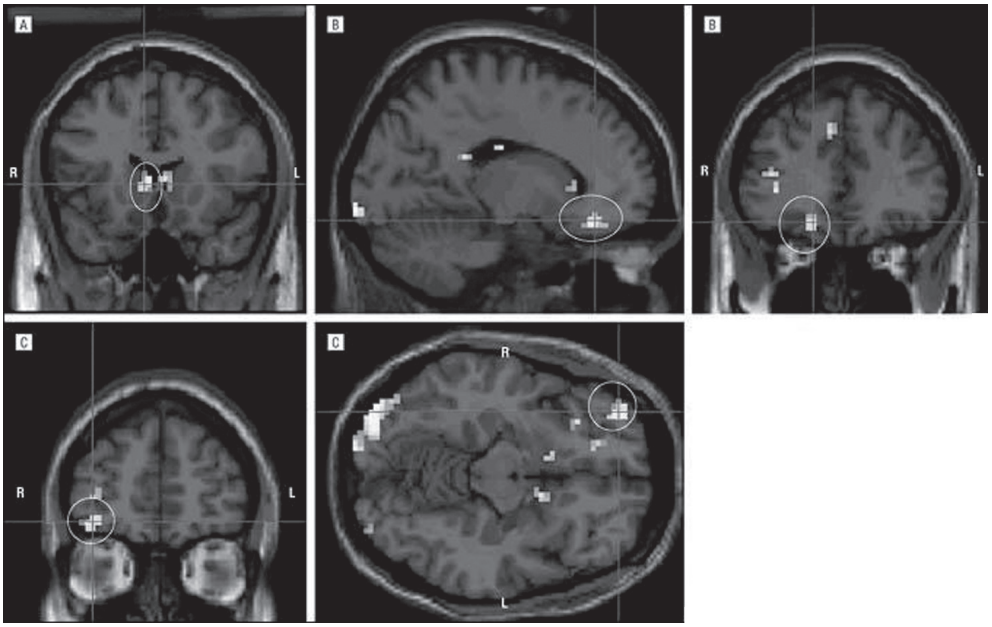

Figure 4.3: Conjunction analysis of overall main effect for reward and interaction effect of controls vs patients with obsessive-compulsive disorder (OCD) for reward superimposed on coronal, transaxial, and sagittal slices from a canonical (MNI [Montreal Neurological Institute] compatible) T1 image as supplied by SPM2 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, London, United Kingdom). Increased blood oxygenation level–dependent responses are shown for control subjects compared with patients with OCD in the right caudate nucleus (A) (border zone ventral striatum encircled; x = 6, y = 18, z = 3); right medial orbitofrontal cortex (OFC) (B) (encircled; x = 15, y = 36, z = –15); and right lateral OFC (C) (encircled; x = 36, y = 51, z = –12). The mask is set at P = .05 for purposes of illustration. L indicates left; R, right.

Table 4.3: Brain regions showing main effects for reward, punishment, and affective switching in OCD and control subjects, as well as for the conjunction of main effects and group interaction effects

		OCD group (N = 20)					Control group (N = 27)					Conjunction of main effects and group interaction effects				
area	L/R	MNI coordinates			z-value	Cluster size¶	MNI coordinates			z-value	Cluster size	MNI coordinates			z-value*	Cluster size¶
		x	y	z			x	y	z			x	y	z		
Reward (CR minus BL)																
												OCD > controls				
												No significant effects				
												Controls > *OCD*				
Lateral OFC	R						36	54	-12	4.37	21	36	51	-12	4.35	1
Medial OFC	R						15	36	-15	4.16	13	15	36	-15	4.49	1
Dorsolateral PFC	R	45	42	-18	3.65†	3	45	42	21	3.70	10					
Parietal sup.	R						30	-63	48	3.77	17					
Parietal inf.	R	27	-63	45	4.01†	20										
Occipital cortex	R	33	-93	0	4.18†	50	36	-93	-9	5.76	173	36	-93	-12	4.79	5
	L	-24	-99	-12	3.53†	6	-33	-96	-12	4.41	31	-36	-93	-3	4.04	1
Caudate nucleus	R						6	18	6	4.43	49	6	18	3	4.49	1
	L						-6	15	6	3.73	49					
Ventral pallidum/nucleus accumbens	L						-12	6	-9	3.76	3					
Punishment ([PRE+PENS+FRE] minus BL)																
												OCD > controls				
												No significant effects				
Lateral OFC	R						33	54	-12	5.45	48	Controls > *OCD*				
Medial OFC	R						18	42	-15	3.74	7	No significant effects				
Anterior PFC	R	39	51	-3	4.31†	20										
Dorsolateral PFC	R	45	39	27	3.94†	42										
Insular cortex	R	33	21	-3	4.33†	26	30	24	-12	4.04	16					
Parietal inf.	R	27	-63	45	4.77	29										

Table 4.3: Continued.

area	L/R	OCD group (N = 20) MNI coordinates x	y	z	z-value	Cluster size¶	Control group (N = 27) MNI coordinates x	y	z	z-value	Cluster size¶	Conjunction of main effects and group interaction effects MNI coordinates x	y	z	z-value*	Cluster size¶
Occipital cortex	R	36	-96	0	4.30†	9	33	-93	-9	5.00	122					
	L						-33	-96	-12	3.78	4					
Affective switching (FRE minus [PRE+PENS])																
												OCD > controls				
												No significant effects				
												Controls > OCD				
Lateral OFC	R	30	51	-15	3.61†	4										
Posterior OFC	L						-18	18	-15	3.70†	8	-18	18	-15	4.15	1
Anterior PFC	R	30	54	15	3.38†	4	36	51	9	4.71	136	36	54	-3	4.53	2
	L	-30	51	6	3.31†	3	-30	60	9	3.85†	29	-31	60	6	4.38	2
Dorsolateral PFC	R						33	45	33	5.09	136	33	45	33	5.45	5
	L	-45	36	27	3.46†	3	-42	33	42	4.17	9	-42	33	42	4.71	1
Insular cortex	R	33	18	6	3.95†	4	33	18	6	4.53	75	36	27	3	3.79‡	1
	L						-33	21	9	4.99	70	-33	21	6	5.37	12
Anterior cingulate							0	30	33	3.69†	15					

Abbreviations: BL = baseline, CR = Correct Responses, FRE = Final Reversal Errors, L = Left, MNI = Montreal Neurological Institute, OCD = Obsessive-Compulsive Disorder, OFC = Orbitofrontal Cortex, PENS = Probabilistic Errors with No Shift, PFC = Prefrontal Cortex, PRE = Preceding Reversal Errors, R = Right

* Z-values refer to the effect for the combination of main effects and group interaction effect

All results at P <.05 FDR-corrected unless indicated otherwise

† P < 0.001 uncorrected

‡ P < 0.06 FDR corrected

¶ No. of voxels

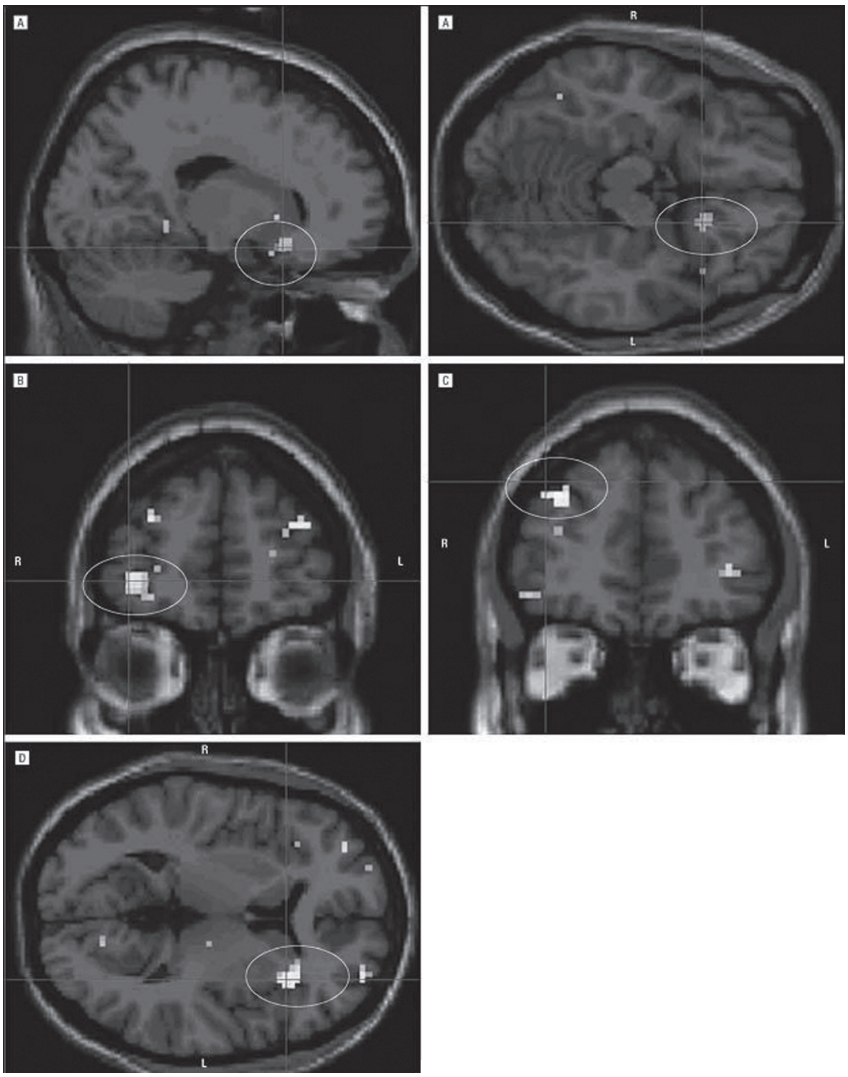

Figure 4.4: Conjunction analysis of overall main effect for affective switching and interaction effect of controls vs patients with obsessive-compulsive disorder (OCD) for affective switching, superimposed on sagittal, coronal, and transaxial slices from a canonical (MNI [Montreal Neurological Institute] compatible) T1 image as supplied by SPM2 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, London, United Kingdom). Enhanced blood oxygenation level–dependent responses are shown for control subjects relative to patients with OCD in the left posterior orbitofrontal cortex (A) (encircled; x = –18, y = 18, z = –15); right anterior prefrontal cortex (B) (encircled; x = 36, y = 54, z = –3); right dorsolateral prefrontal cortex (C) (encircled; x = 33, y = 45, z = 33); and left anterior insular cortex (D) (encircled; x = –33, y = 21, z = 6). The mask is set at $P = .05$ for purposes of illustration. Significant effects in structures B, C, and D were found bilaterally (not shown in this figure). L indicates left; R, right.

the OFC together with each subject's mean EPI). Conjunction analyses demonstrated greater reward-associated activity in the right medial and lateral OFC, bilateral occipital cortex, and right caudate nucleus (border zone ventral striatum) in controls relative to the OCD group (Figure 3). No areas were found showing hyperactivity for patients compared with controls.

Punishment

When contrasting all punishment events with baseline events ([PREs + PENSs + FREs] – BLs), controls showed activity in the right medial and lateral OFC, right insular cortex, and bilateral occipital cortex. In contrast, patients demonstrated inferior parietal cortex activity. At an uncorrected significance level of $P<.001$, additional areas were found activated in the OCD group, ie, in the right anterior PFC, right DLPFC, right insular cortex, and right occipital cortex. Conjunction analyses did not reveal significant group differences for punishment-associated brain activity. An additional analysis subtracting baseline events from punishment events not leading to a shift ([PREs + PENSs]– BLs) showed the same main effects in both groups as the contrast ([PREs + PENSs + FREs] – BLs), albeit with the exception of right insular activity and at a slightly lower threshold ($P<.001$ uncorrected). Again, a conjunction analysis did not reveal significant group x task differences.

Affective switching

To assess the main effect of affective switching, punishment events not leading to a shift were subtracted from punishment events prior to a shift (ie, FREs – [PREs + PENSs]). In controls, this contrast revealed activity in the left posterior OFC, bilateral anterior PFC, bilateral DLPFC, bilateral insula, and anterior cingulate cortex. No significant activations were found in the patient group at $P<.05$ corrected. However, at $P<.001$ uncorrected, activity was observed in the right lateral OFC, bilateral anterior PFC, left DLPFC, and right insular cortex. Conjunction analyses showed increased BOLD responses in the left posterior OFC, bilateral anterior PFC, bilateral DLPFC, and bilateral insular cortex (right-sided at borderline significance level [$P<.06$]) for controls vs patients with OCD (Figure 4.4). The opposite contrast did not reveal significant differences.

Correlation analyses

In patients, no significant correlations were found between BOLD responses during reward, punishment, or affective switching on the one hand and symptom severity ratings on the other (Hamilton Depression Rating Scale, Montgomery-Asberg Depression Rating Scale, and Beck Depression Inventory for depression; Yale-Brown Obsessive Compulsive Scale and Padua Inventory–Revised for OCD). Nor did we find significant correlations between 3 contrasts of interest and performance scores.

Discussion

To our knowledge, the present functional magnetic resonance imaging study is the first to investigate orbitofrontal function in OCD employing a reversal learning task. This paradigm allowed the investigation of reward and punishment processing as well as affective switching, ie, the alteration of behavior by switching to new associations after a reversal of stimulus-reinforcement contingencies. Moreover, these effects were assessed with the aid of a scanning sequence specifically sensitive to OFC signal (Deichmann et al., 2003). As was hypothesized, patients showed impaired overall task performance reflected by a significantly lower number of accumulated points by the end of the task. This was found to be associated with a smaller number of correct responses (CRs) as well as a greater number of spontaneous errors (SEs). Our findings of impaired overall performance are in accordance with some (Abbruzzese et al., 1997; Cavedini et al., 2002), but not all (Hermesh et al., 1999; Nielen et al., 2002), previous neuropsychological studies using tasks addressing OFC function in OCD. These discrepant results may be explained by major differences in task implementation (ie, object alternation, decision-making, olfactory discrimination, and reversal learning tasks), medication status, and patient inclusion criteria. However, compared with these previous studies, the current paradigm provides direct support for the hypothesis of OFC dysfunction in patients with OCD not receiving medication by showing abnormal neural responsiveness during cognitive challenge.

Imaging results showed differential activity between groups in the OFC-striatal circuit, among other areas, during reward processing and affective switching. Specifically, patients with OCD recruited the right medial and lateral OFC as well as the right caudate nucleus (border zone ventral striatum) to a lesser extent than controls during reward processing. During affective switching, patients showed decreased activity compared with controls in the left posterior OFC in addition to the bilateral insula, bilateral anterior PFC, and bilateral DLPFC. It can be argued that comorbid depression may have confounded these between-group differences. However, we found no significant correlations between task-induced brain activity and depression severity ratings in patients. Moreover, post hoc analyses performed after excluding patients with OCD with comorbid depression revealed similar group differences for reward and affective switching (data not shown).

The finding of lower task-induced activity of the OFC-striatal circuit in the present study is remarkable because a wealth of data have demonstrated increased perfusion and glucose uptake in these regions in resting-state neuroimaging designs in OCD (Baxter et al., 1988; Lacerda et al., 2003; Saxena et al., 2004), although conflicting results have also been reported (Busatto et al., 2000). Enhanced baseline activity is not likely to explain decreased task-associated activity as observed in our patients with OCD, however. First, OFC-striatal hypoactivity was found only for reward and affective switching but not for punishment; second, the contrast assessing affective switching compares 2 different punishment events and does not include baseline activity, ruling out ceiling effects as a possible explanation. It is interesting that task-induced

hypoactivity in brain regions associated with resting-state hyperactivity has been reported before in OCD because Rauch and coworkers (1997; 2001) demonstrated decreased striatal responsiveness in OCD during implicit learning, in both a positron emission tomography and a functional magnetic resonance imaging design. Taken together, these findings suggest that OFC-striatal dysfunction in OCD is associated with increased resting-state activity together with decreased responsiveness on cognitive challenge. Future research may address this issue by combining resting-state and cognitive activation paradigms within a single session.

Current neurobiological models of OCD emphasize the involvement of the OFC-striatal circuit in the pathogenesis of this disorder (Saxena et al., 1998; Schwartz, 1999; Baxter et al., 2001), although the exact nature of this dysfunction is insufficiently clear. As outlined previously, this neural loop is associated with motivational behavior, in particular processing of reward and punishment, and rapid reversal of stimulus-reinforcement associations. Consequently, dysfunctional OFC-striatal circuitry in OCD may be the neural substrate of deficient modulation of emotional information with subsequent ineffective behavioral adaptation being core features of this disorder (Schwartz, 1999; Aouizerate et al., 2004). The present findings of reward-associated activity in the right OFC and ventral caudate in healthy controls but not in patients with OCD appear to be in line with these models. With respect to affective switching, patients showed less activity in the left posterior OFC compared with control subjects. Interestingly, the posterior region of OFC has been found to be associated with reversal learning impairments in a recent study of subjects with left-lateralized OFC/ventromedial brain lesions (Fellows et al., 2003). The posterior OFC is part of a paralimbic circuit encompassing, among other areas, insular and cingulate cortices (Augustine, 1996; Mesulam, 2000). The functional relationship between these structures may explain functional abnormalities in anterior cingulate and insula during affective switching in OCD, although only the latter region was found to be hypoactive in our study. Although speculative, the observed OFC-striatal deficiencies in OCD on reward and affective switching may be the neural correlates of a failure of compulsive behavior to alleviate obsession-caused anxiety and cognitive-behavioral inflexibility despite changing reinforcing signals in the environment, respectively (Schwartz, 1999). Clearly, this hypothesis is in need of further empirical testing.

In addition to these paralimbic regions, we found decreased activation in OCD during affective switching for brain areas that are normally involved in "executive" functions, ie, the bilateral DLPFC and anterior prefrontal cortex. In a recent article, we reported the engagement of these structures in affective switching and concluded that this may reflect cognitive set switching per se as well as inhibitory control (Remijnse et al., 2005). The involvement of these regions has been reported during decision-making in another recent study (Cohen et al., 2005), suggesting that these areas support the computational aspects not only of affective switching but also of decision-making. Our finding of diminished activations in paralimbic and executive brain structures during affective switching in OCD points to an impairment of both emotional and cognitive aspects in reversal learning in this disorder. Inadequate functioning of dorsal and ventral prefrontal-striatal loops is in agreement with pathophysiological models of OCD

focusing on an altered balance between inhibitory (dorsolateral) and excitatory (ventromedial) frontal-striatal circuits (Alexander et al., 1990; Saxena et al., 1998; Baxter et al., 2001).

Contrary to expectation, conjunction analyses failed to show group differences for punishment events in the present study despite clear-cut differences in group main effects because right medial and lateral OFC activity was seen in controls but not in patients, whereas the opposite was true for right inferior parietal activity. Previous cognitive activation paradigms during functional neuroimaging using response conflict tasks have associated OCD with increased anterior cingulate cortex activity both on errors (Ursu et al., 2003; Gehring et al., 2000) and during correct responses encompassing high-conflict situations (Ursu et al., 2003; Maltby et al., 2005; van der Wee et al., 2003). These results corroborated the notion that OCD is characterized by a dysfunctional error recognition system that has its origin in aberrant anterior cingulate cortex and OFC activity (Pitman, 1987). It is assumed that this is the neural substrate of the continual sense in patients with OCD that something is wrong (Schwartz, 1999; Aouizerate et al., 2004; Ursu et al., 2003; Gehring et al., 2000; van der Wee et al., 2003). Discrepant results between these studies and the present experiment may be explained by different methods of error sensation induction, ie, external negative feedback in our reversal learning task vs internally generated error detection in response conflict tasks (Ursu et al., 2003; Gehring et al., 2000).

It is interesting that our finding of OFC hypoactivity for reward but not for punishment processing in OCD may be related to recent data from a tryptophan depletion study in healthy volunteers (Rogers et al., 2003). These authors showed that lowering serotonergic transmission altered the processing of reward but not of punishment-related information during a decision-making task, implying that serotonin selectively modulates reward processing, most likely mediated by the OFC (Rolls, 2000). These findings suggest that OFC hypoactivity during reward processing in subjects with OCD is due to abnormal serotonin (5-hydroxytryptamine) transmitter function, in accordance with the commonly assumed role of brain serotonergic systems in the pathophysiology of OCD (Baumgarten et al., 1998).

In contrast to the presumed serotonergic regulation of OFC function, dopaminergic activity is intimately associated with normal basal ganglia function, including reward processing in the ventral striatum (Koepp et al., 1998; Schultz, 1998). In the context of our finding of reward-related ventral striatal hyporesponsiveness in OCD, it is of interest that recent single photon emission computed tomography ligand studies reported abnormal dopamine transporter density and D2 receptor binding in the basal ganglia in OCD (van der Wee et al., 2004; Denys et al., 2004). Further research to clarify the relationship between OCD and dopamine dysfunction is obviously warranted.

The present study is not without limitations. First, we used a new reversal learning task that, although employed successfully in a group of healthy volunteers (Remijnse et al., 2005), has not been validated before in subjects with OCD. This implies the need for a replication of the present results with a different task known to validly probe the OFC in OCD. Second, effect sizes for reward- and punishment-associated activity were only modest, in particular

for interaction effects. Given our fairly robust sample size, the most likely explanation is that OFC signal is difficult to capture, even with a specifically tailored sequence. Third, mean symptom severity in our OCD group was only mild to moderate (mean Yale-Brown Obsessive Compulsive Scale score = 20.8), and our sample was clinically heterogeneous, despite evidence that different neuronal mechanisms may underlie various OCD subdimensions (Saxena et al., 2004). The current findings may therefore possibly reflect a diluted effect that is specific to one of the OCD symptom dimensions.

In conclusion, the present study has shown that abnormal OFC-striatal activity is associated with impaired performance during an OFC-sensitive reversal learning task in OCD, consistent with a proposed role for this circuit in the pathogenesis of this disorder. Future research will need to further specify the significance of aberrant activity in these structures on reward and affective switching processing in relation to OCD symptoms.

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Chapter 5

Differential frontal-striatal and paralimbic activity during reversal learning in major depressive disorder and obsessive-compulsive disorder

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Abstract

Several lines of research suggest a disturbance of reversal learning – reward and punishment processing, and affective switching – in patients with major depressive disorder (MDD). Obsessive-compulsive disorder (OCD) is also characterized by abnormal reversal learning, and often comorbid with MDD. However, neurobiological distinctions between both disorders are unclear. Functional neuroimaging (activation) studies directly comparing MDD and OCD are lacking. We investigated the performance of twenty non-medicated OCD-free patients with MDD, 20 non-medicated MDD-free patients with OCD, and 27 healthy controls on a self-paced reversal learning task in an event-related design during functional magnetic resonance imaging. Compared with healthy controls, both MDD and OCD patients displayed prolonged mean reaction times, but normal accuracy. In MDD subjects, mean reaction times were correlated with disease severity. Imaging results showed MDD-specific hyperactivity in anterior insula during punishment processing, and in putamen during reward processing. Moreover, BOLD responses in dorsolateral and anterior prefrontal cortex during affective switching showed a linear decrease across controls, MDD, and OCD. Finally, the OCD group showed blunted responsiveness of the orbitofrontal (OFC)-striatal loop during reward, and in OFC and anterior insula during affective switching. This study shows frontal-striatal and (para)limbic functional abnormalities during reversal learning in MDD, in the context of generic psychomotor slowing. These data converge with currently influential models on the neuropathophysiology of MDD. Moreover, this study reports differential neural patterns in frontal-striatal and paralimbic structures on this task between MDD and OCD, confirming previous findings regarding the neural correlates of deficient reversal learning in OCD.

Introduction

Reversal learning is a neuropsychological function crucial for socio-emotional learning and behavior in primates (Rolls, 1999). It is defined as the ability to associate neutral stimuli with their rewarding or punishing values, and to alter these associations upon reversing reinforcement contingencies (Dias et al., 1996; Rolls, 1999). Several lines of evidence indicate that reversal learning (also termed affective switching) is disturbed in Major Depressive Disorder (MDD), both at a clinical, behavioral and neural level.

Clinically, MDD is by definition characterized by 'anhedonia' (APA, 1994) and patients with MDD experience a negative thought bias (Beck, 1963). Neurocognitive studies have reported aberrant responding to reward and punishment feedback in depressed patients (Henriques et al., 1994; Elliott et al., 1996; Must et al., 2006), as well as a reduced ability to exert inhibitory control during an affective switching (go/nogo) task (Murphy et al., 1999). At a neurochemical level, there is abundant evidence that the pathophysiology of MDD is characterized by underlying dysfunctional serotonin (5-hydroxytryptamine (5-HT)) transmission (Mann et al., 1996), and various manipulations of 5-HT neurotransmission in human volunteers (Rogers et al., 1999; Chamberlain et al., 2006) have induced impaired performance on two-choice discrimination reversal tasks. For instance, acute tryptophan depletion (ATD) has been shown to affect reversal learning in healthy subjects (Murphy et al., 2002; Evers et al., 2005), and to induce a temporary relapse of depressive symptoms in recovered patients with MDD (Smith et al., 1997).

Finally, lesion and neuroimaging studies in nonhuman and human primates have implicated the orbitofrontal (OFC)-striatal circuit in reversal learning (Dias et al., 1996; Fellows & Farah, 2003; Clark et al., 2004), which is one of the brain's parallel frontal-striatal circuits supposedly involved in the pathophysiology of MDD (Alexander et al., 1990; Rogers et al., 2004). However, recent neuroimaging work has shown the engagement of additional frontal cortical brain areas in reversal learning, in particular dorsolateral prefrontal cortex (DLPFC), anterior PFC, anterior insula, and anterior cingulate cortex (ACC) (Remijnse et al., 2005a; Budhani et al., 2006), i.e. regions also implicated in MDD (Drevets, 2000; Phillips et al., 2003; Mitterschiffthaler et al., 2006).

Taken together, these findings suggest that performance of reversal learning may be impaired in MDD, associated with functional abnormalities in frontal-striatal and (para)limbic brain regions. To date, one neuropsychological study reported a preserved ability to acquire and reverse a probabilistic discrimination, but an incapacity for depressed patients to maintain response set in the face of misleading negative feedback after having attained criterion for successful discrimination (Murphy et al., 2003).

Obsessive-compulsive disorder (OCD) is frequently a comorbid disorder with MDD (Overbeek et al., 2002) and shares several features with MDD, including symptomatic overlap (Ninan & Berger, 2001) and clinical improvement following serotonergic antidepressants (Levine et al., 2001). However, MDD and OCD differ with respect to core clinical symptoms and

neuropsychological profiles (Purcell et al., 1998; Joel et al., 2005). Ideally, identification of shared and distinct neural substrates for MDD and OCD may lead to a biologically grounded distinction between these disorders (Chamberlain et al., 2005; Chamberlain & Sahakian, 2006). We know of only two neuroimaging studies directly comparing these two disorders (Edmonstone et al., 1994; Saxena et al., 2001) demonstrating increased activity in bilateral putamen, but diminished activity in left hippocampus (for MDD versus OCD) during resting-state. To date, neuroimaging activation studies employing cognitive or mixed cognitive/emotional paradigms in MDD and OCD have not yielded consistent findings regarding differential involvement of brain areas in these disorders (Drevets, 2000; Phillips et al., 2003; Remijnse et al., 2005b), whereas comparative studies in this field are lacking.

We have recently published on the neural correlates of reversal learning in a group of healthy volunteers (Remijnse et al., 2005a), and also in comparison with a sample of OCD patients (Remijnse et al., 2006). The goal of the present study was two-fold: first, we sought to explore the neural correlates of reversal learning using fMRI in a sample of unmedicated patients with MDD, compared with our healthy control group that has been described before (Remijnse et al., 2005a). Based on existing neuropsychological and neuroimaging data, we hypothesized impaired performance in the patient group, associated with abnormal OFC-striatal (Fellows & Farah, 2003; Clark et al., 2004), DLPFC and anterior PFC, ACC, and insular activations (Remijnse et al., 2005a; Budhani et al., 2006). Second, the present study aimed to compare MDD and OCD directly in a single activation design. We recently demonstrated impaired reversal learning in OCD, associated with abnormal OFC-striatal, DLPFC, anterior PFC and anterior insular activity compared with healthy controls (Remijnse et al., 2006). However, since this previous OCD sample included patients having comorbid depression, we assembled a new group of MDD-free, unmedicated OCD patients for the current study. Based upon the sparse direct-comparison neuroimaging literature (Edmonstone et al., 1994), we hypothesized that patients with MDD may show increased putamen activity, compared with OCD patients.

Materials and Methods

Subjects

Twenty patients with OCD-free MDD, 20 patients with OCD and currently (but not lifetime) free of MDD, and 27 healthy controls participated in this study (Table 5.1). The current OCD group consisted of 13 MDD-free OCD patients that also participated in our previous study (Remijnse et al., 2006), and seven newly recruited patients. Diagnoses and comorbidity were established by experienced clinicians with the Structured Clinical Interview for DSM-IV Axis-I disorders (SCID) (First et al., 1996). Exclusion criteria were the presence of alcohol or substance abuse at the time of study, and major internal or neurological disorders. In the MDD group, comorbidity was as follows: social anxiety disorder (N=3), generalized anxiety disorder

Table 5.1: Demographic and clinical data for patients with major depressive disorder (MDD), patients with obsessive-compulsive disorder (OCD), and for the healthy control group

	MDD (N=20) Mean (SD)	OCD (N=20) Mean (SD)	Controls (N=27) Mean (SD)	Between-groups comparison P-value
Sex (Female/Male)	8/12	15/5	19 / 8	.04 †
Age (years)	35 (range 21-54y)	34 (range 19-54y)	32 (range 22-53y)	.64 *
Handedness (R/L)	16/4	17/3	23/4	.87 †
Education (range 1-10)‡	8.0 (2.1)	8.5 (1.1)	8.6 (1.4)	.41 *
Total Y-BOCS severity score		22.2 (5.1), range 11-31		
Number of OCD patients with prior MDD / mean length in months since remission of MDD		8 / 36m		
Padua-IR	42.4 (32.5)¶	59.7 (27.8)¶	11.5 (10.4)	<.001* MDD=OCD>COϕ
BDI	25.6 (7.6)¶	12.2 (7.7)#	1.7 (2.6)	<.001* MDD>OCD>COϕ
HDRS-17	19.1 (4.1)	6.9 (4.0)§	0.4 (0.9)	<.001* MDD>OCD>COϕ
MADRS	29.7 (4.7)	9.1 (6.5)¶	0.6 (0.9)	<.001* MDD>OCD>COϕ
HARS	19.9 (5.0)¶			

* ANOVA † chi-square test ϕ post-hoc Tukey and Scheffe tests: p<.05
‡ 1 denotes primary school unfinished, 10 denotes university graduated
¶ assessed in 18 patients
#assessed in 17 patients
§assessed in 15 patients
Abbreviations: BDI = Beck Depression Inventory, HDRS = Hamilton Depression Rating Scale, HARS = Hamilton Anxiety Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, OCD = Obsessive-Compulsive Disorder, Padua-IR = Padua Inventory Revised, Y-BOCS = Yale-Brown Obsessive-Compulsive Scale

(N=1), panic disorder without agoraphobia (N=1), pain disorder (N=1), cannabis abuse in early (N=1) and sustained (N=1) full remission. Twelve patients were free from comorbidity, and six patients suffered from their first lifetime depressive episode.

In the OCD group, 9 patients were diagnosed with 'pure' OCD, and the following disorders were comorbid: posttraumatic stress disorder (N=1), panic disorder (N=2), generalized anxiety disorder (N=4), dysthymic disorder (N=4), social anxiety disorder (N=4), opioid abuse in sustained full remission (N=1). Moreover, comorbid Tourette disorder was clinically diagnosed in 1 patient. Mean duration of illness was 19.9 years in this group. At the time of the study, all patients and control subjects were free from psychotropic medication for at least two weeks, and in case of fluoxetine or antipsychotic medication for at least one month. Eight patients in the MDD group and 7 patients in the OCD group were medication-naïve, and the mean length of drug-free interval was 16 months in the MDD sample and 30 months in the OCD group. All

participants gave written informed consent and the study was approved by the ethical review board of the VU University Medical Center.

To assess symptom characteristics and severity scores, the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS; Goodman et al., 1989) was administered in OCD patients only, whereas the Padua-IR was used to measure all participants' obsessive-compulsive (OC) characteristics. To rate the presence and severity of depressive symptoms in all three groups, the Beck Depression Inventory (BDI; Beck et al., 1961), the 17-item Hamilton Depression Rating Scale (HDRS-17; Hamilton, 1967) and the 10-item Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979) were used. The Hamilton Anxiety Rating Scale (HARS; Hamilton, 1959) was administered in MDD patients only. Due to logistic problems in the patient groups, five patients with OCD failed to be interviewed with the HDRS-17, or with the MADRS (N=2), and two MDD patients failed to be interviewed with the HARS.

Two OCD patients and two MDD patients did not return the Padua-IR questionnaire. Three OCD patients and two MDD patients did not return the self-report BDI.

Reversal learning task and experimental procedure

We used a self-paced, probabilistic reversal learning task with an affectively neutral baseline (Figure 5.1) that has been described previously (Remijnse et al., 2005a). Each trial in the experimental task consisted of two stimuli - a cartoon of a bus and a tie – presented at either side of a screen with randomized locations, for 3000ms maximally. Subjects selected either stimulus by pressing the left or right button on a button box. Each trial ended with the presentation of positive or negative feedback in the form of a 2000ms display of both the number of points won or lost in that trial, and the amount of accumulated points in the task up to that trial. This was followed by a fixation cross for 1000ms.

Upon a correct response, either positive or negative feedback was given based on an 80:20 ratio, consisting of gaining or losing a random amount of 80-250 points. A correct response with a reward outcome was defined as a 'Correct Response'. A correct response that was probabilistically given negative feedback ('Probabilistic Error') could either lead to a shift in stimulus selection ('Probabilistic Error with Shift'), or not lead to such a shift ('Probabilistic Error no Shift'). The chance of a second, consecutive Probabilistic Error was 1:10 after a first Probabilistic Error. False responses ('Spontaneous Errors') were always given negative feedback. Criterion for reversal was reached after 6-10 correct responses (randomized). Immediately after reversal (unknown to the subject), a false response (according to the new criterion) not leading to a shift to the new correct stimulus was designated a Preceding Reversal Error, and the last false response prior to a shift a Final Reversal Error.

Affectively neutral baseline trials consisting of two different, equivalent stimuli (the cartoon of a car and a pair of trousers) were randomly presented interspersed with every 7th experimental trial on average. Baseline trials were never presented more than once consecutively, and put a minimal load on working memory (subjects were instructed in advance which of the two baseline stimuli to select), thus minimizing possible interference effects. Responses in this

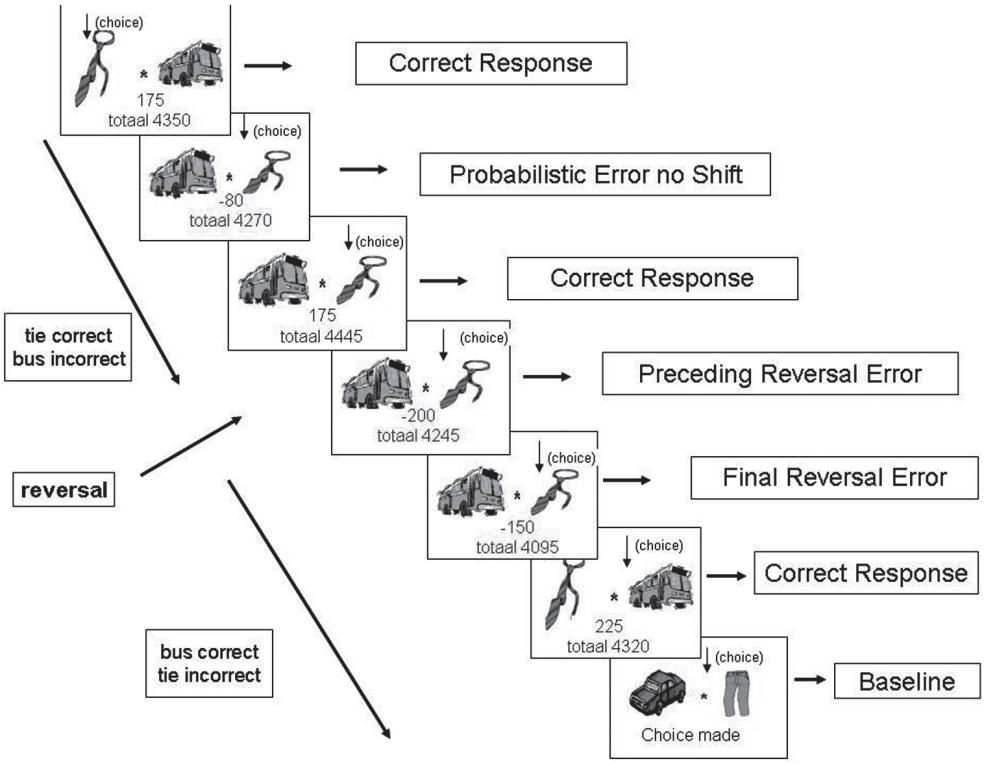

Figure 5.1: The reversal learning task. In this example (consecutive trials are running from top-left to bottom-right) all events of interest are displayed. See Materials and Methods section for details

baseline task were given neutral feedback ('choice made') for 2000ms, followed by a fixation cross for 1000ms. The scanning session ended after 400 trials (including baseline trials) and lasted circa 25min. After the scanning session, participants received the total amount of accumulated points during the task divided by 1000 in euros.

Imaging procedure

Imaging data were collected using a 1.5-T Sonata MR system (Siemens, Erlangen, Germany) with a standard receiver head coil. Task stimuli were projected on a screen at the end of the scanner table, visible through a mirror mounted above the subject's head. Two magnet-compatible response boxes were used to record the subject's responses.

T2*-weighted echo-planar images (EPI) with blood oxygenation level-dependent (BOLD) contrast were acquired. A customized EPI sequence sensitive to OFC signal was used (Deichmann et al., 2003; Remijnse et al., 2006). The acquisition plane was tilted parallel to the air/tissue interface of the OFC for each subject (0-15 degrees from the anterior-posterior commissure line). Using this sequence with a repetition time of 2.18s and an echo time of

45ms, 35 slices (3x3mm in-plane resolution; 2.5mm slice thickness; matrix size 64x64) were obtained.

Data analysis

Demographic and behavioral data were analyzed using SPSS software (version 11.5 for Windows; SPSS Inc, Chicago, Ill). For behavioral analysis, we assessed mean numbers of baseline trials, Correct Responses, Probabilistic Errors no Shift, Final Reversal Errors, Preceding Reversal Errors, Probabilistic Errors with Shift, and Spontaneous Errors, as well as mean reaction times (RTs) for these events, and the number of points accumulated by the end of the task. Performance differences between groups were assessed by one-way analyses of variance (ANOVA) with Group (MDD vs. OCD vs. controls) as between-subject factor and Event Type as within-subject factor. Additionally, correlations were calculated between performance measures and depression or OC severity measures for the MDD and the OCD group, respectively.

Imaging analysis was performed using SPM2 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, London, UK). Images were reoriented, slice-timed and realigned to the first volume. The resulting mean image was then co-registered with the whole-brain EPI-volume, and images were normalized to MNI-space as defined by a SPM T2* template and spatially smoothed using a 6mm FWHM Gaussian kernel. Statistical analysis was carried out in the context of the general linear model, in which each event was modelled using a delta function convolved with the canonical hemodynamic response function (HRF). The following events were modelled to the onset of the feedback presentation, as defined previously: (1) baseline events, (2) Correct Responses, (3) Probabilistic Errors no Shift, (4) Preceding Reversal Errors, and (5) Final Reversal Errors. Two events were modelled as events of no interest: (6) Spontaneous Errors, and (7) Probabilistic Errors with Shift; we excluded the latter from analysis since these were regarded as part of a subject's trial-and-error strategy instead of capturing a genuine set shift in stimulus-reinforcement associations. Movement parameters were included in the model as regressors of no interest.

The following contrasts were computed: (1) Correct Responses minus baseline trials to assess the main effect of reward, (2) (Probabilistic Errors no Shift) + (Preceding Reversal Errors) + (Final Reversal Errors) minus baseline trials to assess the main effect of all punishment events, and (3) (Final Reversal Errors) minus (Probabilistic Errors no Shift + Preceding Reversal Errors) to subtract punishment events not leading to a shift from punishment events prior to a shift, i.e. to isolate affective switching (Remijnse et al., 2005a). Contrasts (1) and (2) involved the affectively neutral baseline to assess the neural substrate of the main effect of reward and punishment, respectively. This ensured that general aspects of motivational processing were not left undetected.

Contrasts were first performed at single subject level. These were then entered into a second level (random effects) analysis by calculating one-sample t-tests on each individual's contrast images for contrasts 1-3. Group main effects for each contrast (appendix A) were analyzed with

one-way ANOVA. Next, we performed Group x Task interaction analyses for our contrasts of interest. Group main effects were adjusted for the whole-brain search volume using the false discovery rate method (FDR) implemented in SPM2 (Genovese et al., 2002), and reported at a significance level of $p<.05$. Interaction effects, masked with the relevant main effect, were reported at $p<.001$ uncorrected for multiple comparisons, or at a slightly lower threshold for regions of a priori interest as mentioned in the introduction ($p<.005$ uncorrected).

Results

Demographic and clinical data

The three groups were adequately matched for age, handedness and education level, but not gender (Table 5.1). A one-way between-groups ANOVA showed main effects for all depression symptom severity measures (BDI, HDRS-17 and MADRS), which was due to MDD patients scoring significantly higher than OCD patients, and OCD patients significantly higher than controls. On the Padua-IR, a one-way between-groups ANOVA revealed a main effect, due to both patient groups scoring higher than controls. A subsequent analysis of Padua-IR scores in the MDD group demonstrated that these were related to the rumination (N=14), precision (N=1), checking (N=2), and impulses (N=1) subdimensions (van Oppen et al., 1995).

Behavioral data

A one-way ANOVA showed performance differences across groups for mean RTs on baseline trials ($F_{2,64}=4.6$; $p<.05$), Correct Responses ($F_{2,64}=4.8$; $p<.02$), Probabilistic Errors no Shift ($F_{2,64}=3.4$; $p<.04$), Preceding Reversal Errors ($F_{2,64}=4.0$; $p<.03$) and Probabilistic Errors with Shift ($F_{2,64}=6.2$; $p<.004$) (Table 5.2). Paired-comparisons showed significant RT differences between patients with MDD and healthy controls on baseline trials (independent samples t-test: $t=-2.9$; $p<.005$), and Preceding Reversal Errors ($t=-2.2$; $p<.04$); between patients with OCD and controls on baseline trials ($t=-2.2$; $p<.05$), Correct Responses ($t=-3.1$; $p<.003$), Probabilistic Errors no Shift ($t=-2.6$; $p<.02$), Preceding Reversal Errors ($t=-2.9$; $p<.005$) and Probabilistic Errors with Shift ($t=-3.5$; $p<.001$), but not between MDD and OCD patients. Furthermore, in the MDD group, we found significant positive correlations between mean RTs and depression severity measures (MADRS, HDRS-17 and BDI) for Correct Responses, Probabilistic Errors no Shift, Final Reversal Errors, Preceding Reversal Errors, Spontaneous Errors, and Probabilistic Errors with Shift (correlations ranging between $r=.44$ and $r=.62$; all $p<.05$). No significant correlations were detected between mean RTs and OC severity scores in the OCD sample.

One-way ANOVA did not reveal significant performance differences across groups for mean numbers of events or points accumulated by the end of the task.

There were no significant correlations between mean numbers of events and depression severity measures in the MDD group, or OC severity measures in the OCD group, except for a negative correlation between mean number of Spontaneous Errors and Y-BOCS scores ($r=-.46$; $p<.04$).

Table 5.2: Behavioral data on the reversal learning task for the group of patients with major depressive disorder (MDD), with obsessive-compulsive disorder (OCD), and for the healthy control group

	MDD (N=20)		OCD (N=20)		Controls (N=27)		Group x Event Type for Mean Numbers (ANOVA)	Group x Event Type for Mean RTs (ANOVA)
Event Type	Mean Number (SD)	Mean RT (SD)	Mean Number (SD)	Mean RT (SD)	Mean Number (SD)	Mean RT (SD)	F-value df = 2, 64	F-value df = 2, 64
Baseline Trials	47 (2.4)	0.86 (0.18)	46 (3.1)	0.82 (0.16)	47 (3.5)	0.73 (0.13)	0.9 NS	4.6* OCD>COϕ MDD>COϕ
Correct Responses	224 (24.8)	0.66 (0.15)	224 (23.2)	0.73 (0.18)	224 (17.1)	0.59 (0.12)	0.01 NS	4.8* OCD>COϕ
Probabilistic Errors no Shift	18 (4.6)	0.64 (0.16)	19 (7.6)	0.69 (0.18)	19 (7.7)	0.57 (0.13)	0.24 NS	3.4* OCD>COϕ
Final Reversal Errors	17 (5.3)	0.67 (0.18)	16 (5.2)	0.72 (0.23)	17 (5.8)	0.60 (0.14)	0.17 NS	2.5 NS
Preceding Reversal Errors	17 (11.0)	0.65 (0.19)	15 (10.5)	0.68 (0.19)	16 (9.4)	0.56 (0.89)	0.22 NS	4.0* OCD>COϕ MDD>COϕ
Spontaneous Errors	54 (29.2)	0.77 (0.16)	59 (25.3)	0.82 (0.20)	55 (23.1)	0.71 (0.19)	0.19 NS	2.1 NS
Probabilistic Errors with Shift	22 (7.0)	0.66 (0.16)	21 (8.0)	0.76 (0.18)	21 (8.2)	0.60 (0.13)	0.07 NS	6.2** OCD>COϕ
Number of accumulated points by end of task	15659 (8195)		15228 (7561)		15524 (5998)		0.02 NS	

Abbreviations: ANOVA = Analysis of Variance, df = degrees of freedom, NS = not significant, RTs = reaction times, CO = controls

* p<.05 ** p<.005. ϕ paired-comparison t-tests: p<.05 ; see text for further between-group details

Imaging data

Reward

Between-group interaction analyses (Table 5.3) demonstrated increased activity in MDD patients compared with healthy controls in the left gyrus precentralis, right superior temporal and occipital cortex, and the left putamen. Comparing MDD patients with OCD patients, MDD patients showed increased activity in right medial OFC, in right superior temporal cortex, left occipital cortex, and right putamen.

Table 5.3: Brain regions showing group interaction effects for reward (Correct Responses minus baseline trials), punishment [(Probabilistic Errors no Shift + Final Reversal Errors + Preceding Reversal Errors) minus baseline trials], and affective switching [Final Reversal Errors minus (Preceding Reversal Errors + Probabilistic Errors no Shift)]

Reward	L/R	MNI coordinates			z-value	Cluster size¶	MNI coordinates			z-value	Cluster size¶
Region		x	y	z			x	y	z		
		MDD > Controls					*MDD > OCD*				
Medial OFC	R						12	33	-12	3.35	1
Gyrus temp superior	R	39	15	-30	3.14	1	39	15	-30	3.40	1
Gyrus precentralis	L	-36	-15	48	3.89	8					
Occipital cortex	R	30	-90	15	3.67	6					
	L						-27	-87	0	3.90	1
Putamen	L	-27	15	0	3.63	5					
	R						24	0	12	3.11	2
		Controls > MDD					*OCD > MDD*				
		No significant activations					No significant activations				
Punishment	L/R	MNI coordinates			z-value	Cluster size¶	MNI coordinates			z-value	Cluster size¶
Region		x	y	z			x	y	z		
		MDD > Controls					*MDD > OCD*				
Insular Cortex	L	-39	21	3	3.37	15	-33	18	3	3.00*	6
Precuneus	R	18	-69	51	3.18	5					
		Controls > MDD					*OCD > MDD*				
							No significant activations				
Occipital cortex	R	36	-93	3	3.10	5					
Affective switching	L/R	MNI coordinates			z-value	Cluster size¶	MNI coordinates			z-value	Cluster size¶
Region		x	y	z			x	y	z		
		MDD> Controls					*MDD > OCD*				
Temporalis sup	R						39	15	-24	3.65	1
	L						-48	15	-18	3.28	7
Parietal inf	R	39	-72	39	3.25	13					

Table 5.3: Continued.

Parietal sup	L	-21	-42	54	3.34	3	-21	-45	54	3.81	7
		Controls > MDD:									
Insular cortex	L						-33	24	9	3.68	7
	R	33	21	6	3.13	11					
Anterior PFC	L	-33	48	-6	3.30	23	-18	51	0	3.61	3
		-24	57	9	3.01*	6					
Dorsolateral PFC	R	48	3	18	3.64	5	45	42	6	2.91*	3
Anterior Cingulate	L	-3	36	18	3.65	10	*OCD > MDD:*				
							No significant activations				
Parietal inf	L	-48	-33	36	3.10	14					
Thalamus	R	6	-15	6	3.12	2					

All activations at $p < 0.001$ uncorrected, except for z-values* ($p < 0.005$)

¶ Number of voxels

Abbreviations: inf = inferior, L = left, MDD = major depressive disorder, MNI = Montreal Neurological Institute, OCD = obsessive-compulsive disorder, OFC = orbitofrontal cortex, PFC = prefrontal cortex, R = right, temp = temporalis, sup = superior

Punishment

Interaction analyses (Table 5.3) demonstrated increased activity in left insular cortex, and right precuneus in MDD patients versus healthy controls. Between-patient group comparisons showed left insular cortex hyperactivity for MDD versus OCD patients, but no activations for OCD versus MDD patients.

Affective switching

Interaction analyses (Table 5.3) showed greater activation in left anterior PFC, right DLPFC, left ACC, right insula, left inferior parietal cortex, and right thalamus in healthy controls vs. patients with MDD (Figure 5.2). The reverse contrast (MDD>controls) showed increased BOLD signal in right inferior parietal, and left superior parietal cortex. When directly

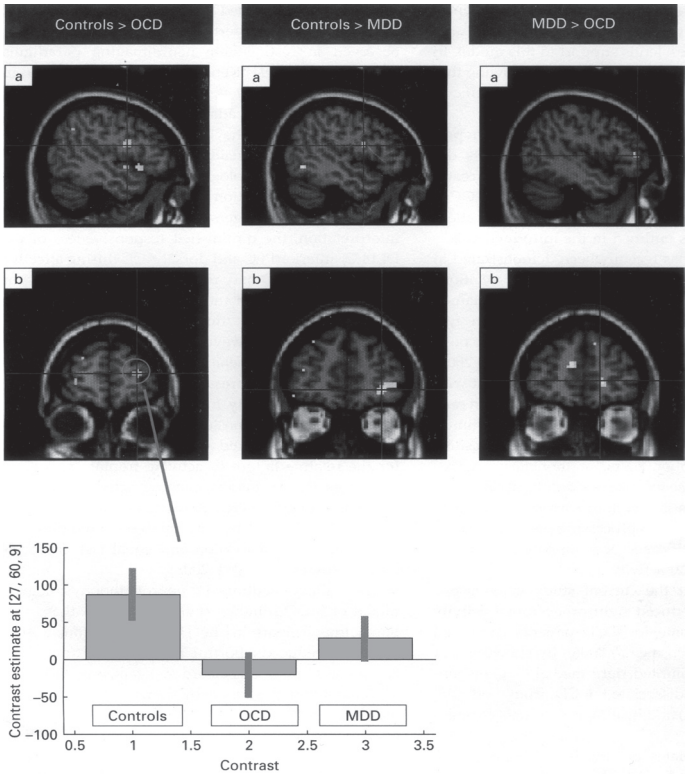

Figure 5.2: Across-group interaction effects for affective switching, superimposed on sagittal and transaxial slices from a canonical (MNI [Montreal Neurological Institute] compatible) T1 image as supplied by SPM2. Increasing BOLD responses for, respectively, patients with OCD, MDD and healthy controls are shown in a) the right dorsolateral prefrontal cortex (DLPFC) (upper left: x=48, y=3, z=18; upper middle: x=48, y=3, z=18; upper right: x=45, y=42, z=6), and b) the left anterior PFC (lower left: x=-27, y=60, z=9; lower middle: x=−33, y=48, z=-6; lower right: x=-18, y=51, z=0). A plot of effect size in the left anterior PFC is displayed for all three groups (x=-27, y=60, z=9).

comparing MDD and OCD patients, we found left anterior PFC, right DLPFC, left insula, bilateral superior temporal, and left superior parietal cortex for MDD>OCD (Figure 5.2), but no activity for OCD>MDD.

Discussion

The present study on reversal learning revealed mean reaction time (RT) differences across two groups of unmedicated patients with either MDD or OCD, and a sample of healthy controls. Patients with MDD were significantly slower to respond on baseline trials and Preceding Reversal Errors compared with normal controls, and there were significant positive correlations between mean RTs and depression severity measures for most event categories in the MDD group. These observations are in line with findings that MDD affects psychomotor reaction speed (Kalb et al., 2006). We found no differences in mean numbers of experimental events or accumulated points between MDD patients and controls. This finding appears to be in accordance with Murphy et al., (2003), who reported preserved ability to learn stimulus-reinforcement associations and to perform affective switching in medicated MDD patients. However, these authors also reported an increased tendency for depressed patients to switch response following misleading negative feedback – a cognitive measure roughly equivalent to the number of Probabilistic Errors with Shift in our task. We failed to replicate this finding, possibly due to major differences in task implementation between studies, e.g. our experimental design – compared with Murphy et al., (2003) – comprised a five-fold larger total number of trials (400 vs. 80), implemented many versus only 2 reversal stages, and included no probabilistic positive reinforcement to incorrect stimuli.

In addition to these findings in the MDD group, patients with OCD performed slower during baseline trials, Correct Responses, Probabilistic Errors no Shift, Preceding Reversal Errors, and Probabilistic Errors with Shift, compared with healthy controls. This observation corroborates an earlier statement that slowness in OCD may be most apparent on executive tests requiring self-initiated organizational strategies - consistent with frontal-striatal abnormality (Roth et al., 2004). However, there were no significant differences in mean numbers of events or accumulated points for OCD subjects compared with the control group. This latter observation is at odds with an earlier study from our group using the same paradigm in a partially different sample of patients with OCD (Remijnse et al., 2006). This discrepancy may be due to differences in OCD patient characteristics: first, the current sample was free of comorbid MDD and contained more patients having 'pure' OCD compared with our prior sample (45% versus 25%). Second, the groups differed with regard to symptom subdimensions (the ratio checkers/non-checkers was smaller in the present sample compared with the former; data not shown).

With regard to imaging results, we found that patients with MDD exhibited increased activity in the left insula on punishment, compared to both healthy control subjects and patients with OCD (the latter at a slightly lower statistical threshold, table 5.3). In MDD, neuroimaging activation studies using affective paradigms have reported increased insular responsiveness

during presentation of negative stimuli in MDD (Fu et al., 2004; Keedwell et al., 2005; Anand et al., 2005). A recent model on the neuropathophysiology of depressive disorder postulates that the insula – together with the amygdala – may be the neurobiological substrate of an increased tendency to identify stimuli as emotional, and to experience predominantly negative affective states (Phillips et al., 2003). The current finding of punishment-related anterior insular hyperactivity in patients with MDD, in corroboration with prior imaging studies, lends support to this model. In addition, it extends previous findings by showing that this assumed role of the anterior insula is *specific* to depression (at least with respect to OCD).

In addition to the MDD-specific insular hyperactivity on punishment, during reward events depressed patients recruited the putamen to a greater extent than healthy controls and patients with OCD. This latter finding is in line with our between-patient group hypothesis as outlined in the introduction section. The putamen has recently been demonstrated to be involved in stimulus-action-reward associations (Haruno & Kawato, 2006). Our finding of putamen hyperactivity upon reward is consistent with two previous imaging activation paradigms using positive valence stimuli in MDD (Mitterschiffthaler et al., 2003; Kumari et al., 2003), but it is in contrast with two other studies (Surguladze et al., 2005; Epstein et al., 2006). Differences in the nature of hedonic stimuli presented (i.e. positive words, happy faces, positive valence picture-caption pairs, or monetary reward) may account for these inconsistent results across studies. Obviously, further research is warranted to clarify the role of the putamen in processing positive affect in MDD, and the significance of its apparent disorder-specific dysfunctional activity.

It is of note that the current study extends our earlier finding of reduced right orbitofrontal activity upon reward outcome for OCD patients compared with controls (Remijnse et al., 2006), by showing that reward-associated blunted right medial OFC responsiveness uniquely dissociated OCD from both depressed (see table 5.3) and healthy individuals (appendix B).

The neural correlates of affective switching have previously been localized in both (para) limbic brain regions (Cools et al., 2002; Remijnse et al., 2005a), and areas involved in cognitive demands - i.e. DLPFC and anterior PFC (Remijnse et al., 2005a; Budhani et al., 2006; see also appendix C). Interestingly, the present experiment demonstrates a pattern of gradual decrease in DLPFC and anterior PFC activity during affective switching for healthy controls, MDD, and OCD (Figure 5.2). In addition, we found a diminished BOLD signal in right insula and dorsal ACC in MDD patients relative to healthy controls. Our findings in the MDD group corroborate a recent fMRI study that reported in unmedicated depressed patients a failure to recruit the right ventrolateral prefrontal cortex (using a region-of-interest analysis with a sphere that encompasses the area we designate as 'right insula') and the DLPFC (using a post-hoc whole-brain analysis), during affective switching (Taylor Tavares et al., 2008).

In MDD, decreased DLPFC and dorsal ACC metabolism and/or perfusion has frequently been observed in resting-state neuroimaging paradigms (Mayberg et al., 1994; Kennedy et al., 2001), as well as in emotional (Bremner et al., 2007), and cognitive imaging activation designs (Okada et al., 2003; Siegle et al., 2007). Blunted activity in DLPFC and dorsal ACC in MDD is generally

considered the neural correlate of symptoms and psychological deficits in MDD such as psychomotor retardation, and executive impairments (Dolan et al., 1993; Rogers et al., 2004). In line with this interpretation, the diminished responsiveness of DLPFC, anterior PFC and dorsal ACC during affective switching in MDD may reflect a reduced capacity for shifting a cognitive set and inhibiting the selection of a previously rewarded stimulus (Garavan et al., 2002; Smith et al., 2004). However, the present study did not show impaired *behavioral* performance during affective switching in depressed subjects. Therefore, the observed hyperactivity for MDD patients during affective switching in posterior, i.e. parietal brain regions, may be considered as compensatory recruitment for the relative failure to activate frontal areas. This converges with previous imaging activation studies that also reported increased parietal brain activity in MDD patients versus healthy subjects, in the presence of reduced ACC activation and equal task performance (Bremner et al., 2004; Bremner et al., 2007).

The above-mentioned neuropathophysiological model of MDD (Phillips et al., 2003) posits that functional impairments in DLPFC and dorsal ACC represent reduced effortful regulation of (negative) emotional states in this disorder. Again, our study is in agreement with this model by showing hypoactivity in these 'executive' brain regions upon a regulatory neuropsychological measure, i.e. affective switching.

Taken together, we suggest that the differential involvement of frontal-striatal and (para) limbic brain regions during reversal learning in MDD and OCD, as observed in the present study, may represent the neural correlates of biased emotional processing and reduced cognitive-behavioral flexibility in MDD and OCD. In addition, our findings in present and past papers (Remijnse et al., 2006) of distinct abnormalities in MDD and OCD appear to be in line with currently influential neurobiological models of these disorders. For OCD, the attenuated responsiveness in OFC-striatal and ACC structures during reward and affective switching events converge with the hypothesis of a dysfunctional (lateral) orbitofrontal loop as a key neurobiological underpinning of clinical and cognitive-behavioral manifestations of OCD (Chamberlain et al., 2005). Likewise, for MDD, the current results of increased insular but decreased dorsal ACC, DLPFC, and anterior prefrontal cortical activity lend support to the proposed limbic-cortical ('ventral-dorsal') dysbalance as a core feature of this disorder (Mayberg, 1997; Mayberg, 2003).

The present study is not without limitations. First, the MDD group differed significantly from the other two groups with regard to the male/female ratio. We know of no previously described direct relationship between gender and the neural substrate of reversal learning, but sex differences may exist with regard to the human 5-HT system (Jans et al., 2007). As outlined in the introduction, reversal learning is dependent on normal 5-HT neurotransmission, and both MDD and OCD have been associated with a dysfunctional 5-HTergic system. Therefore, we cannot rule out that group interaction neural effects on reversal learning may have been mediated by differential between-group 5-HT system functioning due to an inverse gender ratio. Second, although the OCD group was free of currently comorbid MDD, these patients scored significantly higher on depression severity measures than the healthy controls.

However, the ratings in our OCD sample were well below consensus-based and computation-based cutoff scores for clinical remission in MDD, i.e. < 7 for the HDRS-17 (Frank et al., 1991) and < 10 for the MADRS (Zimmerman et al., 2004). Also, a large and significant gap remained between OCD and MDD patients on all depression severity scores in this study.

In conclusion, our study shows differential frontal-striatal and paralimbic activity during reward, punishment, and affective switching in unmedicated patients with either MDD or OCD compared with healthy controls. It would be of interest if future studies in MDD and OCD could further differentiate between cognitive and emotional aspects of these aberrant brain activations during reversal learning, for example by directly comparing BOLD responses during *affective* as opposed to *cognitive* switching behavior.

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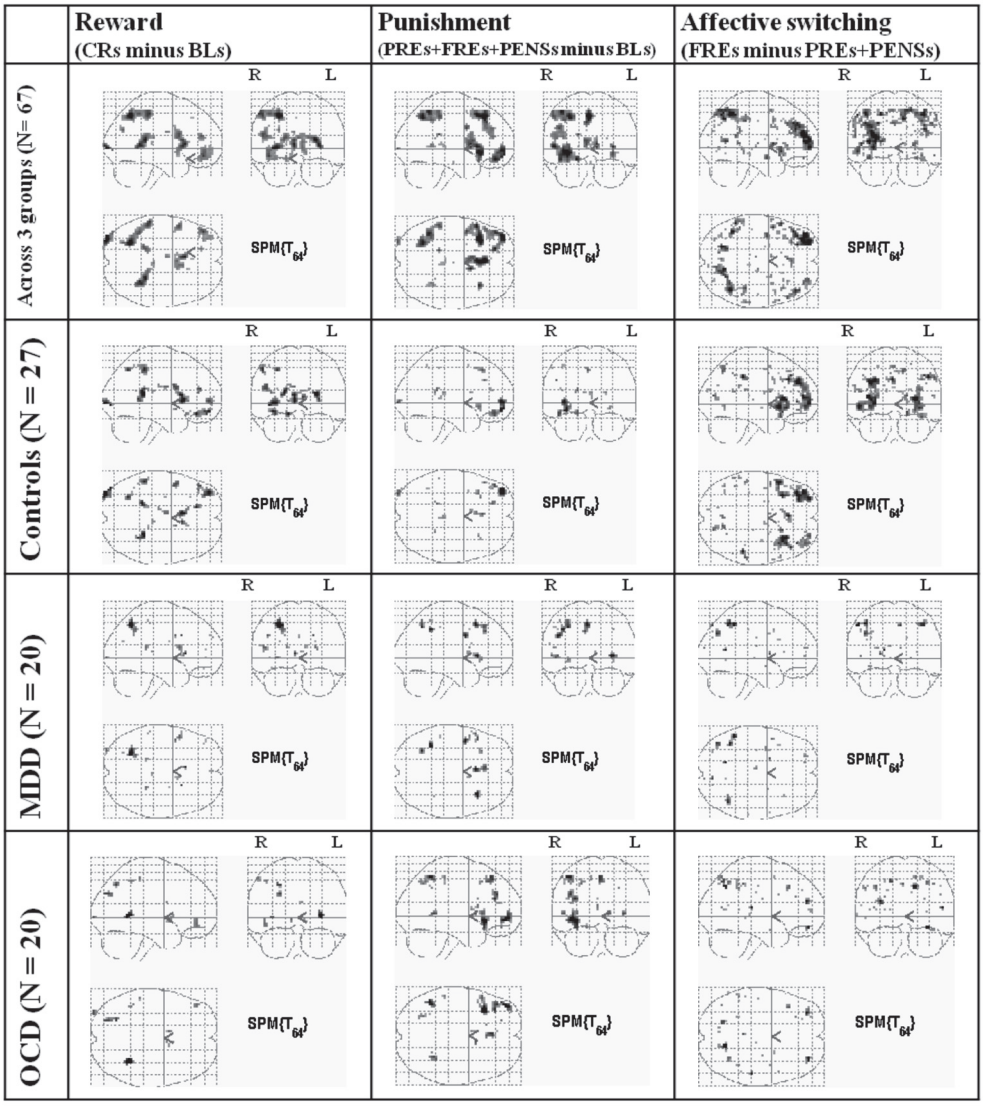

Appendix A: 'Glass brain' renderings showing task main effects as well as group main effects for reward, punishment and affective switching.

Overall, healthy control subjects showed more activations on reward and affective switching than patient group subjects, whereas activations on punishment were roughly equal across groups. Importantly, not all apparent between-group differences reached statistical significance. See text and tables for details.

Appendix B: Brain regions showing interaction effects for the obsessive-compulsive disorder (OCD) versus healthy control group on reward, punishment, and affective switching

OCD vs controls		Reward				Punishment				Affective switching			
	L/R	MNI coordinates				MNI coordinates				MNI coordinates			
Region		x	y	z	z-value	x	y	z	z-value	x	y	z	z-value
		Controls > OCD				*Controls > OCD*				*Controls > OCD*			
Lateral OFC	R	36	54	-12	2.98*	No significant activations							
Medial OFC	R	15	36	-15	3.70								
Posterior OFC	L									-18	15	-15	3.28
Gyrus temp. superior	R									54	-51	21	3.58
Parietal inf	R									54	-36	30	3.57
Insular cortex	L									-30	21	9	5.08
	L									-36	15	9	4.24
	L									-36	27	-6	3.78
	R									33	18	12	3.35
Anterior PFC	L									-27	60	9	3.34
Dorsolateral PFC	R									48	3	18	3.47
Anterior Cingulate	L									-6	36	18	3.84
Cuneus	L	-30	-87	0	3.53	*OCD > Controls*				*OCD > Controls:*			
						No significant activations							
Temporal medius cortex	R									60	-60	15	3.11
Caudate	R	6	18	6	2.43*								
		OCD > Controls											
		No significant activations											

L = left, R = right, MNI = Montreal Neurological Institute, OFC = orbitofrontal cortex, PFC = prefrontal cortex.
All activations at $p < 0.001$ uncorrected, except for z-values* ($p < 0.005$ uncorrected)

Appendix C: Task main effects collapsed across the three groups for reward, punishment, and affective switching

Region	L/R	Reward MNI coordinates				Punishment MNI coordinates				Affective switching MNI coordinates			
		x	y	z	z-value	x	y	z	z-value	x	y	z	z-value
Lateral OFC	R	42	45	-12	4.68	39	54	-3	5.25				
		33	51	-15	3.01	33	57	-9	5.04				
Medial OFC	R	18	42	-12	4.03	21	45	-15	5.15				
Posterior OFC	R	12	21	-15	3.41	33	21	-15	4.35				
Anterior PFC	R									36	54	9	4.92
										30	57	0	4.00
										27	51	18	4.74
	L									-27	57	3	3.61
DLPFC	R	45	42	18	4.50	42	42	30	4.01	48	6	39	3.64
						48	33	30	4.03				
	L									-42	39	27	4.20
										-42	45	33	4.10
Gyrus frontalis inf	R	51	9	21	4.70	45	3	30	4.56				
Dorsomedial PFC	R					3	27	48	5.69	3	27	36	3.69
						6	33	39	4.68				
Insular cortex	R					36	21	-6	5.96	48	6	6	4.15
						51	18	3	5.13	33	27	3	3.64
	L					-33	21	3	4.86				
						-33	24	6	4.40				
Temporal sup cortex	R									57	-48	18	3.68
Parietal cortex sup	R	57	-33	51	5.03					42	-54	51	4.56
		42	-48	51	4.52								
	L									-42	-57	48	4.75
Parietal cortex inf	R					30	-60	45	5.40				
						54	-36	48	4.49				
Occipital cortex	R	33	96	0	6.33	30	-96	0	4.32				
		39	-87	-3	4.30								
Caudate nucleus	R	6	18	6	5.96	6	12	12	4.51				
	L	-6	9	0	4.39	-9	9	6	5.09				

L = left, R = right, MNI = Montreal Neurological Institute, OFC = orbitofrontal cortex, PFC = prefrontal cortex.
All activations at $p < 0.05$ false discovery rate (FDR)-corrected for multiple comparisons

Chapter 6

Cognitive inflexibility in obsessive-compulsive disorder and major depression is associated with distinct neural correlates

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Submitted

Abstract

Obsessive-compulsive disorder (OCD) and major depressive disorder (MDD) are frequently comorbid psychiatric disorders, and dysfunctional frontal-striatal circuits are putatively engaged in the pathophysiology of both disorders. However, neurobiological distinctions between OCD and MDD are insufficiently clear, and comparative neuroimaging studies for these two disorders are extremely scarce. Several lines of research suggest abnormal cognitive flexibility in OCD and MDD, and frontal-striatal brain circuits constitute the neural substrate of intact cognitive flexibility. The objective of this study was to assess both performance and (common and distinct) neural correlates of task switching, a measure of cognitive flexibility, in OCD and MDD. To this aim, eighteen non-medicated MDD-free patients with OCD, 19 non-medicated OCD-free patients with MDD, and 29 matched healthy controls were assessed during the performance of a self-paced letter/digit task switching paradigm in an event-related design during functional magnetic resonance imaging. Main outcome measures were differences in switch costs, reaction times, and error rates on switch and repeat events, as well as blood oxygen level-dependent (BOLD) signals on switching performance across groups. Results showed that both patient groups revealed increased response latencies relative to controls during repeat events, but only in OCD patients these were associated with decreased error rates. In addition, both patients groups were characterized by successful task switching behavior, despite differential neural activation patterns. Specifically, patients with OCD showed enhanced activations of the putamen, anterior cingulate and insula. Both patient with OCD and MDD failed to show anterior prefrontal cortex activation during switching. In conclusion, this study shows subtle, differential behavioral abnormalities on a measure of cognitive flexibility in MDD and OCD, associated with differential frontal-striatal brain dysfunction in both disorders. These findings may add to the development of biological markers that more precisely characterize complex and frequently co-morbid neuropsychiatric disorders as OCD and MDD.

Introduction

Obsessive-compulsive disorder (OCD) and major depressive disorder (MDD) are frequently co-morbid psychiatric disorders (Overbeek et al., 2002) that share several features such as symptomatic overlap (Ninan et al., 2001) and clinical improvement following serotonergic antidepressants (Levine et al., 2001). Recent neurobiological models of OCD have emphasized abnormal activity in prefrontal cortex (i.e. orbitofrontal cortex (OFC) and dorsolateral prefrontal cortex (DLPFC)), anterior cingulate cortex (ACC), and subcortical (caudate and putamen) brain regions, as well as in (para)limbic structures such as insula and amygdale (Aouizerate et al., 2004; Remijnse et al., 2005; Mataix-Cols et al., 2006; Menzies et al., 2008; Huey et al., 2008). In MDD, neurobiological models have similarly outlined prefrontal cortical, paralimbic and subcortical abnormalities, involved in the pathophysiology of this disorder (Rogers et al., 2004; Chamberlain et al., 2005a; Drevets et al., 2008). Despite these commonalities at a clinical and neurobiological level, OCD and MDD also differ with regard to symptom constellations (APA, 1994) and neuropsychological profiles (Joel et al., 2005; Purcell et al., 1998). Thus, it has been stated that a challenge for modern-day neuropsychiatry research is to find common and distinct neurobiological correlates of depression and OCD, i.e. to identify discriminating endophenotypes such as neuropsychological probes for neuroimaging use (Chamberlain et al., 2005a; 2005b). A promising neuropsychological paradigm in this context is cognitive flexibility - defined as the ability to rapidly change response strategies upon altering task-relevant information in the environment (Evers, 2006; Fineberg et al., 2010) - that is likely to be impaired in both OCD (Chamberlain et al., 2009) and MDD (Ebmeier et al., 2006). Several ways of operationalizing cognitive flexibility have been introduced in laboratory settings, e.g. intra/extradimensional set shifting and reversal learning (Robbins, 2007). However, such paradigms conflate switching with contingency learning (Robbins, 2007), yet feedback-based learning is a cognitive domain that itself has been shown to be disturbed in MDD (Clark et al., 2009) and OCD (Nielen et al., 2009). A neuropsychological tool for measuring cognitive flexibility uncontaminated by contingency learning is task switching, in which subjects perform task A and – after several trials – switch to task B upon a cue, then after several trials back to A and so on (Rogers et al., 1995). At a behavioral level, task switching paradigms are characterized by a 'switch cost', i.e. increased reaction times (RTs) and error rates upon switch trials relative to repeat trials, reflecting enhanced cognitive demands during the former events compared to the latter (Monsell, 2003; Dreher et al., 2002). Human lesion studies have shown increased switch costs during task switching in patients with (especially left-sided) prefrontal cortical damage compared with controls (Rogers et al., 1998; Aron et al., 2004). Moreover, patients with early-stage Huntington's disease (Aron et al., 2003) and patients with Parkinson's disease (Cools et al., 2001) were found to have increased switch costs for RTs and error rates on task switching experiments, suggesting intact basal ganglia function is a prerequisite for adequate task switching performance. Finally, functional neuroimaging studies in healthy volunteers have shown activity upon task switching - accompanied by behavioral switch costs - in DLPFC

(DiGirolamo et al., 2001; Dove et al., 2000; Smith et al., 2004), medial PFC (DiGirolamo et al., 2001), inferior parietal cortex (DiGirolamo et al., 2001; Dove et al., 2000; Smith et al., 2004; Sohn et al., 2000), ACC (Smith et al., 2004), anterior PFC (Rushworth et al., 2002) and putamen (Smith et al., 2004; Rubia et al., 2006). Indeed, these frontal-striatal, parietal and (para)limbic neural networks that constitute the neural substrate of intact task switching, are similar to brain circuits supposedly dysfunctional in both MDD (Chamberlain et al., 2005a; Drevets et al., 2008) and OCD (Remijnse et al., 2005; Mataix-Cols et al., 2006; Menzies et al., 2008; Huey et al., 2008).

Only one neuropsychological task switching study in OCD has been published (Moritz et al., 2004) that failed to find enhanced switch costs in patients with OCD compared with healthy controls, despite numerous reports in the literature of deficits in OCD on related measures of cognitive flexibility, i.e. intra-dimensional set-shifting (Veale et al., 1996), extra-dimensional set-shifting (Veale et al., 1996; Watkins et al., 2005) (but see Purcell et al., 1998; Nielen et al., 2003) and reversal learning (Valerius et al., 2008) (but see Chamberlain et al., 2007). Possibly, the large amount of medicated and co-morbid depressed OCD patients in the Moritz et al. (2004) study may explain the lack of performance differences between patient and control groups. In MDD, no controlled neuropsychological task switching studies have been published so far.

To summarize, OCD and MDD are neuropsychiatric disorders characterized by overlapping symptom profiles and cognitive rigidity at the clinical phenotype level. Moreover, separate lines of neuroimaging research have pointed to similar neural correlates in these disorders (Huey et al., 2008; Drevets et al., 2008). Thus, the field is in need of identifying endophenotypes that more precisely characterize such complex neuropsychiatric disorders, as well as shared and distinct neural markers that ideally will lead to a more biologically grounded diagnostic classification for frequently co-morbid disorders such as OCD and MDD (Chamberlain et al., 2006; 2009).

We have recently published – to our knowledge - the first neuroimaging activation study directly comparing OCD and MDD, and demonstrated decreased activations in DLPFC, anterior PFC, inferior parietal cortex and ACC in both patients groups relative to healthy controls during affective switching in a reversal learning design (Remijnse et al., 2009). Also, anterior insula activity was found to differ between patient groups, suggesting differential emotion-related neural processing in OCD and MDD (Remijnse et al., 2009). However, as noted previously, (affective) switching and learning are confounded measures in a cognitive flexibility paradigm like reversal learning (Robbins, 2007). Therefore, in order to assess the neural correlates of *isolated* switching behavior in unmedicated patients with OCD and MDD relative to controls, we conducted the present study using a task switching design in a three-group functional magnetic resonance imaging (fMRI) experiment. Based on the above-reviewed literature on neuropsychological and neuroimaging findings in OCD and MDD, and based on our own recent between-groups findings (Remijnse et al., 2009), we hypothesized impaired task performance (i.e. increased switch costs) in OCD and MDD accompanied by abnormal activations in DLPFC, anterior PFC, ACC and insula. In addition, we expected differential insula activity between patient groups.

Materials and methods

Subjects

Eighteen patients with OCD (without MDD), 19 patients with MDD (without OCD), and 29 healthy controls participated in this study. Patients were recruited from psychiatric outpatient clinics and by Internet advertisements. Diagnoses and comorbidity were established by experienced clinicians with the Structured Clinical Interview for DSM-IV Axis-I disorders (SCID) (First et al., 1996). Exclusion criteria were the presence of alcohol or substance abuse, and major internal or neurological disorders. In the OCD group, 8 patients were diagnosed with 'pure' OCD, and the following disorders were comorbid: posttraumatic stress disorder (N=1), panic disorder (N=2), generalized anxiety disorder (N=4), dysthymic disorder (N=4), social anxiety disorder (N=4), opioid abuse in sustained full remission (N=1), and Tourette's syndrome (N=1). In the MDD group, comorbidity was as follows: social anxiety disorder (N=3), generalized anxiety disorder (N=1), panic disorder without agoraphobia (N=1), and pain disorder (N=1). Twelve MDD patients had no comorbid diagnosis. Healthy controls were recruited by advertisements and screened for the absence of current or past psychiatric and neurological diseases, as well as substance abuse.

At the time of the study, all patients and control subjects were free from psychotropic medication for at least two weeks, and in case of fluoxetine or antipsychotic medication for at least one month. All participants gave written informed consent and the study was approved by the ethical review board of the VU University Medical Center.

To assess symptom characteristics and severity scores, the Yale-Brown Obsessive-Compulsive Scale (Goodman et al., 1989) (Y-BOCS) was administered in OCD patients only, whereas the Padua-Inventory Revised (Sanavio, 1988) (Padua-IR) was used to measure all participants' obsessive-compulsive (OC) characteristics. To rate the presence and severity of depressive symptoms in all three groups, the Beck Depression Inventory (Beck et al., 1961) (BDI), the 21-item Hamilton Depression Rating Scale (Hamilton, 1967) (HDRS-21) and the 10-item Montgomery-Asberg Depression Rating Scale (Montgomery et al., 1979) (MADRS) were used.

Task switching paradigm

We used a modified self-paced task switching (letter/digit) paradigm based on Sohn et al. (2000), graphically outlined in figure 6.1. Each trial consisted of two stimuli - a letter and a digit – presented side by side on a screen, for 4000ms maximally. Subjects selected either stimulus by pressing the left or right button on a button box, after which a fixation cross was presented for 500ms. Each letter/digit pair was presented in either blue or red color. The trial color cued the task to be performed. In the letter task, subjects indicated whether the letter presented was a vowel or a consonant. In the digit task, subjects indicated whether the digit presented was odd or even. Letters were taken from the set {a, e, i, u, b, c, d, f} and digits were taken from the set {2, 4, 6, 8, 3, 5, 7, 9}. Two consecutive trials never contained the same letter or digit.

Color-task and stimulus-response associations were counterbalanced across participants. Trial color changes, and therefore task switching, occurred randomly after 4-6 trials to avoid predictability. The first trials immediately after task switching were defined as 'switch events' (SE), all other trials as 'repeat events' (RE). The task ended after 32 discrimination stages, i.e. after 31 task switches.

Subjects received task instructions beforehand consisting of the specific color-task and stimulus-response associations. Moreover, they were encouraged to minimize response RTs and to avoid errors. These instructions were shown on the screen and were repeated orally by the experimenter. Subjects practiced the task twice, once within at most two weeks before the scanning session using a computer, and the second time in the scanner prior to the actual experiment.

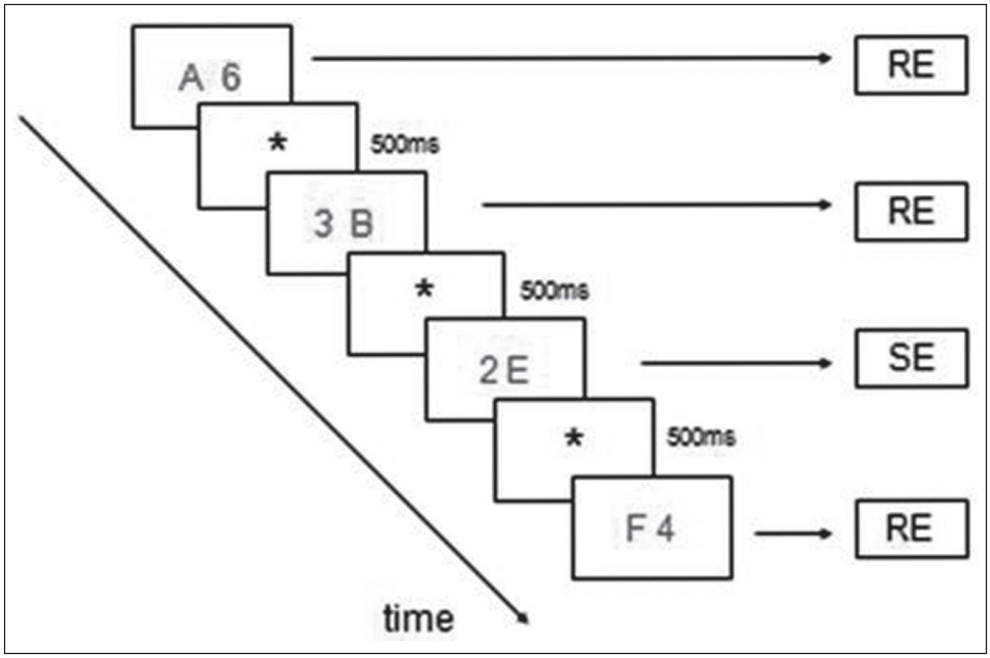

Figure 6.1: The letter/digit task switching paradigm. In this example (consecutive trials are running from top-left to bottom-right) the events-of-interest are displayed. Subjects are presented two stimuli on each trial, i.e. a letter and a digit, for 4000ms maximally. Subjects select either stimulus by pressing the left or right button on a button box, after which a fixation cross is presented for 500ms. Each letter/digit pair is presented in either blue or red color. The trial color cues the task to be performed. In the letter task, subjects indicate whether the letter presented is a vowel or a consonant. In the digit task, subjects indicate whether the digit presented is odd or even. Two consecutive trials never contain the same letter or digit. Trial color changes, and therefore task switching, occurs randomly after 4-6 trials to avoid predictability. The first trials immediately after task switching are defined 'switch events' (SEs), all other trials as 'repeat events' (REs). Color-task and stimulus-response associations were counterbalanced across participants.

Imaging procedure

Imaging data were collected using a 1.5-T Sonata MR system (Siemens, Erlangen, Germany) with a standard circularly polarized head coil. Task stimuli were generated by a Pentium PC and projected on a screen behind the subject's head at the end of the scanner table. The screen was visible for the subject through a mirror mounted above the subject's head. Two magnet-compatible response boxes were used to record the subject's responses. In order to reduce motion artefacts, the subject's head was immobilized using foam pads.

T2*-weighted echo-planar images (EPI's) with blood oxygenation level-dependent contrast (BOLD) were acquired in each session. Using this sequence with a TR of 2.18s and a TE of 45ms., 35 slices (3x3mm in-plane resolution; 2.5mm slice thickness; matrix size 64x64) per image were acquired. The first two images in each session were automatically discarded by the scanner before the task started. Scanning was manually finished after the task had ended.

A whole-brain EPI-image for each subject was also acquired using the same sequence (40-43 slices per image, 3 images in total) as well as a structural image using a 3D coronal T1-weighted sequence (voxel size 1x1x1.5 mm, 160 sections).

Data analysis

Demographic and behavioral data were analyzed using SPSS software (version 11.5 for Windows; SPSS Inc, Chicago, Ill). Switch costs (SEs minus REs) in each group were computed using paired samples t-tests for mean RTs and error rates. Furthermore, mean RTs and error rates for SEs and REs as well as switch costs were compared between groups using one-way ANOVAs with group (MDD vs. OCD vs. controls) as between-subject factor and event type (RTs, error rates, and switch costs) as within-subject factor. Correlations were calculated between performance measures and severity of obsessive-compulsive symptoms (Padua-IR and Y-BOCS) as well as depression severity (MADRS, BDI, and HDRS-21) in the OCD and MDD group, respectively. Alpha was set at $p<0.05$.

Imaging analysis was performed using SPM5 software (Wellcome Department of Cognitive Neurology, London, UK). Images were reoriented, slice-timed and realigned to the first volume. The resulting mean image was then co-registered to the whole-brain EPI-volume, and images were normalized to MNI-space as defined by a SPM T2* template and spatially smoothed using a 6mm Full Width at Half Maximum Gaussian kernel. Statistical analysis was carried out in the context of the general linear model, in which SEs were modeled using a delta function convolved with the canonical hemodynamic response function. The contrast-of-interest (SEs minus the implicit baseline) was first computed at single subject level.

Next, task and group main effects were computed by performing one-way ANOVAs in a second level (random effects) analysis. Furthermore, we performed group x task interaction analyses. Main effects for task and for group were adjusted for the whole-brain search volume using the false discovery rate (FDR) method implemented in SPM (Genovese et al., 2002), and reported at a significance level of $p<.05$, unless otherwise indicated. Group x task interaction effects, masked inclusively with the relevant main effect to restrict the search volume to those voxels

showing a main effect of task, were reported at p<.001 uncorrected. Finally, we performed regression analyses (reported at p<.001 uncorrected) between OC (Padua-IR and Y-BOCS) and MDD (BDI, MADRS, HDRS-21) severity scores, and task effects in the OCD and MDD group, respectively.

Results

Demographic and clinical data

The three groups were adequately matched for age, handedness and educational level, but not for gender (table 6.1). A one-way ANOVA revealed main effects for all depression severity measures (BDI, MADRS, HDRS-21), due to MDD patients scoring significantly higher than OCD patients, and the latter group scoring significantly higher than healthy volunteers. On the Padua-IR, a one-way ANOVA showed a main effect due to both patient groups scoring significantly higher than the control group, but no significant difference between patient groups. A subsequent analysis of Padua-IR scores in the MDD group demonstrated that these were mainly related to the rumination (N=13), precision (N=1), checking (N=2), and

Table 6.1: Demographic and clinical data for patients with obsessive-compulsive disorder (OCD), patients with major depressive disorder (MDD), and healthy controls

	OCD (N=18) Mean (SD)	MDD (N=19) Mean (SD)	Controls (N=29) Mean (SD)	Between-groups comparison P-value
Sex (Female/Male)	14/4	7/12	20/9	0.02#
Age (range)	33 (19-54)	35 (21-54)	33 (22-53)	0.77‡
Handedness (R/L)	16/2	15/4	25/4	0.67 #
Education (range 1-10)‡	8.5 (1.2)	8.0 (2.1)	8.6 (1.3)	0.42‡
Total Y-BOCS severity score	22.7 (4.9) (range 11-31)			
Number of OCD patients MDD with prior MDD / mean length in months since remission of	8/36			
Padua-IR, mean (S.D.)	58.2 (25.8)[c]	43.9 (32.8)[d]	10.9 (10.2)	<.001‡ MDD=OCD>CO*
BDI	10.7 (6.0)[b]	24.9 (7.1)[e]	1.8 (2.6)	<.001‡ MDD>OCD>CO*
HDRS-21, mean (S.D.)	10.1 (4.6)[a]	20.1 (4.4)	0.6 (1.4)	<.001‡ MDD>OCD>CO*
MADRS, mean (S.D.)	8.8 (6.7)[c]	29.5 (4.7)	0.8 (1.4)	<.001‡ MDD>OCD>CO*

chi-square ‡ One-way ANOVA * Tukey and Scheffe post-hoc tests: p < 0.05
[a] assessed in 13 patients
[b] assessed in 15 patients
[c] assessed in 16 patients
[d] assessed in 17 patients
[e] assessed in 18 patients

impulses (N=1) subdimensions, whereas in the OCD group Padua-IR scores were related to the checking (N=10), rumination (N=4), washing (N=1) and precision (N=1) subdimensions (van Oppen et al., 1995).

Behavioral data

Table 6.2 shows behavioral data on the task switching paradigm for the three groups. We found a significant switch cost (i.e. SEs versus REs) for mean RTs in each of the three groups (controls: 1474ms vs. 1025ms, paired samples t-test: t=-11.1; p<.0001. OCD: 1540ms vs. 1179ms; t=-6.8; p<.0001. MDD: 1664ms vs. 1155ms, t=-11.2; p<.0001). We also found a significant switch cost for mean error rates in the healthy control group (9.4 vs. 5.5, paired samples t-test: t=-2.5; p=.03), and in the OCD group (4.1 vs. 2.5, t=-2.0; p=.05), but not in the MDD group (7.0 vs. 5.6, t=-1.6; p=.12).

One-way ANOVAs showed no significant differences across groups for switch costs on RTs (F=2.2; p=.11) nor on error rates (F=1.1; p=.33), and a trend significant performance difference across groups for mean RTs on REs (F=2.8; p =.06). Planned comparisons revealed a significant RT difference between OCD patients and controls on REs (ANOVA: F= 5.8; p=.02), a trend significant RT difference between MDD patients and controls on REs (F=3.0; p=.09), but no between-patient groups RT difference on REs (F=0.08; p=.77). Furthermore, one-way ANOVAs showed no performance difference across groups for mean RTs on SEs (F=2.0; p=0.13) nor for error rates on REs (F=2.2; p=0.11), or on SEs (F=1.8; p=0.17). However, planned comparisons showed that OCD patients had a significantly lower RE error rate than controls (F=5.4; p=.02). We found a trend significant RT difference on SEs between MDD and controls (F=3.6, p=.06) and a trend significant error rate difference on SEs between OCD and controls (F=3.5; p=.07). Correlations between performance measures and disease severity in the MDD group showed a significant positive correlation between MADRS scores and mean RTs on SEs (r=.45; p=.05). In the OCD group, a significant negative correlation was found between Y-BOCS scores and error rates on SEs (r=-.55; p=.02) and a trend significant negative correlation between Y-BOCS scores and error rates on REs (r=-.45; p=.06). No significant correlations were found for total Padua-IR scores and performance measures in OCD.

Imaging data

Task and group main effects

Across groups, main effects of task were found in frontal-striatal circuitry, in particular DLPFC, anterior PFC, and putamen (figure 6.2A), in addition to parietal and occipital brain regions. These activations were also found in the healthy control group, but patient groups failed to show BOLD effects in several of these brain regions, i.e. the OCD group lacked activations of anterior PFC and DLPFC, and the MDD group showed no DLPFC and only minimal anterior PFC activations at our a priori threshold (table 6.3).

Table 6.2: Behavioral data on the task switching paradigm for patients with obsessive-compulsive disorder (OCD), patients with major depressive disorder (MDD), and healthy controls

Event type	OCD (N = 18)				MDD (N = 19)				Controls (N = 29)				ANOVA Groupx Event type (RTs)		ANOVA Groupx Event type (Error rates)	
	RTs		Error %		RTs		Error %		RTs		Error %		F value	P value	F value	P value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD				
Repeat events (REs)	1179	203	2.5	2.4	1155	300	5.6	7.0	1025	220	5.5	5.1	2.84	0.06	2.2	0.1
													OCD>CO: p=.02*		OCD<CO:p=.02*	
													MDD=CO: p=.09*		MDD=CO:p=.92*	
													OCD=MDD:p=.77*		OCD=MDD:p=.08*	
Switch events (SEs)	1540	247	4.1	4.1	1664	359	7.0	8.9	1474	325	9.4	11.2	2.0	0.1	1.8	0.2
													OCD=CO: p=.46*		OCD=MDD:p=.07*	
													MDD=CO: p=.06*		OCD=CO:p=.54*	
													MDD=CO: p=.23*		OCD=MDD:p=.22*	
Switch cost (SEs minus	T value	P value	T value	P value	T value	P value	T value	P value	T value	P value	T value	P value	ANOVA GroupXEvent (RT switch cost)		ANOVA GroupXEvent (error rate switch cost)	
REs)#	-6.8	.0001	-2.0	.05	-11.2	.0001	-1.6	.12	-11.1	.0001	-2.5	.03	2.2	0.11	1.1	0.33

paired samples t-tests *Planned comparisons: between-group ANOVAs

Table 6.3: Task main effects (N = 66) and group main effects for healthy controls (N = 29), patients with obsessive-compulsive disorder (OCD; N = 18) and patients with major depressive disorder (MDD; N = 19). All activations at p<0.05 FDR corrected unless indicated

		Task main effects (N = 66)					**Controls (N = 29)**					**OCD patients (N = 18)**					**MDD patients (N = 19)**				
region		MNI coordinates			Cluster	z-value	MNI coordinates			Cluster	z-value	MNI coordinates			Cluster	z-value	MNI coordinates			Cluster	z-value
	L/R	x	y	z			x	y	z			x	y	z			x	y	z		
Parietal inf	L	-30	-63	39	469	5.09	-48	-36	45	83	5.50						-48	-42	39	1	3.24#
		-42	-45	45		4.63	-30	-63	39	52	5.20										
		-51	-27	36		4.37															
	R	42	-27	39	119	5.34						42	-27	42	30	4.64					
		45	-39	45		4.65						45	-39	45		4.28					
Putamen	R	24	3	-12	239	5.66	24	6	-6	44	5.05	21	9	6	31	3.81	21	15	-9	4	3.59#
		27	0	9		3.85															
	L	-24	6	3	384	6.13	-27	15	-3	70	4.42	-21	6	0	132	5.40	-24	9	3	9	3.27#
		-27	-3	-3		5.77	-27	0	-6		4.36	-12	9	-3		4.30					
Caudatus	R						21	-3	21	10	3.73										
	L											-18	15	9	1	3.17					
Temporalis inf	R						48	-75	0	16	4.82										
	L						-48	-63	-9	46	4.85										
							-39	-66	0		3.92										
Postcentral gyrus	R						42	-27	39	20	4.77										
	L											-48	-18	30	27	4.11					
Fusiform gyrus	R						36	-60	-15	11	4.65						45	-18	-24	5	3.80#
	L	-57	-42	-12	47	3.71#															
		-51	-48	-18		3.91															
Parietal sup	L	-12	-66	57	45	3.84															
Precuneus/Occipital Superior	R	24	-72	33	180	4.46	6	-72	48	14	4.45	18	-66	48	8	3.96					
		9	-72	48		4.43															
Precentralis gyrus	L						-54	0	39	6	3.78										
Anterior PFC	R	27	39	15	10	3.49	21	51	-3	4	3.56										
	L	-27	54	3	25	3.63	-27	54	-9	1	3.14#						-36	42	0	1	3.13#
		-36	45	0		3.18															
frontalis medius/pre-motor	L						-36	-6	57	2	3.60	-30	0	48	11	3.97					
	R																30	0	51	5	3.79#
DLPFC /frontalis medius	L	-30	-3	54	55	3.93	-27	12	48	2	3.38#										
		-24	0	45		4.07	-30	39	21	2	3.29#										
	R	30	0	51	134	4.00															
		30	-9	27		4.02															
DLPFC (frontalis inferior)	L	-42	6	30	15	3.53															
Ventromedial (frontalis medialis)	L	-6	3	54	8	3.48															
Cingulate gyrus	R											6	6	42	1	3.20					

# p < 0.001 uncorrected

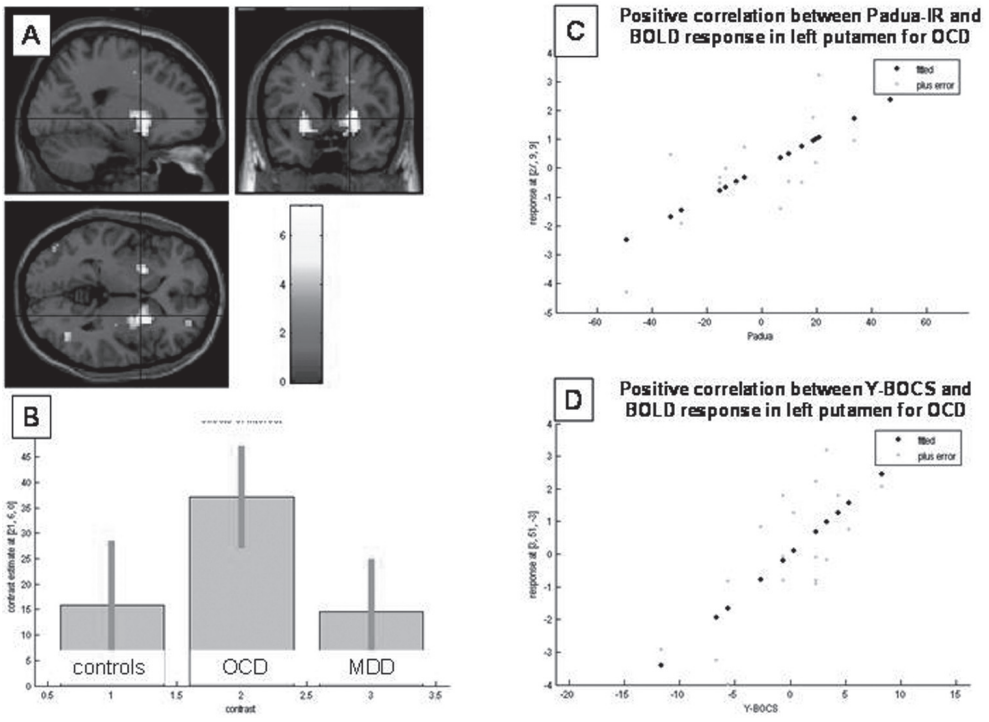

Figure 6.2: (A) Task main effects for switching, superimposed on sagittal, transaxial and coronal slices from a canonical (MNI [Montreal Neurological Institute] compatible) T1 image as supplied by SPM. Enhanced BOLD responses are shown in the putamen bilaterally. (B) A plot of effect size in the left putamen is displayed for all three groups (MNI coordinates: x=-21, y=6, z=0), showing increased activation in this brain area for patients with obsessive-compulsive disorder (OCD) relative to patients with major depressive disorder (MDD) and the control group. (C) Positive correlation (R=.67, p=.004) between total Padua-IR scores and BOLD response in the left putamen (MNI coordinates: x=-27, y=9, z=9) within the OCD group. (D) positive correlation (R=.70, p=.001) between total Y-BOCS scores and BOLD response in the left putamen (MNI coordinates: x=-21, y=15, z=0) within the OCD group.

Group x task interaction effects

Healthy control subjects showed increased activity in left anterior PFC compared with OCD patients. In contrast, patients with OCD revealed increased BOLD responses in right ACC (figure 6.3A), left putamen (figure 6.2B), and left postcentral gyrus, compared with controls. Furthermore, healthy controls demonstrated increased activity in right anterior PFC and left inferior parietal hyperactivity relative to MDD patients. No significantly increased activations were found for MDD patients compared with controls. Comparisons between patient groups showed significantly enhanced signal in bilateral putamen, right insula, left postcentral gyrus, right precuneus, and left supramarginal gyrus for OCD relative to depressed subjects. No significant activation differences were found for MDD versus OCD patients (table 6.4).

Table 6.4: Group X Task interaction effects on the task switching paradigm for the group of patients with obsessive-compulsive disorder (OCD), patients with major depressive disorder (MDD), and healthy controls

Regions	L/R	Cluster size#	MNI coordinates			z-value
			x	y	z	
				Controls>OCD		
Anterior PFC	L	2	-27	51	-12	3.50
				OCD>controls		
ACC	R	3	0	15	27	4.58
Postcentral gyrus	L	7	-48	-18	30	3.98
Putamen	L	3	-21	6	0	3.33
				Controls>MDD		
Parietal inf	L	4	-45	-36	45	3.70
Anterior PFC	R	5	21	54	0	3.72
				MDD>controls		
				No significant activations		
				OCD> MDD		
Postcentral gyrus	L	9	-54	-18	27	4.00
Putamen	L	2	-21	0	6	3.56
	R	3	24	15	3	3.49
Precuneus	R	3	18	-66	48	3.22
insula	R	2	36	-3	6	3.43
		2	33	-15	12	3.39
Supramarginalis gyrus	L	2	-48	-39	27	3.10
				MDD>OCD		
				No significant activations		

All activations at p<.001 uncorrected. #Number of voxels

Regression and covariance analyses

In patients with OCD, we found a significant negative correlation between total Padua-IR scores and left anterior PFC activity (MNI coordinates: -15, 57,3; r=-.56; p=.023), a significant positive correlation between Y-BOCS scores and right ACC activity (MNI coordinates: 6,15,33; r=.56; p=.014; figure 6.3B), and significant positive correlations between Y-BOCS and Padua-IR scores, and left putamen activity (-21,15,0; r=.70; p=.001; and -27,9,9; r=.67; p=.004; figure 6.2C and 6.2D). Patients with MDD showed no significant correlations between depression severity scores and group imaging effects.

Finally, we performed analyses of covariance with gender as a dummy variable to investigate whether the observed group x task interaction effects could be explained by the previously reported skewed male/female ratio across groups. This analysis showed that the described effects persisted after controlling for differences in gender.

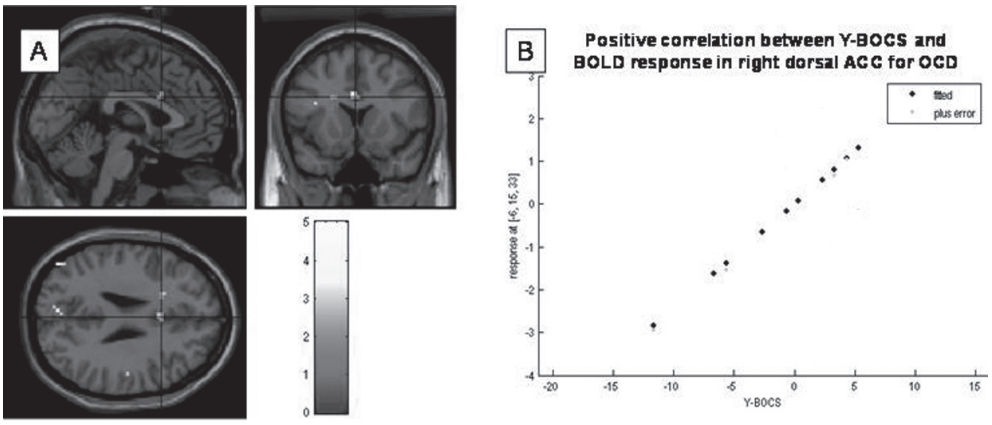

Figure 6.3: (A) Between-group interaction effect of patients with obsessive-compulsive disorder (OCD) versus healthy controls for switching, superimposed on sagittal, transaxial and coronal slices from a canonical (MNI [Montreal Neurological Institute] compatible) T1 image as supplied by SPM. Enhanced BOLD responses are shown for patients with OCD relative to controls in the dorsal anterior cingulate cortex (MNI coordinates: x=0, y=15, z=27). (B) Positive correlation (R=.56, p=.014) between total Y-BOCS scores and BOLD response in the right dorsal anterior cingulate cortex (ACC) (MNI coordinates: x= 6, y=15, z=33) within the OCD group.

Discussion

The present study is the first to investigate the performance on and the neural substrate of a measure of cognitive flexibility uncontaminated by contingency learning, in groups of unmedicated patients with OCD and MDD relative to healthy controls. The currently used task switching paradigm yielded a robust switch cost for mean RTs in each group, and for error rates in the OCD and control group. Possibly, we failed to find an error rate switch cost in the MDD group because these patients tended to slow down their responses on SEs, resulting in a near-significant RT difference between MDD and controls on SEs. In addition, a significant positive correlation was found in MDD between MADRS scores and RTs on SEs, implying that depression severity is associated with slower switch performance. The assessment of within-group switch costs in our task is essential since it is a core behavioral phenomenon in the concept of task switching (Rogers et al., 1995; Monsell, 2003). We failed to find between-group switch cost differences which is in line with recent task switching studies in OCD and MDD (Page et al., 2009; Woolley et al., 2008; Halari et al., 2009; Gu et al., 2008). Further between-group performance analyses showed prolonged RTs on REs in the OCD group compared with controls. Interestingly, this increased RE response latency in OCD was associated with a reduced RE-related error rate in OCD compared with controls, suggesting that slower performance in OCD is compensatory for the sake of accuracy. This OCD-specific behavioral finding is in line with the (partially trend significant) negative correlations we

found between Y-BOCS scores and error rates on REs and SEs in the OCD group, indicating that switch performance becomes more accurate with increasing OC severity. In contrast, although patients with MDD tended to disproportionally slow down on SEs, RTs and error rates on both REs and SEs in these patients were similar to those in controls. Taken together, the present study provides evidence for differential performance patterns on task switching in both patient groups. In OCD, we found OC-severity to be beneficial to accuracy at the expense of prolonged responding during repetition. In contrast, depression severity in MDD is associated with increased response latencies during switching without a compensatory effect for accuracy. Our behavioral findings for the OCD group are at odds with the study of Gu et al.(2008) who demonstrated a significantly higher error rate on switch events in patients with OCD versus healthy controls. Possibly, the large number of medicated patients in this study (Gu et al., 2008), and differences in task implementation between the present and mentioned (Gu et al., 2008) study, may explain this discrepancy. Nevertheless, the existence of conflicting behavioral results in the literature stresses the need for replication of the presently reported task switching impairments in OCD and MDD.

With regard to imaging results, we found - as hypothesized - abnormal (i.e. attenuated) activity in task-relevant brain areas such as anterior PFC during switching both in OCD and MDD, compared with healthy controls. Moreover, in OCD subjects, left-lateralized anterior PFC hypoactivity was negatively correlated with total Padua-IR scores. The anterior PFC is a higher-order cognitive brain area and has been implicated in coordinating multiple separate cognitive operations in the pursuit of a higher behavioral goal (Ramnani et al., 2004). Task switching in a letter/digit design may be considered an executive demand integrating several cognitive operations - e.g. reconfiguring a new task set while inhibiting the previous task set, and updating appropriate task-associated stimulus-response mappings – in order to attain a higher behavioral goal. Apparently, both patient groups in our study failed to activate the anterior PFC when challenged with a cognitive probe, which corroborates previous reports in MDD during a complex planning task (Elliott et al., 1997) and a verbal fluency task (Pu et al., 2008). It also concurs with frequently observed hypoactivation of DLPFC in MDD (Siegle et al., 2007) and in OCD (van den Heuvel et al., 2005), assumed to be the neural correlate of psychomotor retardation (Dolan et al., 1993) and executive impairments at a clinical level in these disorders (Rogers et al., 2004; van den Heuvel et al., 2010).

It should be noted, however, that our common finding of switch-related reduced activity in anterior PFC in OCD and MDD relative to controls does not necessarily imply similar dysfunctional neural mechanisms in both patient groups. For instance, given the fact that OCD patients showed enhanced accuracy during repetition trials, one may argue that the observed anterior PFC hypoactivity in this patient group during switching is in fact driven by enhanced BOLD responses on REs. However, we were unable to assess neural activity during repetition trials, given the rapid event-related design of our study. Notably, we previously also reported reduced recruitment of the anterior PFC in OCD and MDD during reversal learning (Remijnse et al., 2006; 2009), which implies that MDD and OCD are commonly characterized by reduced

recruitment of the anterior PFC during switching, either within an affective (Remijnse et al., 2006; 2009) or cognitive context.

In the present study, the MDD group also showed reduced task-related activations in the inferior parietal cortex, which corroborates a recent neuroimaging task switching study in depressed adolescents (Halari et al., 2009). Inferior parietal involvement in task switching has been associated with attention shifting (Sohn et al., 2000) and with facilitation of stimulus-response reversals during task switching (Barber et al., 2005). Moreover, MDD subjects showed reduced recruitment of the precuneus compared with OCD patients. Precuneus activations during task switching have been proposed to reflect attentional demands when updating stimulus-response associations (Barber et al., 2005). Taken together, these results indicate that MDD is characterized by blunted responsiveness in attention-related brain regions compared with both controls and OCD patients. This blunted signal in attention-related brain areas upon switching in MDD may underlie the previously outlined increased switch-related response latencies at a behavioral level in this group, and putatively reflect deficits in attention control at the clinical level of this disorder (Gotlib et al., 2010).

In contrast to brain areas that we found *under*activated in the patient groups, the putamen showed *increased* activity in OCD compared with controls (left-lateralized) and depressed patients (bilaterally). In addition, putamen activity was correlated with OC severity as measured using Padua-IR and Y-BOCS in the OCD sample. Although traditionally assumed to be primarily involved in sensorimotor functions, the putamen has increasingly been associated with cognitive functions including cognitive flexibility (Groenewegen et al., 2007). For instance, Monchi et al. (2001; 2006) have demonstrated the involvement of the putamen in planning and executing a self-generated novel action – a cognitive demand likely to be also at stake during switch behavior in the current experiment. OCD has been associated with increased metabolism and regional cerebral blood flow (rCBF) in the putamen at rest (Perani et al., 1995), and with putamen grey matter volume increases using voxel-based morphometry (VBM) (Pujol et al., 2004; Huyser et al., 2009; Radua et al., 2010). A recent narrative review on impulsivity and compulsivity postulated a dysfunctional 'compulsive' frontal-striatal circuit in OCD, in which overactivity of the putamen (and caudate) may drive compulsive behaviors as seen in OCD (Fineberg et al., 2010), possibly explaining current and previous observations of hyperactivity in putamen for these patients. However, as was noted previously, switch-related hyperactivity in the putamen as found in the present study may be driven by decreased responsiveness of this structure to REs. The putamen (as part of the dorsolateral striatum) has long been associated with the forming of habits (Groenewegen et al., 2007) (i.e. well-established stimulus-response associations), and attenuated signal in this brain region during task repetition may therefore reflect a decreased ability to implicitly learn stimulus-response associations in OCD, relative to the other groups.

As expected, we found increased task-related engagement of the right dorsal ACC in OCD compared with controls, and right dorsal ACC activity in OCD was positively correlated with Y-BOCS scores. It is well established that the ACC plays a pivotal role in 'error monitoring'

(Krawczyk, 2002) – presumably a relevant cognitive demand during task switching (Robbins, 2007) –, as well as in mediating negative emotional states (Huey et al., 2008). The ACC forms part of a paralimbic circuit encompassing, among other areas, the anterior insula (Mesulam, 2000). Interestingly, and as hypothesized, patients with OCD also showed differential i.e. increased (right) anterior insula activity compared with depressed patients. The insula is important in the identification of aversive stimuli (Phillips et al., 2003; Paulus et al., 2010), and recent reviews posit the joint activation of ACC and (right-lateralized) anterior insula as the anatomical substrate of (negative) emotional awareness together with arousal-driven behavior (Craig, 2009; Medford et al., 2010). Thus, whereas reduced anterior PFC activity conjoint with increased putamen recruitment may represent the neural substrate of a switching strategy specific to OCD, we also observed enhanced involvement of an arousal-related paralimbic brain circuit that may reflect increased error monitoring or the 'something is wrong'- feeling characteristic of patients with OCD (Aouizerate et al., 2004; Huey et al., 2008). Clearly, this switch strategy distinguishes OCD from MDD and healthy controls. The observed hyperactivity in a paralimbic circuit during events that elicit response conflict (i.e. switching) is in line with other fMRI studies in OCD that also found ACC hyperactivity in paradigms encompassing various high-conflict situations (van den Heuvel et al., 2010; Ursu et al., 2003; van der Wee et al., 2003). The present study extends these previous results by showing that this increased paralimbic activity during high-conflict situations is unique for OCD relative to MDD. However, our finding of OCD-specific increased BOLD responses in ACC during switching is at odds with two previous neuroimaging reports on task-switching in OCD that reported hypoactivity in this brain area for these patients (Page et al., 2009; Gu et al., 2008). This discrepancy may be due to the use of different task switching designs, or to differences in patient characteristics, e.g. predominantly female patients with OCD in our study versus predominantly (Gu et al., 2008) or only (Page et al., 2009) male patients with OCD in the other two. In addition, higher levels of co-morbid depression symptoms were reported in these previous studies (mean BDI = 15.5 (Gu et al., 2008) and 18.7 (Page et al., 2009)) compared with ours (mean BDI = 10.7). The latter may especially be relevant, since in the present study our sample of depressed patients (mean BDI = 24.9) failed to activate the ACC both in group and group x task analyses, a finding that is congruent with another recent neuroimaging task switching study in depressed adolescents (Halari et al., 2009).

The current study is not without limitations. First, although total Padua-IR scores were considerably higher in the OCD compared with the MDD group, between-patient group differences on this measure were not significant. However, analyses of Padua-IR subdimensions in both groups showed that MDD patients (in contrast to OCD patients) predominantly scored on rumination, a cognitive phenomenon that is itself highly characteristic of depression (Gotlib et al., 2010). Moreover, the Padua-IR is known to poorly differentiate between OCD and MDD (Goodarzi et al., 2005). Second, although the OCD group was free of currently co-morbid depression, patients with OCD scored significantly higher than controls on depression severity measures. However, ratings on these measures in the OCD group were well below

computation-based cutoff scores for clinical remission in MDD (e.g. < 10 for the MADRS (Zimmerman et al., 2004)), and a large, significant gap still remained between OCD and MDD patients on all depression scores in this study.

In conclusion, the present fMRI study is the first to report common and distinct behavioral and neural patterns on a 'pure' cognitive neuroimaging activation paradigm in OCD and MDD. In the current experiment, we used a promising neuropsychological tool, i.e. cognitive flexibility, for probing neurobiological distinctions between these disorders. Our results contribute to the process of identifying endophenotypes in complex and frequently co-morbid neuropsychiatric disorders, such as OCD and MDD. Presumably, this will lead to a better diagnostic characterization and to more specific treatments for OCD and MDD in the future.

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Chapter 7

The major symptom dimensions of obsessive-compulsive disorder are mediated by partially distinct neural systems

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Abstract

Obsessive-compulsive disorder (OCD) is a clinically heterogeneous disorder characterized by multiple, temporally stable symptom dimensions. Preliminary functional neuroimaging studies suggest that these symptom dimensions may have distinct neural substrates. Whole-brain voxel-based morphometry was used to examine the common and distinct neuroanatomical (structural) substrates of the major symptom dimensions of OCD. First, we compared 55 medication-free patients with OCD and 50 age-matched healthy control subjects. Multiple regression analyses were then used to examine the relationship between global and regional gray matter (GM) and white matter (WM) volumes and symptom dimension scores within the patient group. OCD patients showed decreased GM volume in left lateral orbitofrontal (BA47), left inferior frontal (BA44/45), left dorsolateral prefrontal (BA9) and right medial prefrontal (BA10) cortices and decreased bilateral prefrontal WM volume. Scores on the 'symmetry/ordering' dimension were negatively correlated with *global* GM and WM volumes. Scores on the 'contamination/washing' dimension were negatively correlated with *regional* GM volume in bilateral caudate nucleus and WM volume in right parietal region. Scores on the 'harm/checking' dimension were negatively correlated with *regional* GM and WM volume in bilateral temporal lobes. Scores on the 'symmetry/ordering' dimension were negatively correlated with *regional* GM volume in right motor cortex, left insula and left parietal cortex and positively correlated with bilateral temporal GM and WM volume. The results remained significant after controlling for age, sex, educational level, overall illness severity, global WM/GM volumes and excluding patients with comorbid depression. The reported symptom dimension-specific GM and WM alterations support the hypothesis that OCD is an etiologically heterogeneous disorder, with both overlapping and distinct neural correlates across symptom dimensions. These results have clear implications for the current neuroanatomical model of OCD and call for a substantial revision of such model which takes into account the heterogeneity of the disorder.

Introduction

Current neuroanatomical models of obsessive-compulsive disorder (OCD) propose that specific frontal-striatal and limbic circuits are involved in the mediation of its symptoms (Saxena et al., 1998; Remijnse et al., 2005; Mataix-Cols and van den Heuvel, 2006). Whereas the findings of functional neuroimaging studies have been relatively consistent with this view, structural neuroimaging studies have been far less consistent. For example, the volume of the caudate nucleus, a key structure thought to be involved in OCD, was found to be decreased (Luxenberg et al., 1988; Robinson et al., 1995), normal (Kellner et al., 1991; Stein et al., 1997; Stein et al., 1993; Aylward et al., 1996; Rosenberg et al., 1997; Bartha et al., 1998), and even increased (Scarone et al., 1992) in OCD patients compared to controls. The same variability applies to other regions of interest (ROIs), including the amygdala (Kwon et al., 2003b; Rosenberg and Keshavan, 1998; Szeszko et al., 1999), thalamus (Gilbert et al., 2000), and the orbitofrontal (Szeszko et al., 1999;Choi et al., 2004;Kang et al., 2004), anterior cingulate (Rosenberg and Keshavan, 1998;Szeszko et al., 2004) and temporal/hippocampal (Kwon et al., 2003) cortices. This obvious lack of replicability among structural neuroimaging studies in OCD can be partially attributed to methodological differences between studies. Small sample sizes have been the norm and some studies have not excluded patients on medication and with comorbid psychopathology. Most morphometric studies in OCD have used manual or semi-automated methods to measure the volumes of brain regions defined a priori as being implicated in OCD, therefore preventing the exploration of other brain regions potentially implicated in the disorder.

The recent use of fully-automated, whole-brain, voxel-based morphometry (VBM) methods (Ashburner and Friston, 2000; Ashburner and Friston, 2001; Mechelli et al., 2005), which overcome some of the limitations of the ROI approach, have also produced mixed results. Kim et al. (2001) were the first to report structural abnormalities in OCD using VBM. They compared 25 medication-free OCD patients and 25 healthy controls and reported increased gray matter volumes in the orbitofrontal, superior and middle temporal, inferior parietal and occipital cortices, thalamus, hypothalamus and insula. They did not investigate differences in white matter volume. Since the publication of this initial study, three further VBM studies in OCD have appeared (Pujol et al., 2004; Valente et al., 2005; Carmona et al., 2007). In the largest of these studies (N=72), Pujol et al. (2004) found decreased gray matter volume in the medial orbitofrontal cortex, dorso-medial prefrontal cortex, and the insulo-opercular region, as well as increased gray matter volume in the ventral putamen and cerebellum. No white matter differences were found. Valente et al. (2005) also found decreased medial prefrontal gray matter volume in their smaller sample of mostly medicated, and comorbid depressive, OCD patients (N=19). However, they reported increased rather than decreased orbitofrontal and insular gray matter volumes. Also, the parahippocampal gyri were larger compared with those of healthy subjects. No white matter measurements were performed. Finally, in a pediatric OCD sample (N=18), Carmona et al. (2007) showed decreased gray matter in

dorsolateral prefrontal, inferior frontal, medial prefrontal and anterior cingulate cortices, as well as decreased white matter in bilateral frontal and right parietal regions.
Based on the current frontal-striatal model of OCD, one might predict abnormalities in the WM tracts that connect the prefrontal cortex with the basal ganglia but only a handful of VBM studies have examined WM abnormalities in OCD. The results of recent diffusion tensor imaging studies, showing decreased fractional anisotropy (a measure of WM connectivity) in the anterior cingulate region and the internal capsule (Szeszko et al., 2005, Yoo et al., 2007, Cannistraro et al. 2007), are consistent with the current model.

In summary, VBM studies in OCD have shown frontal-striatal and limbic gray matter alterations, although the implicated regions and the direction of the differences between patients and healthy controls have been inconsistent so far. Again, these discrepant findings may be partially attributable to a number of methodological issues, such as insufficient power (with the exception of the Pujol et al. (2004) study), comorbidity, and medication confounds. Another important source of variability is the clinical heterogeneity of OCD. It is becoming increasingly clear that OCD is not a unitary disorder and that it consists of multiple potentially overlapping symptom dimensions (Leckman et al., 2007; Mataix-Cols et al., 2005), which are temporally (Mataix-Cols et al., 2002; Rufer et al., 2005) and transculturally (Matsunaga et al., 2008) stable. Several preliminary functional neuroimaging studies have suggested that these symptom dimensions may be mediated by partially distinct neural systems (Mataix-Cols et al., 2004; Saxena et al., 2004; An et al., 2008; Lawrence et al., 2007). It is therefore plausible that the above inconsistencies in structural neuroimaging studies of OCD can be partially attributable to the clinical heterogeneity of the recruited samples. In support of this idea, Pujol et al. (2004) found that patients with elevated scores on the 'aggressive/checking' dimension had significantly reduced gray matter volumes in the right amygdala. Similarly, Valente et al. (2005) showed a distinct pattern of correlations between various symptom dimension scores and gray matter volumes, although these analyses were probably underpowered. Clearly, more research is needed in large patient samples to identify the structural neuroanatomical correlates of the major symptom dimensions of OCD employing validated instruments.
The present VBM study aimed to build upon the existing functional neuroimaging literature by examining the common as well as distinct structural (GM and WM) correlates of the major symptom dimensions of OCD ('contamination/washing', 'harm/checking' and 'symmetry/ordering') in a large sample of unmedicated patients (N=55). If the hypothesis that different symptom dimensions have distinct neuroanatomical substrates is confirmed, the results would have profound implications for the current neuroanatomical model of OCD.

Materials and Methods

Participants

Fifty-five unmedicated patients meeting DSM-IV criteria for OCD and 50 age-matched healthy controls participated in the study. OCD patients were recruited from the outpatient clinic for anxiety disorders of Stichting Buitenamstel Geestgronden in Amsterdam, the outpatient clinic for anxiety disorders of GGZ Nijmegen, the Netherlands Anxiety, OCD & Phobia Foundation, and by advertisements on the internet. Exclusion criteria were the presence of major somatic disorders, other major psychiatric disorders (except depression), and use of psychotropic medication. Subjects had to be off antidepressive and antipsychotic medication for at least 4 weeks prior to the scan and were asked not to use benzodiazepines during the two weeks prior to the scan.

Fifty healthy controls were recruited among hospital and university staff and by advertisements on the internet. They were interviewed to exclude any psychiatric and somatic disorders. The ethical review board of the VU University Medical Center approved the study and all participants provided written informed consent.

Measures

Diagnoses were established using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P) (First et al., 1996). The severity of OCD symptoms was assessed with the 10-item clinician-administered Yale Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al., 1989a; Goodman et al., 1989b).

Two complementary methods were employed to ascertain the presence and severity of the most prevalent symptom dimensions in this sample (contamination/washing, harm/checking and symmetry/ordering). First, all patients and controls were asked to complete the Dutch version of the Padua Inventory-revised (Padua-IR) (Sanavio, 1988; van Oppen et al., 1995), a widely used and reliable self-administered measure of obsessive-compulsive symptoms. Here, we were interested in three of its sub-scales: "washing" (10 items; score range: 0-40), "checking" (7 items; score range: 0-28), and "precision" (6 items: score range: 0-24), corresponding to the three major symptom domains under study.

Second, each of the major categories of the Y-BOCS symptom checklist was assigned a score of 0 (absent symptom), 1 (symptom present but not major reason for concern) or 2 (prominent symptom). The major symptom dimension scores were then computed using the algorithm described by Mataix-Cols et al. (1999). Briefly, the 'contamination/washing' score was the sum of 'contamination obsessions' and 'washing/cleaning compulsions' divided by 2; the 'harm/checking' score was the sum of 'aggressive obsessions' and 'checking compulsions' divided by 2; and the 'symmetry/ordering' score was the sum of 'symmetry obsessions', 'ordering compulsions', 'repeating compulsions' and 'counting compulsions' divided by 4. Dividing by the number of items in each dimension ensured comparable score ranges across dimensions. Because very few patients in our sample endorsed hoarding or sexual/religious symptoms these dimensions were not computed in this study.

Due to administrative problems, Y-BOCS and Padua-IR data were unavailable for 8 and 5 subjects, respectively.

MRI acquisition and processing

All images were acquired using a 1.5 T MRI system (Magnetom Sonata, Siemens, Erlangen, Germany) with a standard radiofrequency receiver head coil. The anatomical scans included 160 coronal slices (slice thickness=1.5 mm) acquired with a 3D gradient-echo T1-weighted sequence (flip angle=8°; Repetition Time, TR=2700 ms; Echo Time, TE=4 ms; Inversion Time, TI=950 ms; bandwidth, BW=190 Hz/pixel). In-plane resolution was 256x192 pixels (pixel size 1 mm^2).

Prior to volumetric analyses, the integrity of the acquired MR images was visually checked using MRIcro (Chris Rorden, http://www.sph.sc.edu/comd/rorden/mricro.html). Images were processed and analyzed using SPM5 (Wellcome Department of Cognitive Neurology, London, UK). The origin of each MR volume was aligned on the anterior commissure.

Voxel-based morphometry

First, DICOM images were converted to Analyze format, followed by cropping to remove the neck using a registration-based approach employing tools from FSL (FMRIB's software library). Using SPM5 with default priors, images were then segmented to generate, for each subject, modulated GM, WM and CSF probability maps in standard MNI-152 space and resampled to 2x2x2mm voxels. These maps were smoothed using a Gaussian kernel of 12 mm full width at half maximum (FWHM) as is customary in VBM, given that the accuracy of cortical registration between subjects is about 1 cm (Ashburner and Friston, 2001), and an absolute minimum threshold of 0.05 was applied. For each tissue type (WM or GM), analyses were restricted to voxels included in a mask obtained by thresholding the corresponding prior probability map at 0.1. In addition to the MNI-152 segments, the GM, WM and CSF probability maps in native space obtained in the same segmentation process were also stored and used to calculate total GM and WM volumes for each individual.

Statistical analyses

Comparisons between OCD patients and controls were conducted separately for regional GM and WM using (1x2) ANOVA as implemented in SPM5. To correct for global GM and WM differences, total GM and WM volumes were added as a regressor (covariate) in the models. The associations between symptom dimension scores within the OCD group and GM/WM volumes were examined using whole-brain multiple regression analyses with the scores of the three major symptom dimensions and total GM/WM volumes as regressors. In addition, to control for potentially confounding variables, we repeated all analyses including age, sex and total YBOCS scores as covariates. Since cluster-based statistics are invalid due to non-stationarity of VBM data (Mechelli et al., 2005), we adopted an a priori voxel-based threshold of $p<0.05$ corrected for multiple comparisons, unless indicated otherwise. For our regions

of interest (striatum, orbitofrontal cortex, lateral and medial prefrontal cortex, posterior parietal cortex and anterior and medial temporal cortex) we employed an initial threshold of $p<0.001$ uncorrected with an extent threshold of 25 voxels, using the small volume correction (SVC) option implemented in SPM5 to establish whether the observed differences were also significant at a corrected level.

Results

Sample characteristics

There were no statistically significant differences in age, sex and handedness between patients and controls (see Table 7.1). Controls had a slightly but significantly higher educational level. The mean total Y-BOCS scores were 22.83 (SD=6.13), corresponding to moderately severe OCD. Ten out of 55 patients with OCD had a comorbid depressive disorder at the time of the scan. As expected, patients had significantly higher scores than controls on all the Padua-IR subscales. All patients endorsed more than one symptom type on the Y-BOCS Symptom

Table 7.1: Sociodemographic and clinical characteristics of the sample

Variable	OCD (N = 55)	Controls (N = 50)	statistics	p-value
Men N (%)	16 (29%)	20 (40%)	$\chi 2 = 1.38$	0.24
Right-handed N (%)	49 (89%)	45 (90%)	$\chi 2 = 0.23$	0.88
Age years, mean ± SD	33.7 ± 9.19 (19-54)	31.4 ± 7.64 (21-53)	t (df = 103) = 1.37	0.18
Educational level# mean ± SD	5.8 (± 1.6)	6.8 (± 1.5)	Mann-Whitney U = 739.5 / Z = -3.4	0.001
Y-BOCS, total* mean ± SD (range)	22.83 ± 6.13 (10-36)			
Padua-IR, total mean ± SD (range)	64.76 ± 26.17 (9-112)	10.8 ± 10.18 (0-43)	t (df = 98) = 13.88	< 0.001
Padua-IR, washing mean ± SD (range)	11.24 ± 11.17 (0-35)	2.22 ± 4.08 (0-21)	t (df = 98) = 5.36	< 0.001
Padua-IR, checking mean ± SD (range)	16.16 ± 7.99 (0-26)	2.08 ± 2.58 (0-13)	t (df = 98) = 12.01	< 0.001
Padua-IR, precision mean ± SD (range)	7.94 ± 5.21 (0-20)	0.80 ± 1.14 (0-4)	t (df = 98) = 9.46	< 0.001

= using an 8 point scale, 1 indicates primary school, 8 university
* = Yale-Brown Obsessive Compulsive Scale (10-item severity score)

Checklist (see Table 7.2). Age of onset negatively correlated with the scores on the symmetry/ordering dimension of the Padua-IR (Spearman's ρ = -0.353, p<0.05) and the Y-BOCS (Spearman's ρ = -0.506, p<0.01), not with the other symptom dimensions.
All patients were unmedicated at the time of the scan. Twenty four (43.6%) patients were medication naïve, and the rest had been medication-free for at least 4 weeks prior to participation in the study. Mean washout period was 26 months (range 1-96 months). Past medication history was as follows: 9 (16.4%) paroxetine, 5 (9.1%) fluoxetine, 2 (3.6%) fluvoxamine, 2 (3.6%) venlafaxine, and 9 (16.4%) used more than one drug in the past, 2 of whom used antipsychotic medication as an augmentation strategy). Medication history was unavailable from 4 (7.3%) patients.

Global gray and white matter volumes

Patients with OCD and healthy control subjects did not significantly differ in global GM and WM volumes (GM: 685±74 and 708±72 ml respectively, p=0.11; WM: 494±59 and 509±64 ml respectively, p=0.21). However, the 'symmetry/ordering' dimension of the Padua-IR was negatively correlated with global GM volume (partial correlation coefficient -0.42, t=-2.84, p=0.007), with a trend for global WM volume (partial correlation coefficient -0.35, t=-1.96, p=0.057). This association was independent from age, sex and disease severity (total Y-BOCS scores), which were also included in the models. The correlation between age of onset and global GM or WM volume was not significant and multiple regression analyses showed that the association between symmetry/ordering symptoms and global GM volume remained significant after controlling for the illness onset. Finally, we repeated these analyses excluding the 10 patients with comorbid depression and the results remained unchanged. Scores on the other symptom dimensions did not correlate with global GM or WM volumes.

Table 7.2: Frequencies of the major symptom categories of the Yale-Brown Obsessive Compulsive Scale - Symptom

Sumptom categories	Number of patients (%) (N=47)
Obsessions	
Aggressive	34 (72%)
Contamination	33 (70%)
Sexual	6 (13%)
Hoarding/saving	8 (17%)
Religious	11 (23%)
Symmetry	25 (53%)
Somatic	18 (38%)
Compulsions	
Washing	22 (47%)
Checking	37 (79%)
Repeating	32 (68%)
Counting	18 (38%)
Ordering	21 (45%)
Hoarding	7 (15%)

Regional gray and white matter alterations in OCD versus controls

Compared with healthy controls, patients with OCD showed significantly decreased regional volume in the left lateral orbitofrontal cortex (Brodmann's area (BA) 47), left inferior frontal cortex (BA44/45), left dorsolateral prefrontal cortex (BA9) and bilateral medial prefrontal cortex (BA10). No regions of increased GM volume were found in patients with OCD (see Table 7.3 and Figure 7.1). White matter volume was decreased in the bilateral prefrontal lobes in patients with OCD (see Table 7.4 and Figure 7.2). No regions of increased WM volume were found. These results were independent from age, sex, educational level and global GM/WM volumes, which were included as covariates in the ANOVAs. To control for the effect of comorbid depressive symptoms, we repeated all analyses with comorbid depression (dummy-coded as present/absent) as an extra covariate and yielding nearly identical results. In fact, the exclusion of the 10 depressed OCD patients resulted in even more strongly significant results (increased cluster sizes and t-values).

Table 7.3: Regional gray matter volume differences between patients with obsessive-compulsive disorder (OCD) and healthy controls

cluster size	T	peak coordinates (MNI)			BA	anatomical region
		x	y	z		
Decreased grey matter in OCD						
475	4.95	-44	42	-6	47	left lateral OFC
134	4.10	-32	34	32	9	left DLPFC
132	4.06	-50	20	16	44/45	left IFC
176	3.89	16	64	-2	10	right medial PFC
60	3.73	-16	64	-2	10	left medial PFC
Increased grey matter in OCD						
no significant results						

Abbreviations: MNI = Montreal Neurological Institute, BA = Brodmann's area, OFC = orbitofrontal cortex, DLPFC = dorsolateral prefrontal cortex, IFC = inferior frontal cortex, PFC = prefrontal cortex

Table 7.4: Regional white matter volume differences between patients with obsessive-compulsive disorder (OCD) and healthy controls

cluster size	T	peak coordinates (MNI)			anatomical region
		x	y	z	
Decreased white matter in OCD					
794	4.41	32	24	20	left prefrontal
	4.10	14	22	34	
	4.04	20	42	22	
350	3.89	-30	14	20	right prefrontal
	3.79	-32	22	18	
	3.68	-40	30	22	
Increased white matter in OCD					
no significant results					

Abbreviation: MNI = Montreal Neurological Institute

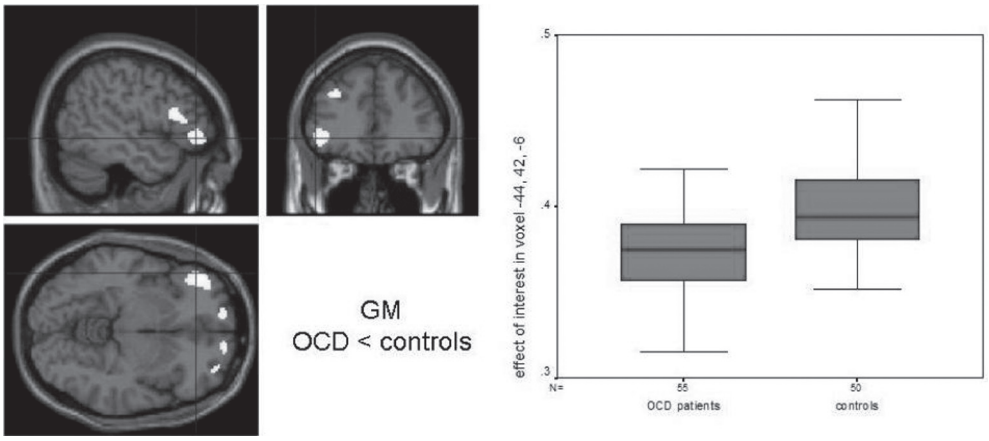

Figure 7.1: Decreased regional gray matter volume in OCD patients (N = 55) compared with healthy controls (N = 50) in left lateral orbitofrontal cortex (BA47), left inferior frontal cortex (BA44/45), left dorsolateral prefrontal cortex (BA9) and right medial prefrontal cortex (BA10). Results shown at $p < 0.001$ uncorrected and minimum cluster size of 25 voxels.

We next conducted a whole-brain regression analysis to examine the relationship between overall OCD symptom severity and regional GM/WM volumes. Total Y-BOCS scores were inversely correlated with GM volume of the left (MNI coordinates x, y, z = -18, -78, -54, t=5.19, cluster size=753 voxels) and right (x, y, z = 22, -84, -50, t=4.05, cluster size=548 voxels) cerebellar cortex.

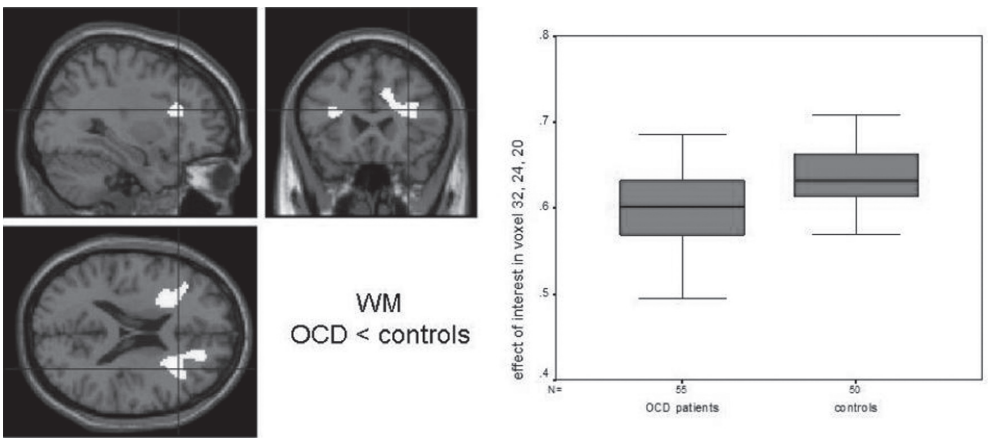

Figure 7.2: Decreased regional white matter volume in OCD patients (N = 55) compared with healthy controls (N = 50) in bilateral prefrontal regions. Results shown at $p < 0.001$ uncorrected and minimum cluster size of 25 voxels.

Table 7.5: Significant whole-brain correlations between regional gray matter volumes and scores on the three major symptom dimensions of OCD (N = 50 for Padua Inventory, N = 47 for Y-BOCS symptom checklist)

cluster size	T	Spearman's ρ	peak coordinates (MNI)			anatomical region
			x	y	z	
Negative correlations with the contamination/washing dimension of Padua Inventory						
116	3.99	-0.34*	-12	4	18	left caudate nucleus
63	3.96	-0.39**	14	2	18	right caudate nucleus
Negative correlations with the contamination/washing dimension of Y-BOCS symptom checklist						
No significant results#						
Negative correlations with the harm/checking dimension of Padua Inventory						
3303	5.44	-0.49**	40	14	-30	right temporal lobe
	5.18	-0.41**	52	4	-36	
	5.17	-0.43**	48	-30	-24	
2237	5.03	-0.39**	-48	-34	-26	left temporal lobe
	4.60	-0.40**	-56	2	-8	
	4.58	-0.46**	-58	-14	-14	
Negative correlations with the harm/checking dimension of Y-BOCS symptom checklist						
49	3.92	-0.40**	54	-58	-16	right temporal lobe
32	3.77	-0.38**	50	-32	-24	
Negative correlations with the symmetry/ordering dimension of Padua Inventory						
510	4.63¥	-0.52**	30	-24	62	right motor cortex
	4.30	-0.38**	30	-60	62	right parietal cortex
	3.87	-0.35*	14	-36	70	
47	4.12¥	-0.44**	-38	-16	10	left insular cortex
44	3.82	-0.32*	-16	-56	66	left parietal cortex
Negative correlations with the symmetry/ordering dimension of Y-BOCS symptom checklist						
142	4.26	-0.59**	-54	-38	40	left parietal cortex
Positive correlations with the contamination/washing dimension of Padua Inventory						
No significant results						
Positive correlations with the contamination/washing dimension of Y-BOCS symptom checklist						
No significant results						
Positive correlations with the harm/checking dimension of Padua Inventory						
No significant results						
Positive correlations with the harm/checking dimension of Y-BOCS symptom checklist						
87	4.54¥	0.50**	-8	-50	50	left precuneus
Positive correlations with the symmetry/ordering dimension of Padua Inventory						
105	4.33	0.41**	-56	-14	-12	left temporal lobe
48	3.59	0.43**	28	6	-32	right temporal lobe
Positive correlations with the symmetry/ordering dimension of Y-BOCS symptom checklist						
No significant results						

¥ = $p < 0.001$ uncorrected and minimal cluster size of 25 voxels. * = Spearman's correlation significant at $p<0.05$, ** = Spearman's correlation significant at $p<0.01$. Abbreviations: MNI = Montreal Neurological Institute. # = There were significant negative correlations in the caudate nucleus bilaterally (left: x, y, z = -16, 10, 18, T=3.40, cluster size=7, Spearman's ρ = -0.40**; right: x, y, z = 16, -4, 20, T=3.43, cluster size=4, Spearman's ρ = -0.44**), which did not survive our a-priori extent threshold of >25 voxels.

Table 7.6: Significant whole-brain correlations between regional white matter volumes and scores on the three major symptom dimensions of OCD (N = 50 for Padua Inventory, N = 47 for Y-BOCS symptom checklist)

cluster size	T	Spearman's ρ	peak coordinates (MNI)			anatomical region
			x	y	z	
Negative correlations with the contamination/washing dimension of Padua Inventory						
135	4.08	-0.43**	28	-56	38	right parietal
Negative correlations with the contamination/washing dimension of Y-BOCS symptom checklist						
97	4.11	-0.46**	36	-68	34	right parietal
Negative correlations with the harm/checking dimension of Padua Inventory						
564	4.91	-0.40**	36	0	-22	right temporal
200	4.61	-0.39**	-38	-14	-20	left temporal
44	4.14	-0.46**	-16	-14	-18	
Negative correlations with the harm/checking dimension of Y-BOCS symptom checklist						
207	4.21	-0.43**	34	-2	-24	right temporal
94	4.02	-0.44**	34	-38	-12	
204	4.51	-0.48**	-32	-8	-24	left temporal
37	3.93	-0.45**	-18	-14	-16	
48	3.85	-0.42**	46	26	20	right prefrontal
47	3.77	-0.41**	-44	24	24	left prefrontal
Negative correlations with the symmetry/ordering dimension of Padua Inventory						
No significant results						
Negative correlations with the symmetry/ordering dimension of Y-BOCS symptom checklist						
No significant results						
Positive correlations with the contamination/washing dimension of Padua Inventory						
No significant results						
Positive correlations with the contamination/washing dimension of Y-BOCS symptom checklist						
No significant results						
Positive correlations with the harm/checking dimension of Padua Inventory						
No significant results						
Positive correlations with the harm/checking dimension of Y-BOCS symptom checklist						
No significant results						
Positive correlations with the symmetry/ordering dimension of Padua Inventory						
30	4.21	0.52**	-36	-14	-20	left temporal
100	3.71	0.35*	36	2	-20	right temporal
Positive correlations with the symmetry/ordering dimension of Y-BOCS symptom checklist						
71	3.72	0.45**	-30	-16	-20	left temporal

* = Spearman's correlation significant at p<0.05, ** = Spearman's correlation significant at p<0.01.
Abbreviation: MNI = Montreal Neurological Institute.

Specific neural correlates of OCD symptom dimensions

Multiple regression analyses using the symptom dimension scores of the Padua-IR (N=50) and Y-BOCS symptom checklist (N=47) and controlling for global GM/WM volumes, demonstrated that each of the studied symptom dimensions had a clearly distinct neural substrate. The results using the Padua-IR and YBOCS symptom checklist were remarkably similar (see Tables 7.5 and 7.6).

Scores on the 'contamination/washing' dimension were negatively correlated with GM volume in the bilateral dorsal caudate nucleus (see Table 7.5 and Figure 7.3a) and WM volume in the right parietal region (see Table 7.6 and Figure 7.4). Scores on the 'harm/checking' dimension were negatively correlated with gray and white matter volume of the bilateral temporal lobes (see Tables 7.5 and 7.6, Figures 7.3b and 7.4). Scores on the 'symmetry/ordering' dimension were negatively correlated with GM volume of the bilateral parietal cortex (see Table 7.5 and Figure 7.3c) and positively correlated with bilateral medial temporal gray and white matter volume (see Table 7.6 and Figure 7.4). At a slightly lower threshold of $p<0.001$ uncorrected (extent threshold 25 voxels), we also found that scores on the 'symmetry/ordering' dimension negatively correlated with GM volume in the right motor and left insular cortices.

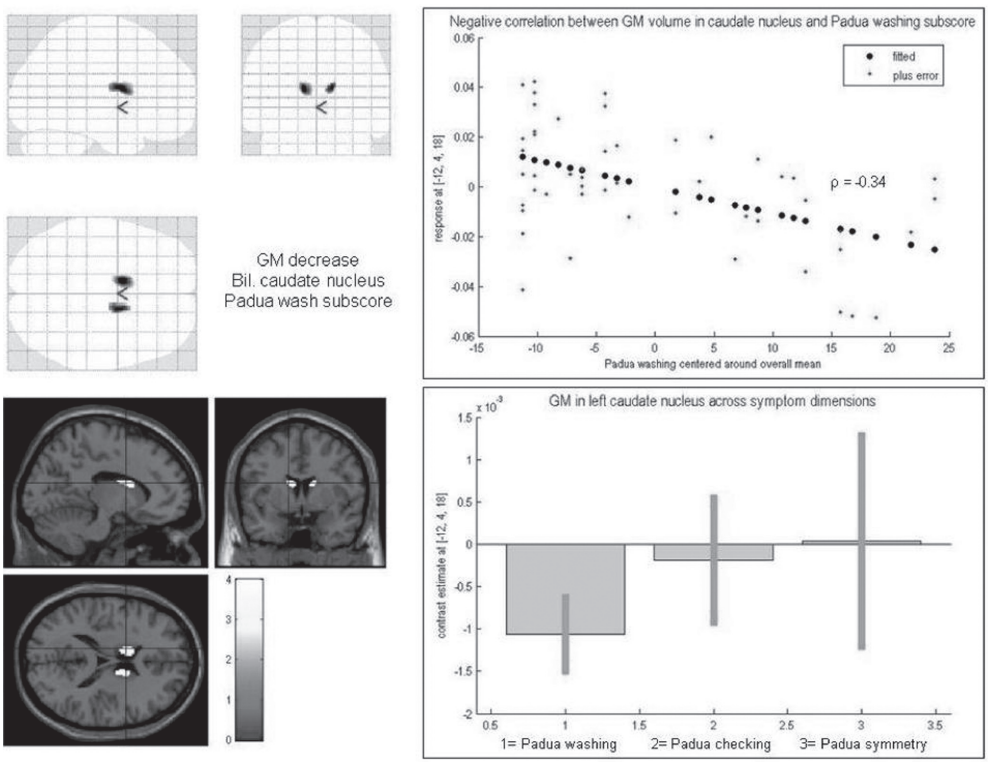

Figure 7.3a: Negative correlations between regional gray matter volume in the bilateral caudate nucleus and scores on the 'contamination/washing' dimension (Padua-IR) in the OCD group (N = 50). Results shown at $p < 0.001$ uncorrected and minimum cluster size of 25 voxels.

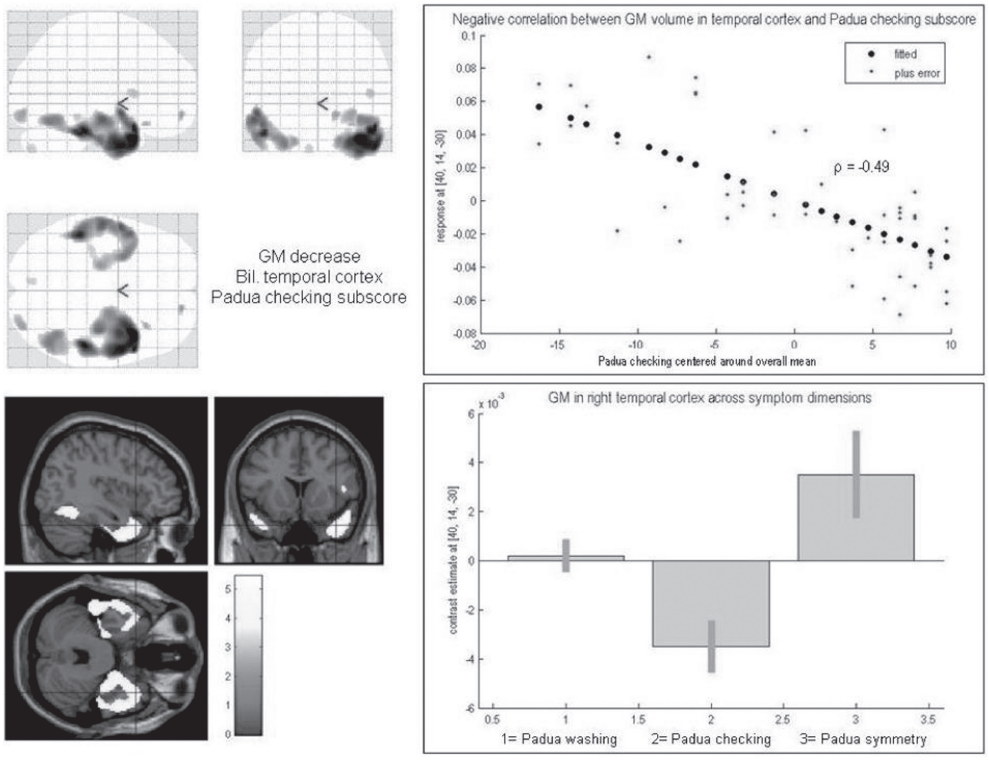

Figure 7.3b: Negative correlations between regional gray matter volume in the bilateral temporal cortex and scores on the 'harm/checking' dimension (Padua-IR) in the OCD group (N = 50). Results shown at $p < 0.001$ uncorrected and minimum cluster size of 25 voxels.

In an additional analysis with age, sex (dummy-coded as man/woman) and total Y-BOCS scores as extra covariates the results appeared to be largely independent from these variables. To control for the effect of comorbid depressive symptoms, we repeated all analyses excluding the 10 OCD patients with comorbid depression and similar results were found.

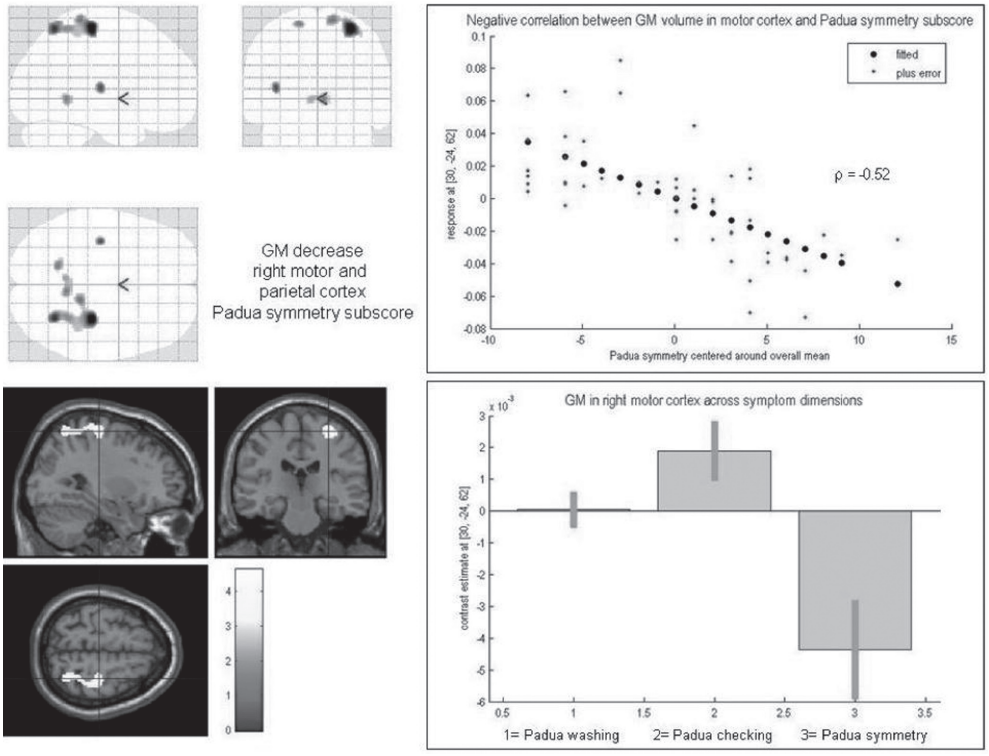

Figure 7.3c: Negative correlations between regional gray matter volume in the right motor and parietal cortex and scores on the 'symmetry/ordering' dimension (Padua-IR) in the OCD group (N = 50). Results shown at $p < 0.001$ uncorrected and minimum cluster size of 25 voxels

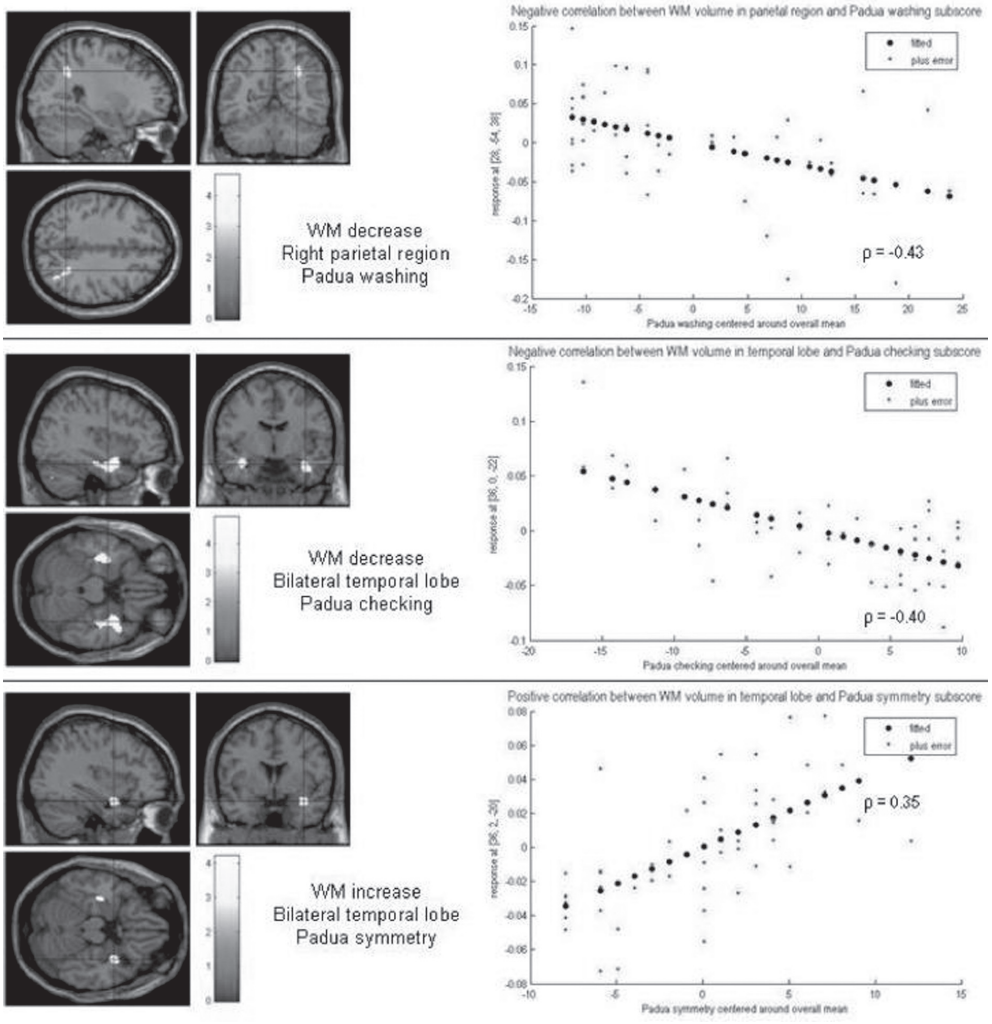

Figure 7.4: Significant correlations between regional white matter volumes and scores on the major symptom dimensions of OCD (N = 50). Top panel: 'contamination/washing' dimension; middle panel: 'harm/checking' dimension; bottom panel: 'symmetry/ordering' dimension. Results shown at $p < 0.001$ uncorrected and minimum cluster size of 25 voxels.

Discussion

To our knowledge this is the first study to explore the structural gray and white matter correlates of the major symptom dimensions of OCD in a large unmedicated patient sample. Previous efforts were limited by the inclusion of small sample sizes (Valente et al., 2005) or a substantial proportion of patients on medication (Pujol et al., 2004; Valente et al., 2005). Furthermore, we addressed this question using two different measures of each symptom dimension to ensure

that the results were robust and replicable. In our analyses, care was taken to control for global illness severity (YBOCS severity scores) and a range of potentially confounding variables, which allowed us to separate the common as well as distinct neural substrates of the major symptom dimensions of OCD.

Common neuroanatomical substrates in OCD compared with healthy controls

Overall, patients with OCD showed significantly decreased GM volume in the left lateral orbitofrontal (BA47), left inferior frontal (BA44/45), left dorsolateral prefrontal (BA9), and bilateral medial prefrontal (BA10) cortices compared with healthy control subjects. Gray matter volume reduction in the orbitofrontal and inferior frontal cortex was also found by Pujol et al. (2004) and Carmona et al. (2007), whereas two other VBM studies reported increased instead of decreased volume in the orbitofrontal cortex (Kim et al., 2001; Valente et al., 2005). Whereas Pujol et al. (2004) described medial orbitofrontal volume reduction (gyrus rectus, BA11), in the present study the orbitofrontal volume reduction was more laterally localized. Recently, Shin et al. (2007) investigated cortical thickness in OCD and reported cortical thinning of the medial orbitofrontal (BA11), lateral orbitofrontal (BA47), inferior frontal (BA45) and dorsolateral prefrontal (BA10) cortices of the left hemisphere. This left-right asymmetry is consistent with our results.

Decreased GM volume of the medial prefrontal cortex (BA 9/10) has consistently been found by others (Valente et al., 2005; Pujol et al., 2004). Volume reduction of the dorsolateral prefrontal cortex has been described both in adults (Shin et al., 2007) and in children (Carmona et al., 2007) with OCD. Dorsolateral prefrontal involvement in OCD corresponds with results from recent functional neuroimaging studies, showing decreased recruitment of the dorsolateral prefrontal cortex during neuro-cognitive testing (van den Heuvel et al., 2005; Remijnse et al., 2006). Medial and dorsolateral prefrontal regions are also involved in emotion regulation and cognitive control processes. Theoretical models of emotion perception suggest a reciprocal interaction between ventral and dorsal circuits in the brain underlying emotional processing (Phillips et al., 2003a). Although this model needs to be tested experimentally in more detail, it is a useful model for psychiatric disorders (Phillips et al., 2003b) and OCD in particular (Mataix-Cols and van den Heuvel, 2006). Decreased volume of these dorsal regions may underlie the impaired cognitive control during emotional processing and cognitive functioning found in OCD (Remijnse et al., 2005).

Reduction of prefrontal GM volume was accompanied with bilateral prefrontal WM volume reduction. At a lower statistical threshold, these regions of decreased WM volume were found to extend into the internal capsule. Although most previous VBM studies did not investigate WM volumes (Kim et al., 2001; Valente et al., 2005) or did not observe WM volume alterations (Pujol et al., 2004), Carmona et al. (2007) also found prefrontal WM volume reduction in their pediatric OCD patients. Decreased WM volume may underlie altered cortico-cortical and cortico-subcortical connectivity in OCD but direct evidence from the few published diffusion tensor imaging studies to date is limited (Szeszko et al., 2005; Yoo et al., 2007; Cannistraro et al., 2007).

There was an inverse correlation between disease severity and bilateral cerebellar GM volume. Although the cerebellum is traditionally considered to be essential for the coordination of movement and motor learning, recent studies have indicated that the cerebellum is also involved in cognitive and emotional processes (Middleton & Sherman 1998; Schmahmann & Caplan 2006). In OCD cerebellar involvement has been reported often, but the direction of the effect is inconclusive so far since both decreased (Nabeyama et al. 2008) and increased (Tolin et al. 2008) activation and decreased (Kim et al. 2001) and increased (Pujol et al. 2004) volume has been described. The cerebellar correlation with disease severity found in the present study parallels the recent finding that decreased cerebellar activation normalized with symptom improvement after 12 weeks of cognitive behavior treatment (Nabeyama et al. 2008; Nakao et al. 2005).

Taken together, these results are consistent with the view that there are some global neural abnormalities present in OCD that may reflect the loss of normal inhibitory processes (Chamberlain et al., 2005; Menzies et al., 2007). These abnormalities would be common to most patients with OCD and, according to recent work, even their unaffected first-degree relatives (Chamberlain et al., 2007; Menzies et al., 2007). However, the diagnostic specificity of these findings still remains to be established as difficulties in inhibitory processes and alterations in the corresponding brain regions may not be exclusive to OCD. Most notably, attention deficit and hyperactivity disorder (ADHD) is also characterized by such abnormalities (Rubia et al., 2005; Smith et al., 2006). It is therefore plausible that these are general vulnerability factors for a number of neuropsychiatric problems including OCD. This is supported by the fact that overall symptom severity of OCD did not correlate with any of the above regions but with the cerebellum bilaterally instead.

Distinct neural substrates across symptom dimensions

The most important contribution of the present study is that different symptom dimensions appear to have distinct neural substrates.

High scores on the 'contamination/washing' dimension were negatively correlated with the volume of the dorsal parts of the bilateral dorsal caudate nucleus. Many previous morphometric and functional neuroimaging studies have implicated the caudate nucleus in OCD, although the direction of the findings has been inconsistent (Remijnse et al., 2005). Because the contamination/washing symptom dimension is one of the most prevalent in OCD (Rasmussen and Eisen, 1992; Mataix-Cols et al., 1999) it may be assumed that previous studies consistently included a large proportion of these patients. Furthermore, contamination-related anxiety is particularly amenable to symptom provocation procedures and this probably played a role in the selective recruitment of these patients in such studies.

At this stage, the functional implications of decreased volume of the dorsal caudate nucleus in patients with prominent washing symptoms remain speculative. However, a possible hypothesis is that the lack of control on compulsive behavior due to dorsal striatal dysfunction results in conditionally reinforced washing rituals accompanied by relatively increased ventral striatal

involvement. The dorsal striatum has been implicated in habit learning and action initiation (Yin et al., 2004). Considering the phenomenological overlap between OCD and addiction (Hollander et al., 2007), these addiction studies may be relevant to understand the striatal role in cleaning behavior in contamination-related OCD. The progression from initial drug use to habitual drug use and ultimately to compulsive drug seeking behavior corresponds with a transition at the neural level from prefrontal cortical to striatal control and from ventral to dorsal striatal involvement (Everitt and Robbins, 2005; Everitt et al. 2008; Volkow et al., 2006). In Huntington's disease, a neurological frontal-striatal disease with often co-morbid obsessive-compulsive behavior, the striatal atrophy also shows a dorsal-ventral gradient (Douaud et al., 2006). Initially, the atrophy mainly affects the dorsal caudate nucleus relatively sparing the ventral striatum.

Turning to the 'harm/checking' symptom dimension, we found that the scores on this dimension were strongly negatively correlated with both gray and white matter volume in the bilateral anterior temporal poles. The anterior parts of temporal lobes including the amygdala and parahippocampal cortices have close connections with the hippocampal formation, the medial and orbitofrontal prefrontal areas and the ventral striatum (Kondo et al., 2005; Munoz and Insausti, 2005). This finding is consistent with that of Pujol et al. (2004) who found a significant inverse correlation between scores in this dimension and right amygdala volume. Checking rituals are most often associated with obsessions about harm and aggression (Leckman et al., 2007; Mataix-Cols et al., 2005). In OCD, patients with high scores on this symptom are at elevated risk from having comorbid anxiety and mood disorders, including panic disorder (Hasler et al., 2005; Rosario-Campos et al., 2006). Consistently, volume reduction in similar regions has been described in panic disorder (Massana et al., 2003a; Massana et al., 2003b) which, like OCD patients with harm/checking symptoms, is characterized by the overestimation of threat.

Interestingly, temporal lobe atrophy in patients with frontotemporal dementia appears to mediate complex compulsive behavior such as checking rituals (Rosso et al., 2001). Rosso et al. (2001) found that atrophy in frontal and subcortical regions was not associated with the development of such compulsive behaviors. Temporal lobe epilepsy is another condition associated with OCD symptoms, with compulsions being more frequently observed than obsessions (Isaacs et al., 2004). The involvement of the anterior temporal lobes in OCD has often been overlooked so far and our results suggest that this might be partially due to the heterogeneity of the disorder. Remarkably, in the current study, gray and white matter volumes were inversely correlated with scores on the 'harm/checking' dimension and positively correlated with scores on the 'symmetry/ordering' dimension. This indicates that recruiting different proportions of patients with these predominant symptom presentations may result in different results or even non-significant results, as these may cancel each other out.

The temporal lobe volume reductions may also be viewed with respect to the neuropsychological hypothesis of altered memory function in OCD patients with predominantly checking rituals. One of the proposed etiologies for checking behavior is the inability to accurately recall

whether an activity is completed correctly (Rachman, 2002). Paradoxically, repeating checking results in even more distrust in one's own memory (van den Hout and Kindt, 2004; van den Hout and Kindt, 2003). Although the confidence in memory seems to be more impaired than memory per se, there is some evidence for this so-called memory-deficit theory, with checkers showing more nonverbal memory deficits than non-checkers (Cha et al., 2007).

Finally, scores on the 'symmetry/ordering' dimension were inversely correlated with global gray matter volume. There was also a trend in the same direction for global white matter volume. No other symptom dimensions were associated with global GM/WM volumes. Patients with high scores in this dimension are known to have an earlier age of onset of their OCD (Mataix-Cols et al., 2005; Leckman et al., 2003) and also an increased risk of having an affected family member (Alsobrook et al., 1999; Hanna et al., 2005a; Hanna et al., 2005b). Therefore, OCD patients with high scores on this symptom dimension may have a more neurodevelopmental and familial form of the disorder. Consistently, the only pediatric VBM study in OCD to date found reduced global GM volumes in patients compared with controls (Carmona et al., 2007). Even though Carmona et al. (2007) did not describe their sample in detail, younger samples tend to include a substantial proportion of patients endorsing symmetry/ordering symptoms (Stewart et al., 2007).

After controlling for global GM and WM volumes, scores on the 'symmetry/ordering' dimension were inversely correlated with regional GM volume in motor, parietal and insular cortices and positively correlated with regional gray and white matter volume in the bilateral anterior temporal poles. However, the correlations with motor and insular cortices need to be interpreted with caution given that these were only significant at a lower statistical threshold. Correlations with motor and somatosensory regional abnormalities are consistent with the known association between the symmetry/ordering dimension of OCD and comorbid tics or Tourette's Syndrome (Leckman et al., 1997; Mataix-Cols et al., 1999). The positive correlations with gray and white volume in the anterior temporal pole in OCD patients with predominantly symmetry/ordering symptoms, is interesting in this respect: Peterson et al. (2007) recently reported increased volume in anterior temporal structures such as the amygdala and hippocampus in a large sample of patients with Tourette's Syndrome. The negative correlation between GM volume of the motor cortex and the symmetry/ordering dimension as found in the present study is inconsistent with the results of Gilbert et al. (2008), who found motor cortex volume negatively correlating with the contamination/washing dimension. However, in the Gilbert et al. (2008) study, correlation analyses were only conducted for regions that showed significant volumetric differences between patients and controls. In the present study we performed whole-brain correlations between symptom dimension scores and regional GM volume, which limits comparability between the two studies.

Although frontal-striatal and limbic brain regions have long been implicated in OCD, less attention has been paid to the possible involvement of the parietal cortex in the pathophysiology of the disorder (Menzies et al., 2008). Previous structural (Kitamura et al., 2006; Szeszko et al., 2005; Carmona et al., 2007; Valente et al., 2005), resting state (Kwon et al., 2003a), and

activation (van den Heuvel et al., 2005) neuroimaging found abnormalities in this brain region. Because the parietal cortex is known to be involved in attention and visuospatial processes (Posner and Petersen, 1990; Cabeza and Nyberg, 2000) as well as various executive functions, such as task switching (Sohn et al., 2000), planning (van den Heuvel et al., 2003) and working memory (Veltman et al., 2003), parietal dysfunction may contribute to the cognitive impairments found in some OCD patients (Menzies et al., 2008). The present study showed a negative correlation between parietal WM volume and the washing dimension, and parietal GM volume and the symmetry dimension. Although we consider it premature to interpret the functional implications of these findings, they indicate that the parietal cortex is particularly involved in these symptom dimensions. One recent study found that set-switching abilities may be particularly impaired in OCD patients with predominant symmetry/order symptoms (Lawrence et al., 2006), but replication is needed.

Strengths and limitations

The use of two different measures of OCD symptoms is a particular strength of the present study because clinician and self-administered measures of OCD symptoms are not perfectly correlated (Mataix-Cols et al., 2004). The fact that we obtained similar results using both types of scales adds to the robustness of the findings. All patients were medication naïve or medication-free for at least 4 weeks prior to inclusion. Although a washout period of 4 weeks may not be sufficient to mitigate all the effects of long-term medication use, this is a methodological advance compared to most previous VBM studies in OCD (Valente et al., 2005; Pujol et al., 2004; Carmona et al., 2007). The effects of psychotropic medication on brain morphometry have been shown mainly for antipsychotic medication, with for example olanzapine treatment resulting in increased volume of the caudate nucleus (Okugawa et al., 2007). However, the use of selective serotonin reuptake inhibitors may also present a confounder in morphometric studies in patients, given that these drugs stimulate neurogenesis. Both in humans (Becker and Wojtowicz, 2007) and non-human species (Lau et al., 2007; Sairanen et al., 2007) antidepressive treatment results in enhanced cell proliferation in the hippocampus, the subventricular zone, and the medial prefrontal cortex.

Another methodological advantage of the present study is the parallel investigation of both gray and white matter morphometry. The only previous VBM results showing white matter abnormalities in OCD were based on a small pediatric sample (Carmona et al., 2007). The investigation of GM and WM in the same subjects provides a more complete insight into the neural systems involved in the disorder.

The present study is not without limitations, however. A weakness is the lack of quantitative measures of comorbid depressive symptoms. Recent re-analyses of the Pujol et al. (2004) sample showed that OCD patients with comorbid major depressive disorder had larger volume reductions in the medial orbitofrontal cortex than OCD patients without comorbid depression (Cardoner et al., 2007). In the present study, no volume reduction was found in the medial orbitofrontal cortex, which may reflect that only 10 of our 55 OCD patients had a comorbid

depression. Whereas we found that the exclusion of these 10 depressed patients did not modify the overall results, we could not completely rule out that subclinical depressive symptoms (measured dimensionally) had an effect on our findings. Our control group was significantly higher educated than the patient group but the inclusion of education level as a covariate in the analyses did not modify the results. We did not assess general intellectual function and did not use a structured instrument to assess handedness. With regard to our statistical method, it should be recognized that whereas the use of uncorrected thresholds carries an obvious risk of Type I error, adopting whole-brain correction for multiple comparisons may be overly conservative; however, the use of small volume correction may present problems due to non-stationary smoothness of VBM data. Because of the small number of patients endorsing hoarding and sexual/religious obsessions, we had to restrict our analyses to the major, i.e., more prevalent, symptom dimensions of OCD. Preliminary neuropsychological (Lawrence et al., 2006) and functional neuroimaging (An et al., 2008; Tolin et al., 2008; Mataix-Cols et al., 2004) studies suggest that compulsive hoarding may constitute yet another neurobiologically distinct dimension of OCD.

Conclusion and future directions

The current study demonstrates common as well as distinct neuroanatomical substrates for the major symptom dimensions of OCD. Between-group analyses revealed that there are some global neural abnormalities present in OCD that may reflect the loss of normal inhibitory processes (Chamberlain et al., 2005; Menzies et al., 2007). However, the diagnostic specificity of these findings still remains to be established and it is plausible that decreased prefrontal gray and white matter volume is a general vulnerability factor for a number of neuropsychiatric problems including OCD. Multiple regression analyses within the patient group revealed that distinct neural systems may be underlying the major symptom dimensions of OCD, although causal relationships cannot be inferred. Our results further confirm the hypothesis that OCD is not a homogeneous disorder and that adopting a quantitative multidimensional approach has great promise in further understanding the set of problems we collectively call OCD (Mataix-Cols and van den Heuvel, 2006; Mataix-Cols, 2006; Mataix-Cols et al., 2005). These results have clear implications for the current psychobiological model of OCD (Saxena et al., 1998; Remijnse et al., 2005; Mataix-Cols and van den Heuvel, 2006) and call for a substantial revision of the model that takes into account the heterogeneity of the disorder. The results of the current study add to a growing neuroimaging literature (Mataix-Cols et al., 2004; An et al., 2008; Lawrence et al., 2007; Saxena et al., 2004; Gilbert et al., 2008) and will hopefully lead to more hypothesis-driven research into the common and specific neural substrates of these symptom dimensions. Multimodal imaging protocols will be necessary to understand the complex relationship between biochemistry, structure and function in relation to each of the major symptom dimensions of OCD.

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Chapter 8

Summary and general discussion

Aim of this thesis

The aim of the current thesis was to assess the neural correlates of cognitive (in)flexibility in obsessive-compulsive disorder (OCD) and major depressive disorder (MDD). In broader terms, we wished to gain more insight into the role of frontal-striatal and frontal-limbic circuits in the pathophysiology of OCD and MDD. To this end, we employed cognitive and emotional activation studies during functional magnetic resonance imaging (fMRI) in a group of patients with OCD, a group of patients with MDD, and a sample of healthy volunteers. Specifically, patients and controls were scanned while performing reversal learning and task switching paradigms, i.e. neuropsychological tasks known to measure cognitive flexibility. Since the use of psychotropic medication is known to affect neurophysiological brain functioning (Norbury et al., 2007), we included only patients with OCD and MDD free of psychotropic medication. The present research was part of a larger, three-center project investigating the role of the prefrontal cortex and serotonin (5-HT) in cognitive flexibility, in young healthy humans (University of Maastricht), rats (Netherlands Institute for Neuroscience) and psychiatric patients (VU University Medical Center).

Summary

Chapter 2 critically reviewed all published neuroimaging studies in OCD up until around 2004 – at the time the experimental work described in the following chapters had just commenced. Apart from the aim to give an overview of the status of neuroimaging-based insights into the pathophysiology of OCD at that time, this review also attempted to relate the findings to an influential emotion processing model (Phillips et al., 2003). Our review showed that dysfunctional frontal-striatal and (para)limbic brain circuits play a pivotal role in the pathophysiology of OCD. Moreover, a functional dissociation appears to exist between ventral and dorsal brain regions. Related to the emotion processing model (Phillips et al., 2003), the reviewed findings in OCD show *hyperactivity* of *ventral* frontal-striatal brain structures and the amygdala during resting-state and symptom provocation designs. This hyperactivity possibly reflects ongoing emotion processing (i.e. tonic symptomatology), and the identification of salient (disorder-specific) emotional stimuli. Moreover, *underactivity* exists in *dorsal* frontal-striatal brain areas – presumably the reflection of a decreased ability to regulate the evoked emotional responses (Phillips et al., 2003). Chapter 2 concluded with an argument for future studies in OCD that combine multi-modal imaging techniques with large-scale and longitudinal designs.

Chapter 3 describes the design and implementation of a self-paced event-related fMRI version of a reversal learning task in 27 healthy volunteers. Although the neural correlates of reversal learning had been described before (O'Doherty et al., 2001, Rogers et al., 2000, Nagahama et al., 2001, Cools et al., 2002), methodological drawbacks of these previous studies (see the introduction of this thesis) prompted us to develop an event-related reversal learning task that included an affectively neutral baseline, with the use of an OFC-sensitive scanning sequence during fMRI. As hypothesized, results showed the involvement of orbitofrontal cortical (OFC) subregions, anterior insula, and ventral striatum, in mediating reward and punishment outcome. Left ventral striatum and left lateral OFC were found to function as dissociable areas for the processing of reward and punishment, respectively. In addition to these main effects of monetary feedback, we showed the ventral frontal-striatal (e.g. OFC) loop, anterior cingulate cortex, and the insula, to be engaged in affective switching. Interestingly, we also described a novel finding of dorsal prefrontal cortical brain areas (e.g. dorsolateral prefrontal cortex, anterior prefrontal cortex) in mediating affective switching – which presumably reflects more cognitive processes engaged in switch performance, such as inhibitory control.

Chapter 4. After having addressed these methodological issues and having identified the neural substrate of our reversal learning task in healthy control subjects, we subsequently employed this paradigm in a group of 20 unmedicated patients with OCD and compared them with our healthy control sample (N=27). To our knowledge, this was the first cognitive activation neuroimaging paradigm challenging the ventral prefrontal-striatal system in OCD. As expected, patients with OCD showed impaired overall task performance reflected by a reduced number of correct responses and accumulated points by the end of the task. These

performance deficits were accompanied by underactivity of the orbitofrontal-striatal circuit on reward processing. Moreover, patients with OCD showed decreased BOLD signal in paralimbic brain regions (e.g. anterior insula) and in dorsal prefrontal brain structures (e.g. DLPFC and anterior PFC) during affective switching. The outlined neural dysfunctions in both ventral and dorsal frontal-striatal loops in OCD when probed with a reversal learning task confirm the previously proposed roles for these frontal-striatal circuits in the pathophysiology of this disorder. However, little is known about the *specificity* of the involvement of frontal-striatal brain circuits in the pathophysiology of OCD.

Chapter 5. In order to fill a lacuna in the knowledge on this topic, we conducted a direct-comparison study with a single activation neuroimaging design in 20 unmedicated patients with MDD (but no OCD) and in a newly assembled group of 20 patients with OCD (but no MDD), using our reversal learning paradigm. Results showed that both patient groups displayed prolonged mean reaction times but normal accuracy compared with 27 healthy volunteers. Imaging results demonstrated differential frontal-striatal and paralimbic activity during reward, punishment and affective switching in patient groups relative to controls. Specifically, patients with MDD exhibited increased activity in the left insula on punishment, increased activity in the putamen on reward, but decreased activity in DLPFC, anterior PFC and anterior cingulate cortex on affective switching –compared with controls. Conversely, patients with OCD showed attenuated signal in right medial and lateral OFC on reward, as well as attenuated signal in anterior PFC, DLPFC, and anterior cingulate on affective switching – relative to controls. Between-patient group analyses revealed that reward-associated blunted right medial OFC responsiveness in the OCD sample dissociated this group from depressed individuals. Moreover, a pattern of gradual decrease in DLPFC and anterior PFC activity during affective switching was found for healthy controls, MDD, and OCD. Thus, despite clinical, phenomenological, neuropsychological, and neurochemical commonalities between OCD and MDD, this study concluded that these frequently co-morbid psychiatric disorders can be discerned by distinct neurophysiological activations on a measure of cognitive flexibility. However, in spite of the fact that reversal learning is a frequently used assay of cognitive flexibility, this neuropsychological paradigm conflates learning with switching. In addition, and related to this issue, reversal learning measures cognitive flexibility within an emotional context and thereby introduces an additional, i.e. motivational factor that may influence task performance and neural activations.

Chapter 6. In order to investigate a 'purely' cognitive form of switching uncontaminated by emotional/motivational factors, we developed a task switching paradigm. We implemented this task in 18 unmedicated patients with OCD, 19 unmedicated patients with MDD and 29 healthy controls during fMRI, with the aim to further deepen our insight into the behavioral and neural correlates of cognitive flexibility in OCD and MDD. We found that both patient groups revealed increased response latencies relative to controls during repeat events, but only patients with OCD additionally showed decreased error rates during repetition. Moreover, both patients groups were characterized by successful task switching behavior, despite

differential neural activation patterns. With regard to the latter, patient with ODC and patients with MDD commonly lacked activation of task-relevant anterior prefrontal cortex during switching, which does not necessarily imply similar dysfunctional neural mechanisms in these two disorders. Patients with OCD also showed enhanced activations of the putamen – possibly the neural correlate of compulsive behavior – and increased activations in anterior cingulate and insula – possibly the reflection of increased error monitoring. Finally, patients with MDD showed reduced task-related activations in the inferior parietal cortex and precuneus, which was interpreted as the neural substrate of deficits in attention control characteristic for this disorder.

Chapter 7. After having examined the neural substrates of cognitive flexibility-related fMRI paradigms in OCD and MDD, we finally conducted a structural neuroimaging experiment employing voxel-based morphometry (VBM) and comparing 55 medication-free subjects with OCD and 50 age-matched healthy controls. Moreover, it examined the relationship between global and regional grey matter (GM) and white matter (WM) volumes on the one hand, and symptom dimension scores within the patient group on the other hand. Results demonstrated that some of the same brain areas showing aberrant activations in OCD during the functional neuroimaging paradigms described in this thesis, were also found abnormal in this VBM analysis – i.e. decreased GM volume in OFC, DLPFC, medial and inferior prefrontal cortex, and decreased prefrontal WM volume, in OCD versus controls. Interestingly, we subsequently found symptom dimension-specific GM and WM alterations within the OCD group, in frontal, temporal, and parietal cortices as well as the caudate nucleus. It was concluded that OCD clearly is a heterogeneous disorder, as reflected by our finding of distinct neural substrates across symptom dimensions.

General discussion

Implications for the neuropathophysiology of OCD

At the start of the current project in 2002, most neurobiological models on the pathophysiology of OCD postulated that obsessive-compulsive symptoms were mediated by hyperactivity in OFC-striatal circuits - putatively due to an imbalance of tone between direct and indirect PFC-striatal-thalamic cortical loops (Saxena et al., 1998). The excessive tone in the ventral frontal-striatal pathway was supposed to reflect a "response bias (…) toward stimuli relating to socioterritorial concerns about danger, violence, hygiene, order and sex – the themes of most obsessions in patients with OCD" (Saxena & Rauch, 2000). These neurobiological models were predominantly based on human lesion studies, structural and resting-state functional neuroimaging studies, as well as symptom provocation neuroimaging paradigms (Saxena & Rauch, 2000, see also **chapter 2** from this thesis). Few cognitive activation neuroimaging designs in OCD had been published at that time, and the ones existing had merely used paradigms challenging 'executive' brain regions with the aid of cognitive probes. The dorsal frontal-striatal circuit in OCD has been investigated by – amongst others – Odile van den

Heuvel and co-workers, who concluded that "altered dorsal frontal-striatal function in OCD patients is responsible for (…) decreased inhibition of ventral frontal-striatal and limbic recruitment in response to disease-relevant emotional cues" (van den Heuvel, thesis 2005, page 176). Importantly, however, the integrity of the ventral frontal-striatal circuit in OCD had not yet been challenged by an OFC-specific neuropsychological task during fMRI at that time. **Chapter 4** of the present thesis describes the first study that investigated the ventral frontal-striatal circuit in patients with OCD using a cognitive-emotional neuroimaging activation paradigm. Our study showed reduced orbitofrontal-striatal activity upon reward receipt and affective switching. We interpreted these abnormalities as the neural substrate of deficient modulation of emotional information with subsequent ineffective behavioral adaptation. However, this task-induced hypoactivity of the ventral-striatal system in **chapter 4** was at odds with the wealth of resting-state studies reporting increased perfusion and glucose uptake in these brain regions – as outlined earlier. One could argue that our result of task-induced hypoactivity in the ventral-striatal circuit may be explained by a 'ceiling effect', i.e. the presumed existence of maximal perfusion and glucose uptake in these brain areas at baseline preventing any additional increase upon cognitive-emotional challenge. However, we ruled out the possibility of a 'ceiling effect', based on the argument that affective switching-induced hypoactivity in OFC was assessed with a contrast comparing two punishment events and did not involve a baseline condition. To date, a satisfying explanation for this apparent discrepancy between repeatedly found resting-state hyperactivity but task-induced hypoactivity in the ventral brain structures in OCD remains elusive (Kwon et al., 2009). Of interest though, our findings of OCD-related hypoactivity in orbitofrontal and dorsolateral prefrontal cortex upon affective switching were later replicated by Chamberlain et al. (2008). In addition, these authors also observed these abnormalities in unaffected relatives of patients with OCD, and concluded that reversal learning-related hypofunction of OFC and DLPFC appears a vulnerability marker (or 'candidate endophenotype') in the search for underlying genetic diathesis of OCD (Chamberlain et al., 2008).

Recent neurobiological models on the pathophysiology of OCD have extended previous models from before 2002. The pathophysiological model of Chamberlain et al. (2005) postulates that OCD may be conceptualized in terms of lateral orbitofrontal loop dysfunction being the neural substrate of the core characteristic of OCD, i.e. a failure in cognitive and behavioral inhibitory processes (e.g. Penades et al., 2007). There are indications that these inhibitory deficits are candidate endophenotypes, since they are also found in unaffected relatives (Menzies et al., 2007; Chamberlain & Menzies, 2009). Our finding of decreased responsiveness in OFC-striatal brain areas in patients with OCD upon affective switching (**chapters 4 and 5**) corroborates this model, since response inhibition of the previously rewarded stimulus is a clear component in reversal learning (Robbins, 2000). Also, the decreased grey matter volume in (left) lateral OFC for patients with OCD relative to controls (**chapter 7**) is in line with the proposed model.

In a recent meta-analysis, Menzies et al. (2008) proposed the inclusion of other brain areas in the pathophysiology of OCD apart from the OFC-striatal circuit. These authors particularly

emphasized the involvement of dorsolateral-striatal, anterior cingulate and parietal brain structures in this disorder, and partly based their recommendation on our published findings described in **chapter 4.** The hypothesis that these brain regions are also engaged in OCD was further corroborated by subsequent findings in **chapters 5, 6, and 7**. These studies add evidence – based on both structural and functional neuroimaging paradigms – that the pathophysiology of OCD is additionally underpinned by abnormalities in anterior cingulate cortex, dorsolateral prefrontal, parietal and temporal brain regions.

A final recent model on the pathophysiology of OCD was put forward by Huey et al. (2008). These authors propose the existence of 'structured event complexes' (SECs), i.e. complex behavioral sequences that are stored in the prefrontal cortex. In healthy subjects, such SECs are released upon a motivational signal (e.g. motivational anxiety), executed by prefrontal-basal ganglia circuits, and their completion is accompanied by a reward signal. In patients with OCD, error signals generated by the ACC combined with a dysfunctional reward system (due to dysfunctional OFC and limbic structures), may lead to a feeling of incompleteness upon completion of an SEC. Additionally, a dysfunctional striatum may be the neural correlate of a lower threshold for releasing SECs and – consequently – for excessive activation of SECs (Huey et al., 2008). Notably, our findings described in **chapter 4** of OFC-striatal hypoactivity provide support for this SEC/OCD theory since deficient OFC and limbic structures are considered to underlie reduced alleviation of anxiety after completion of a SEC. In addition, our report of OFC hypoactivity on affective switching is supportive of the presumed lack of a feeling of completing an action, which consequently results in repetitive SEC execution (Huey et al., 2008).

Over the last few years, a tendency in the neurobiological literature on OCD has become manifest to view beyond diagnostic boundaries, and to group OCD and related neuropsychiatric disorders along dimensions instead of categories (Fineberg et al., 2010; van den Heuvel et al., 2010). One such highly relevant phenomenological dimension is the impulsive-compulsive spectrum. A recent narrative review on impulsivity and compulsivity posits separate but intercommunicating 'impulsive' and 'compulsive' frontal-striatal circuits in the human and non-human primate brain (Fineberg et al., 2010). Dysfunctions in these parallel loops may underlie characteristic and partly overlapping clinical as well as neurocognitive features of OCD and related disorders, e.g. trichotillomania and pathological gambling. This review concluded that impulsivity and compulsivity are both multidimensional characteristics themselves, and that OCD bears elements of either one - although it should be regarded as a predominantly 'compulsive' disorder. Consequently, at a neuronal level, OCD is underpinned by structural and functional abnormalities in brain regions associated with both the compulsive circuit (i.e. OFC and dorsal striatum - putamen and dorsal caudate) and the impulsive circuit (i.e. ACC and ventral striatum/nucleus accumbens). Several findings described in this thesis substantiate this model. For instance, we reported neurocognitive impairments in reversal learning within the group of OCD (**chapter 4**), which lends support to cognitive inflexibility being a reflection of compulsivity. In addition, at a neural level, dysfunctional OFC-striatal

activations upon a measure of compulsivity (reversal learning; **chapter 4 and 5**) converge with this model, as well as putamen hyperactivity upon task switching (**chapter 6**). Finally, the structural abnormalities in our VBM-analysis, i.e. decreased grey and white matter in several ventral and dorsal prefrontal areas in patients with OCD relative to healthy controls (**chapter 7**), corroborate this model.

The experimental work in the present thesis was primarily designed as *neuroimaging* and not *neuropsychological* studies. This study design is reflected by the relatively low numbers of participants in the experiments, and by the fact that neuropsychological tasks should be applicable within a scanner environment. As a result, robust conclusions on the neurocognitive profile of OCD based on task behavior in our OCD sample cannot be drawn. However, with these restrictions in mind, we may conclude that performance data in patients with OCD point at cognitive rigidity as a characteristic for this disorder. This conclusion is based on the fact that patients with OCD exhibited generic psychomotor slowing (**chapter 5**) and impaired overall task performance (**chapter 4**) during reversal learning, as well as increased response latencies putatively beneficial to accuracy during repetition in task switching (**chapter 6**). Notably, performance results during reversal learning were somewhat inconsistent, since patients with OCD showed task deficits in one study (**chapter 4**) that were absent in another (**chapter 5**). We attributed these behavioral differences to the fact that our newly assembled OCD patient group in **chapter 5** was free of comorbid depression, consisted of more patients having 'pure' OCD, and differed regarding symptom subdimensions – relative to our previous sample. Recent neurocognitive studies using reversal learning paradigms in OCD have similarly shown inconclusive results on this topic: MDD-free patients with OCD either showed prolonged reaction times with increasing severity of compulsions (Valerius et al., 2008) or no impairments at all (Chamberlain et al., 2007) – relative to healthy controls. It should be noted that both these studies included relatively low numbers of OCD patients (N= 20 in either study), and a majority of OCD subjects on medication (N = 12 and N = 16). Taking our behavioral findings and those recently published (Valerius et al., 2008; Chamberlain et al., 2007) together, we conclude that the performance deficits on reversal learning may be restricted to prolonged reaction times in OCD. Future behavioral research using larger samples of comorbidity-free and medication-free OCD patients should provide conclusive evidence on this issue.

In summary, the results presented in this thesis aid in understanding the neurocognitive and neurophysiological profile of OCD, specifically with regard to cognitive flexibility. Moreover, findings described in this dissertation have already contributed to newly developed models on the pathophysiology of OCD.

Implications for the neuropathophysiology of MDD

Major depressive disorder is not only characterized by sustained negative affect, but also by a constellation of motor, cognitive, motivational, and autonomic dysfunctions. Consequently,

the neural substrate of the depressive syndrome consists of structural and/or functional abnormalities in a widely distributed network of neocortical, striatal, (para)limbic and brainstem sites. In 2002, at the start of the present project, influential pathophysiological models of MDD had emphasized a limbic-cortical (corresponding to a 'ventral-dorsal') imbalance in this disorder (e.g. Mayberg, 1997; Drevets, 2000). A neurobiological model on dysfunctional emotion processing and behavior in MDD proposed that enhanced activity in ventral brain regions, i.e. amygdala, insula, ventral prefrontal areas and ventral striatum, might underlie an increased tendency to identify stimuli as emotional, and to experience negative affective states. Conversely, a decreased activity in dorsolateral and dorsomedial prefrontal structures might reflect impairments in executive function and effortful regulation of emotional behavior, characteristic of depressed patients (Phillips et al., 2003). These mentioned models, however, were largely based on human brain lesion studies, post-mortem findings and resting-state neuroimaging designs (Mayberg, 1997; Drevets, 2000; Phillips et al., 2003). They were only sparsely based on cognitive or emotional neuroimaging activation paradigms, since the number of studies combining neuropsychological with neurophysiological techniques in patients with depression were limited at that time (Rogers et al., 2004). In fact, no neuroimaging activation paradigm specifically and directly challenging the ventromedial prefrontal cortex/OFC in patients with MDD had been published by then (Rogers et al., 2004), and the field was in need of such a design. Since then, a wealth of functional neuroimaging activation studies in MDD has emerged. Still, our experiment described in **chapter 5** of this thesis was – to our knowledge – only the second neuroimaging activation paradigm that explicitly probed the OFC in MDD using a reversal learning task – after Taylor Tavares et al. (2008) who employed a similar paradigm, and, importantly, reported comparable results as we did. These and other neuroimaging activation studies in MDD that appeared since 2002 have confirmed and refined the above-mentioned pathophysiological models in MDD. For instance, our results described in **chapter 5,** in concordance with those from Taylor Tavares et al. (2008), commonly showed that patients with MDD fail to recruit dorsal prefrontal cortical areas (i.e. dorsomedial/dorsolateral PFC and dorsal ACC) upon switching - as predicted by the model of Phillips et al. (2003). At the same time, both Taylor Tavares et al. (2008) and our results point at increased limbic responses (in amygdala and insula, respectively) upon the receipt of negative feedback. It should be noted, though, that the neural findings described by Taylor Tavares et al. (2008) were assessed using slightly different imaging contrasts, relative to ours. Taken together, the common findings of dorsal prefrontal hypoactivity conjoint with limbic hyperactivity during reversal learning may be interpreted as a reduction in 'top-down control' which is putatively characteristic of patients with depression (Clark et al., 2009; Eshel & Roiser, 2010). This dorsal-ventral imbalance corroborates the outlined pathophysiological models suggesting cortical-limbic abnormalities in MDD, yet extends these models by showing a *functional dissociation* in a frontal-limbic network, leading to disruptive behavior (Taylor Tavares et al., 2008). Newer neuroimaging techniques using connectivity analyses are able to examine the mutual impact that activities in different regions exert over one another. Interestingly, recent

neuroimaging activation studies employing such analyses have indeed reported abnormal connectivity in frontal-limbic (Almeida et al., 2009) and frontal-striatal circuits (Heller et al., 2009) during emotion processing in MDD. Such findings from connectivity analyses confirm the assumed disruption of frontal-limbic and frontal-striatal networks in the pathophysiology of depression.

Apart from the outlined frontal-limbic network findings in depression, one more imaging result in the sample of patients with MDD deserves consideration. We consistently reported decreased activity of the anterior PFC in MDD during switching, both within an affective (i.e. reversal learning) and cognitive (i.e. task switching) context - see **chapters 5 and 6**, respectively. The anterior PFC (also termed frontopolar cortex) is "one of the least well understood regions of the human brain" (Ramnani & Owen, 2004; see also Uylings et al., 2010) and "arguably the least studied region of prefrontal cortex" (Walsh et al., 2009). Therefore, our finding of anterior PFC hypoactivity during switching in MDD is not easy to interpret, although it is tempting to consider reduced activity in this brain region as part of the generally diminished signal in dorsal prefrontal, 'cognitive' brain structures – as discussed above. Interestingly, though, a recent behavioral study investigated the performance of depressed patients on a 'cognitive branching task', specifically aimed to determine anterior PFC function in MDD. These authors failed to find performance deficits in depressed relative to control subjects on the branching condition, possibly due to small sample sizes (11 depressed patients versus 11 controls) (Walsh et al. 2009). Thus, it would be interesting if future studies investigated the exact role of the anterior PFC in cognitive functioning in general, and employed cognitive neuroimaging tasks using specific anterior PFC tasks in MDD.

Although the functional MRI experiments described in this thesis were not primarily designed as neuropsychological studies (see also the previous paragraph on OCD with regard to this topic), the behavioral data in the MDD group in our studies may warrant some conclusions. A consistent finding was that depressed patients showed increased reaction times compared with controls, a difference that was either significant (on reversal learning; **chapter 5**) or near-significant (on task switching; **chapter 6**). This MDD-related increased response latencies included responses on baseline trials in the reversal learning task, suggesting a *generic* psychomotor slowing instead of a specific task-related delay. Moreover, this disorder-related slowing was additionally confirmed by positive correlations between reaction times in MDD and several depression severity measures (i.e. BDI, MADRS, Ham-17) in both tasks. Thus, at a behavioral level, we may conclude that our studies consistently point to psychomotor slowing in depression, which is associated with disease severity. This finding has been observed before in purely neurocognitive tasks (Kalb et al., 2006), and provides empirical support for one of the DSM-IV criteria for MDD i.e. ' psychomotor retardation' (APA, 1994). We failed to find performance differences other than increased response latencies in the depressed group, however. As indicated, tailoring task paradigms for use in a neuroimaging design may result in a loss of sensitivity to identify neurocognitive impairments. Future neuropsychological studies

on cognitive flexibility or neuroimaging studies encompassing large numbers of participants should further investigate the presence of additional performance deficits in MDD.

In summary, the findings on MDD described in this dissertation by and large confirm predictions made by earlier pathophysiological models on MDD, and in addition refine these models by showing a functional dissociation in frontal-limbic and frontal-striatal circuits in MDD.

Implications for the issue of comorbidity between OCD and MDD

As stated throughout this thesis, OCD and MDD share several clinical and neurobiological commonalities, yet differ with regard to DSM-IV criteria and neuropsychological profiles. Both psychiatric disorders often occur simultaneously in one individual; a recent investigation showed that 40.7% of all patients with OCD also fulfill the criteria of a co-morbid MDD (Ruscio et al., 2010). Thus, the challenge is to find common and distinct neurobiological correlates of depression and OCD. This research objective may also have implications for the current debate on whether the upcoming DSM-V should maintain separate categories for depression and anxiety or include these into a supercategory of 'internalizing disorders' (Holden, 2010; see also www.dsm5.org). Of relevance for this comorbidity issue is the fact that direct-comparison neurocognitive or neuroimaging studies in OCD and MDD are extremely scarce. Interestingly, a very recent neuropsychological study employed a task switching paradigm in a sample of patients with OCD, a sample of patients with MDD and a group of healthy controls. Both patient groups exhibited cognitive rigidity compared with controls, but there were no between-patient group behavioral differences (Meiran et al., 2010a). This similar performance deficit in MDD and OCD relative to controls led the authors to conclude that cognitive inflexibility may be a common risk factor for both disorders. However, this between-patient group finding on task switching does not converge with the one we describe in **chapter 6** of this thesis, and may be explained by the relatively low numbers of participants in the Meiran et al. (2010a) study (OCD: N = 8, MDD: N = 9) and by the fact that all patients were taking psychotropic medication.

Our between-patient group findings described in **chapters 5 and 6** are best summarized as follows: at a behavioral level, the task switching design tended to better discriminate between OCD and MDD than did the reversal learning task, since we clearly demonstrated a differential performance pattern in both groups on the former paradigm which was absent in the latter. This between-task difference may be explained by the suggestion that the task switching paradigm is "the most precise measure of cognitive rigidity to date" (Meiran et al., 2010a; 2010b). Consequently, task switching may thus be more sensitive in detecting subtle between-patient group differences in cognitive flexibility relative to reversal learning. Specifically, our task switching experiment showed that patients with OCD exhibited enhanced accuracy with increasing OC-severity, at the expense of prolonged response times during repeat trials. In contrast, depression severity in MDD was associated with increased response latencies during

switching. This tendency of depressed patients to disproportionally slow down their reaction times on switch events, may have led to a relatively decreased number of switch-related errors in this group, and - subsequently – to the MDD-specific finding of an absent error rate switch cost.

At a neural level, between-patient group findings on task switching and reversal learning are difficult to reconcile, due to the fact that the directions of group x task interaction effects on BOLD responses of switching ('flexibility') measures were exactly opposite; i.e. patients with MDD showed hyperactivity in several brain regions relative to subjects with OCD on reversal learning, but the opposite comparison yielded no activations. In contrast, patients with OCD showed increased activity in several brain structures compared with depressed subjects on task switching, whereas the reverse comparison showed no activations. This discrepancy may be due to intrinsic disorder-related neurobiological characteristics of OCD and MDD that differentially manifest themselves in neurophysiological measures of cognitive flexibility. Future studies should elaborate on this topic by conducting additional comparative studies using different neuropsychological activation designs in neuroimaging settings. Alternatively, this discrepancy may have been due to differential between-patient group performance during baseline trials used for computing the respective switching contrasts. Specifically, both patients with OCD and MDD showed behavioral impairments relative to controls (i.e. response latencies) on one of the event types (i.e. 'preceding reversal errors') that constitute the baseline trials in the reversal learning-related affective switching contrast. However, only patients with OCD showed abnormal performance relative to controls (i.e. increased reaction times and a reduced error rate) on 'repeat events' that constitute (conjoint with the between-events fixation star) the baseline trials in the task switching contrast. Thus, these performance differences may be the behavioral correlates of a patient group x baseline interaction effect on switching measures-related BOLD responses. We cannot exclude this possible explanation, particularly because we were unable to assess neural activity during repeat events, given the rapid event-related design of our task switching study (**chapter 6**).

Taken together, the results from our comparative studies in OCD and MDD indicate that in both disorders differential frontal-striatal and frontal-limbic neural networks during tasks of cognitive flexibility are recruited. Consequently, our results support the view that OCD and MDD have different neural substrates and should therefore be regarded as separate disorders – at least when it comes to cognitive (in)flexibility in these disorders.

Strenghts and limitations

The studies described in this dissertation have some methodological strengths and limitations. The fact that we only included patients *off medication* is a strength of our experiments. Although the inclusion of unmedicated patients has become more common in neuroimaging research over the past few years, it is still not a standard procedure (e.g. Surguladze et al., 2010; Harrison et al., 2009). Presumably, the medication status of patients is relevant for neuroimaging results, since antidepressant medication affects brain activity on neurocognitive

probes in healthy volunteers (Norbury et al., 2007; Harmer et al., 2006). These latter findings suggest that psychotropic medication also modulates functional neuroimaging activations in patient samples, *independent* of symptomatic state, and thereby introduces a confounding factor (Savitz & Drevets, 2009). Another strength of our studies is that we examined two patient samples with partly related psychiatric disorders in comparison with a healthy control group, thereby gaining more insight into the *specificity* of disorder-related abnormalities relative to healthy controls.

With regard to the limitations of the presented studies, some general caveats of neuroimaging in psychiatric disorders should be mentioned. First of all, functional neuroimaging findings are inherently *correlational*, reflecting the present state of the (psychiatric) participant in the scanner. Thus, the functional neuroimaging paradigm leaves uncertain whether dysfunctional brain activities should be interpreted as the *cause* of any disease process, or as the *consequence* of a pathogenic disorder-intrinsic brain process. Notably, even anatomical differences in brains of patients versus controls may (partly) be the *result* of brain structure changes following repeated long-lasting behaviors or cognitive processes (Uylings et al., 2005; Maia et al., 2008), which may also have consequences for the interpretation of our own VBM study (**chapter 7**). Finally, functional brain alterations may even be the consequence of aspecific disorder-associated neural processes such as arousal-related neurophysiological states, due to distress in the scanner environment (Maia et al., 2008; van den Heuvel, thesis 2005). The latter potential confounder may be addressed by registering state anxiety/distress on a visual analogue scale (VAS) – which we failed to do in our experimental groups. We did assess, however, the degree of obsessive-compulsive symptoms in our OCD patient group during the scanning procedure using a self-developed rating scale, and ruled out this factor as a possible confounding variable.

A second issue concerns the exact relationship between anatomical and functional brain alterations in psychiatric disorders such as OCD and MDD. Both kind of abnormalities are often reported within one disorder and in the same brain regions (e.g. in frontal-striatal and frontal-limbic loops), but are mostly assessed during separate neuroimaging experiments. Functional and structural neuroimaging assessments are therefore potentially confounding measures in determining the pathophysiology of a (psychiatric) disorder (Savitz & Drevets, 2009). An example of this can be found in the present thesis: **chapter 7** describes OCD-related decreased grey matter volume in left dorsolateral prefrontal cortex, which is the same brain structure that was found hypoactive in patients with OCD during affective switching in **chapter 4**. Consequently, the question arises whether the finding of hypoactivity in DLPFC during switching is either independent from or secondary to the finding of volume loss in this same area. Moreover, methodological limitations of the VBM method as a morphometric approach should be taken into account (Tisserand et al. 2002). The results described in **chapter 4** and **chapter 7** were assessed in two different samples of OCD patients, excluding direct comparisons between the two studies. This topic concerning the exact relationship between functional and structural alterations within one brain region and within one patient group remains unresolved

to date. Recently, however, an overlap of functional and anatomical maps was created using compiled data from a meta-analysis of VBM-analyzed structural abnormalities in OCD and a meta-analysis of symptom-induced neural correlates of OCD assessed with fMRI. The only brain region showing both anatomical alterations and dysfunctional activity was the left lateral OFC (Rotge et al., 2010). Future studies, however, should elaborate on this issue, since it is of great importance for the interpretation of neuroimaging results, and for the consequences it has regarding pathophysiological models in OCD and MDD.

Finally, we should mention some limitations on the topic of patient inclusion: we selected a clinically heterogeneous OCD sample regarding OCD symptom dimensions, despite evidence of differential neurophysiological mechanisms underlying these various symptom dimensions (e.g. Mataix-Cols et al., 2004). Moreover, we included a mixed OCD sample with regard to age-of-onset in spite of evidence that brain activity differs between early (childhood) onset and late (adult) onset OCD (Busatto et al., 2001). Consequently, we cannot rule out the possibility that the inclusion of heterogeneous OCD patient samples has diluted some of our behavioral and imaging findings within the OCD group.

Suggestions for future research

Our argument at the end of **chapter 2** for future studies in OCD that combine multi-modal imaging techniques with large-scale and longitudinal designs is still highly relevant. Ideally, a cohort of children partly with and without high familial risks for OCD would be followed prior to having obtained a diagnosis until far into adulthood. This would provide a rich and dynamic view of the unfolding of pathology in the brain affected by OCD (Maia et al., 2008). For the same reason, longitudinal and multi-modal neuroimaging studies are warranted in MDD (Savitz & Drevets, 2009).

A more specific suggestion for future research based on the findings in this thesis, would be a refinement of the described neuropsychological tasks for neuroimaging use. For instance, our reversal learning paradigm measured the learning of associations between neutral stimuli and their rewarding or punishing values, as well as the alteration of behavior when reinforcement contingencies changed. However, the affective values of these stimuli are currently defined by disorder-aspecific rewards and punishment, i.e. monetary feedback. It cannot be excluded, for instance, that depressed patients attribute relatively low value to the gain or loss of money, given the fact that anhedonia is a characteristic of this disorder (APA, 1994). Therefore, the sensitivity of a reversal learning task may be enhanced by employing more primary reinforcements - such as pleasant and unpleasant stimuli in different sensory modalities – instead of reinforcements at an abstract level (money). Alternatively, disorder-specific rewards and punishment may be used such as obsession-provocative versus matched neutral pictures in patients with OCD.

Furthermore, it would be of interest to investigate whether the described abnormalities in this thesis for OCD and MDD have either trait or state characteristics. To determine this issue, longitudinal studies are needed using repeated-measurements designs in which the same neuropsychological tasks are employed in patients when they are in a remitted state.

Interestingly and of relevance, a recent fMRI study examined the neural correlates of reversal learning in an unmedicated, depression-free OCD group before and after patients were treated with cognitive-behavioral therapy. Results showed changes in basal ganglia activations between pretreatment and follow-up measurements, but failed to find alterations in OFC over time in the OCD group compared with controls (Freyer et al., 2010). Similar repeated-measurement studies using reversal learning or task switching paradigms in MDD are currently lacking. Such proposed test-retest designs determining trait or state characteristics may aid in the search for endophenotypes, i.e. intermediate phenotypes between the genotype and the clinical phenotype of a disorder. Neuropsychological probes for functional neuroimaging use are considered ideal candidates for such markers, since they have strong heritability and are therefore closer to the genetic predisposition of a disorder than the clinical phenotype (Chamberlain & Menzies, 2009). Being heritable traits associated with increased risk for a disorder, an alternative way of identifying endophenotypes is to study unaffected relatives of patients. Studies using this approach are also highly encouraged in unaffected relatives of patients with OCD and MDD, and a recent tendency to develop this line of research has emerged both for OCD (e.g. Menzies et al., 2007; Chamberlain et al., 2008) and for MDD (van der Veen et al., 2007).

Finally, we need more direct-comparison neuroimaging studies between related psychiatric disorders, to determine common and distinct neural correlates of such disorders. The present thesis described studies in OCD and MDD, but comparative neuroimaging studies between OCD and other anxiety disorders are also important but are nevertheless extremely scarce (Radua et al., 2010). The same is true for comparative neuroimaging studies between unipolar depressive disorder and bipolar depressive disorder (Savitz & Drevets, 2009). Such comparative studies have great value for the research agenda for the DSM-V, which aims to apply findings from basic and clinical neurosciences to guide psychiatric classification in the future (APA, 2002).

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Samenvatting in het Nederlands

Cognitieve flexibiliteit in patiënten met een obsessieve-compulsieve stoornis en patiënten met een depressie

Functionele neuroimaging studies naar 'reversal learning' en 'task switching'

Dit proefschrift beschrijft de resultaten van onderzoek naar hersengebieden die betrokken zijn bij cognitieve flexibiliteit in gezonde vrijwilligers, in patiënten met een obsessieve-compulsieve stoornis (OCS) en in patiënten met een depressie. De gebruikte techniek om hersenactiviteit te meten is een vorm van beeldvormend onderzoek, genaamd 'functionele neuroimaging'. Alle proefpersonen in ons onderzoek zijn gescand in een 'magnetic resonance imaging' (MRI) scanner terwijl zij neuropsychologische taken uitvoerden; dit wordt functionele MRI (fMRI) genoemd. De toegepaste neuropsychologische taken in dit onderzoek (de 'reversal learning' taak en 'task switching' taak) waren speciaal door ons ontwikkeld om cognitieve flexibiliteit te meten. Met behulp van software en statistiek is na afloop van de fMRI experimenten bepaald en berekend welke hersengebieden actief waren bij het uitvoeren van genoemde taken. Doel van ons onderzoek was of en in welke mate de drie experimentele groepen (gezonde vrijwilligers, OCS-patiënten en depressieve patiënten) verschilden in geactiveerde hersengebieden op cognitieve flexibiliteit.

Begrippenkader

Patiënten met een ***obsessieve-compulsieve stoornis*** (vroeger 'dwangneurose' geheten) hebben last van dwanggedachten (obsessies) en/of dwanghandelingen (compulsies) waardoor hun dagelijkse leven aanzienlijk beïnvloed wordt. Obsessies worden gedefinieerd als hardnekkige, steeds terugkerende gedachten of beelden die iemand angstig of gespannen maken. Deze gedachten of beelden gaan vaak over besmet worden of zelf besmetten, of over twijfels ten aanzien van het eigen handelen en angst om als gevolg van nalatigheid verantwoordelijk te zijn voor een catastrofe. Ook een extreme behoefte aan symmetrie en orde komt vaak voor, net als gedachten met een agressieve inhoud. De dwanggedachten veroorzaken vaak een voortdurend gevoel 'dat er iets niet klopt'; bijvoorbeeld de deur die niet op slot is, of de handen die niet schoon zijn. Compulsies worden gedefinieerd als steeds terugkerende handelingen of rituelen die soms zichtbaar zijn voor de buitenwereld, of soms zich uitsluitend afspelen in iemands hoofd. Vaak voorkomende compulsies zijn wassen, ordenen, controleren of checken, tellen, herhalen en verzamelen. De functie van compulsies is per definitie het opheffen of verminderen van de angsten en twijfels die voortkomen uit de obsessies. Helaas duurt dit gewenste effect van compulsies maar kort, en vaak keren obsessies snel weer terug. Op basis van de inhoud van obsessies en compulsies zijn er inmiddels minstens 4 robuuste en over de tijd stabiele symptoomdimensies binnen OCS te onderscheiden, namelijk 1. symmetrie/ordenen, 2. smetvrees/wassen, 3. controleren, 4. verzamelen.

Patiënten met een ***depressieve stoornis*** zijn somber en kunnen nauwelijks meer genieten van

dingen die voorheen plezierig waren. Daarnaast hebben depressieve patiënten vaak last van minderwaardigheidsgevoelens, vermoeidheid, cognitieve problemen, slaap- en eetstoornissen en doodsgedachten. Zij lijden vaak onder steeds terugkerende negatieve gedachten die hun leven nadelig beïnvloeden.

Gezonde proefpersonen die aan dit onderzoek meededen, hadden geen psychiatrische of neurologische stoornis in het heden of het verleden, en zij gebruikten geen verslavende middelen.

Cognitieve flexibiliteit kan gedefinieerd worden als het vermogen om doelgericht gedrag te vertonen en bij te sturen in een continu veranderende omgeving. Een adequaat vermogen tot cognitieve flexibiliteit is essentieel voor gezond psychisch functioneren, voor een bevredigende adaptatie aan de omgeving, en - uiteindelijk - voor de overleving van ieder mens. Uitgebreid dier- en humaan experimenteel onderzoek over de afgelopen decaden heeft laten zien dat de prefrontale cortex (PFC) en de basale ganglia (ook wel genoemd het 'striatum') bij uitstek de hersengebieden zijn die cognitieve flexibiliteit mogelijk maken. Bovendien spelen deze hersengebieden een belangrijke rol bij de integratie van motivationele informatie die cognitieve flexibiliteit voor een groot deel stuurt. Met ***motivationele informatie*** wordt hier bedoeld alle externe en interne stimuli die een organisme ontvangt en die een positieve ('belonende') of negatieve ('bestraffende') waarde vertegenwoordigen. In het bijzonder is bij cognitieve flexibiliteit binnen een motivationele (of 'affectieve') context de 'orbitofrontale cortex' (OFC), een onderdeel van de PFC, betrokken.

Er zijn verschillende argumenten om te veronderstellen – gebaseerd op eerdere wetenschappelijke bevindingen – dat patiënten met OCS en patiënten met een depressie een gebrek aan cognitieve flexibiliteit vertonen. Ten eerste kan vanuit de aard van beide stoornissen al afgeleid worden dat dit het geval is. Immers, de rigiditeit die zowel obsessies als compulsies kenmerkt, veronderstelt dat patiënten met deze stoornis verminderd in staat zijn tot flexibiliteit in denken en gedrag. Bij depressieve patiënten wijst de geringe flexibiliteit van steeds dezelfde, terugkerende negatieve gedachten ('ruminaties') in dezelfde richting. Een tweede aanwijzing dat cognitieve inflexibiliteit een wezenlijk kenmerk is van OCS en depressie, wordt gevonden in de neuropsychologische literatuur. Hieruit is frequent gebleken dat zowel patiënten met OCS als patiënten met depressie, slechter scoren op diverse maten van cognitieve flexibiliteit dan gezonde vrijwilligers. Tot slot zijn er uitgebreide aanwijzingen in de 'neuroimaging'-literatuur dat hersengebieden die in het algemeen betrokken zijn bij cognitieve flexibiliteit (zie hierboven), disfunctioneel zijn in patiënten met OCS of depressie.

Samenhangend met genoemde aanwijzingen voor verminderde cognitieve flexibiliteit in OCS en depressie, zijn er ook redenen om aan te nemen dat de verwerking van motivationele informatie gestoord verloopt in deze psychiatrische aandoeningen. Op fenomenologische gronden lijken patiënten met OCS bijvoorbeeld een inadequate beleving van 'straf' te hebben; zij hebben immers het voortdurende gevoel 'dat er iets niet klopt' (zie boven). Daarnaast lijkt er een verstoorde beleving van 'beloning' in deze patiënten te bestaan; compulsies zijn immers bedoeld om angst en twijfel op te heffen – hebben dus eigenlijk een 'belonende' functie –

maar slagen hierin meestal maar kort of niet. Analoog aan de situatie in OCS, lijkt er ook in depressie een stoornis in de verwerking van straf en beloning te bestaan; depressie is bij uitstek de stoornis waarin het vermogen tot genieten ontbreekt en waarin 'belonende' prikkels dus blijkbaar abnormaal verwerkt worden. De terugkerende ruminaties van patiënten met deze stoornis wijzen daarnaast in de richting van een gestoorde verwerking van prikkels die een 'bestraffend' karakter hebben. Naast deze fenomenologische argumenten, zijn er opnieuw verschillende aanwijzingen vanuit de neuropsychologische en de 'neuroimaging'-literatuur, dat hersengebieden betrokken bij motivationele processen, afwijkend functioneren in patiënten met OCS en patiënten met een depressie.

Bovenstaande uiteenzetting laat dus zien dat zowel OCS als depressie gekenmerkt wordt door cognitieve rigiditeit en door inadequate verwerking van motivationele informatie. Dit roept de vraag op in hoeverre deze psychiatrische stoornissen eigenlijk van elkaar verschillen en in hoeverre zij overlappen, met name op het niveau van neurale disfuncties. Deze vraag is des te meer relevant aangezien uit epidemiologische onderzoeksgegevens blijkt dat OCS en depressie zeer frequent comorbide stoornissen zijn. Het aantal 'neuroimaging' studies dat OCS en depressie met elkaar vergelijkt, is echter minimaal tot nu toe.

Abstracte concepten als 'cognitieve flexibiliteit' en een 'motivationele context' moeten eerst geoperationaliseerd worden, dat wil zeggen omgezet worden in bruikbare neuropsychologische taken om ze vervolgens empirisch te kunnen onderzoeken. Voor dit onderzoek hebben wij twee neuropsychologische taken ontwikkeld (gebaseerd op taken die eerder in de literatuur werden beschreven) die cognitieve flexibiliteit meten, de ene binnen en de andere buiten een motivationele context. De taak die cognitieve flexibiliteit meet *binnen* een affectieve context is de 'reversal learning' taak. ***Reversal learning*** kan gedefinieerd worden als het vermogen om gedrag flexibel aan te passen op geleide van feedback middels 'straf' en 'beloning'. Onze 'reversal learning' taak bestond uit 2 dezelfde stimuli die in iedere experimentele trial aan de proefpersoon werden gepresenteerd. De proefpersoon moest steeds één van beide stimuli selecteren en de associatie van elk van beide stimuli met straf of beloning alterneerde per reeks trials ('reversal'), zodat de proefpersoon steeds moest switchen in de te selecteren stimulus. Wij definieerden binnen onze taak 3 'events' waarop hersenactiviteit gemeten werd, namelijk: 1. tijdens het ontvangen van beloning, 2. tijdens het ontvangen van straf en 3. tijdens het (affectief) switchen. De taak die cognitieve flexibiliteit meet *buiten* een affectieve context is de 'task switching' taak. ***Task switching*** kan gedefinieerd worden als het vermogen om alternerend te switchen tussen twee taken, op geleide van een externe 'cue'. Onze 'task switching' taak is een zogenaamde cijfer/letter taak, waarin een proefpersoon per trial twee stimuli kreeg aangeboden – een cijfer en een letter. De kleur waarin de trial werd aangeboden, (blauw of rood) vormde de externe 'cue' die bepaalde welke van de twee taken de proefpersoon moest uitvoeren. De lettertaak bestond uit het bepalen of de aangeboden letter een klinker of medeklinker is, de cijferaak bestond uit het bepalen of het aangeboden cijfer even of oneven is. Wij definieerden binnen onze taak 1 'event' waarop hersenactiviteit werd gemeten, namelijk tijdens het switchen van de ene taak naar de andere.

Het onderzoek dat wordt beschreven in dit proefschrift, startte in 2002. Het was onderdeel van een bredere, door NWO-gefinancierde wetenschappelijke studie, waarin ook het Nederlands Instituut voor Neurowetenschappen (NIN) en de Universiteit van Maastricht participeerden. De belangrijkste vraagstelling van het project als geheel was: wat is de rol van de OFC in cognitieve flexibiliteit? De specifieke vraag voor ons VUmc project was: welke hersengebieden (inclusief de OFC) zijn betrokken bij cognitieve(in)flexibiliteit – zowel binnen als buiten een motivationele context - bij patiënten met OCS en patiënten met depressie, vergeleken met gezonde vrijwilligers?

Samenvatting van de hoofdstukken

Hoofdstuk 1 is de inleiding van het proefschrift waarin bovenstaande begrippen als OCS, depressie, cognitieve flexibiliteit, 'reversal learning' en 'task switching' worden uiteengezet.
Hoofdstuk 2 bevat een uitgebreid overzicht van alle gepubliceerde 'neuroimaging' studies in patiënten met OCS tot aan 2004. Dergelijk onderzoek werd voor het eerst eind jaren tachtig van de vorige eeuw uitgevoerd. Dit overzicht van alle gepubliceerde literatuur bestrijkt dus een periode van ruim 15 jaar. Al dit onderzoek dat beschreven wordt in de literatuur heeft ten doel (gehad) om OCS te definiëren in termen van (dis)functionele hersengebieden. Uit ons overzicht blijkt dat de besproken studies nogal verschillen in methodologie, bijvoorbeeld wat betreft onderzoeksopzet en de toegepaste analysetechniek. Dit hoofdstuk eindigt met een pleidooi om in de toekomst longitudinale studies uit te voeren met behulp van nieuwe technieken, zoals multimodale 'neuroimaging', in voldoende grote patiëntgroepen. Met behulp van dergelijk onderzoek kan het neurale substraat van OCS zo optimaal mogelijk in kaart worden gebracht.
Hoofdstuk 3 beschrijft de eerste van een reeks experimentele studies in onze onderzoeksgroepen. Het beschrijft de methodologische aspecten van de door ons voor fMRI geïntroduceerde 'reversal learning' taak, en het neurale substraat ervan in 27 gezonde proefpersonen. De resultaten tonen dat inderdaad de OFC, tezamen met andere PFC gebieden, het striatum en diverse posterieure breingebieden, het neurale substraat vormen van onze 'reversal learning' taak.
Nadat we het neurale correlaat van onze 'reversal learning' taak gedefinieerd hadden in hoofdstuk 3, pasten we deze taak vervolgens toe in een groep van 20 patiënten met OCS die we vergeleken met de controlegroep van 27 gezonde proefpersonen. Omdat het gebruik van psychoactieve medicatie hersenactiviteit beïnvloedt, selecteerden we uitsluitend medicatievrije patiënten met OCS. Dit experiment staat beschreven in **hoofdstuk 4**. We onderzochten zowel groepsverschillen in gedrag (dat wil zeggen in neuropsychologische uitkomstmaten op de 'reversal learning' taak) als in hersenactiviteit op beloning, straf, en (affectief) switchen. De resultaten laten zien dat patiënten met OCS slechter scoorden op gedragsmaten tijdens 'reversal learning', en dat zij bovendien verminderde hersenactiviteit vertoonden, met name verminderde activiteit in de OFC en in het striatum op beloning en op (affectief) switchen. Er

was geen verschil in hersenactiviteit op straf tussen de twee groepen. Het lijkt er dus op dat OCS gekarakteriseerd wordt door disfunctionele OFC-striatale activiteit tijdens het ontvangen van beloning en tijdens het uitvoeren van switchgedrag, maar niet tijdens het ontvangen van straf. Wellicht vormen deze hersendisfuncties het neurale correlaat van cognitieve inflexibiliteit en inadequate motivationele verwerking, zoals die gezien worden in het klinische beeld van OCS.

De resultaten uit hoofdstuk 4 zijn interessant, maar zeggen nog niets over de *specificiteit* van de gevonden afwijkingen in OCS. Met andere woorden, om een uitspraak te doen over in hoeverre deze afwijkingen specifiek zijn voor OCS, en niet bijvoorbeeld ook voor andere psychiatrische patiëntgroepen gelden, moet OCS vergeleken worden met een andere patiëntengroep. In **hoofdstuk 5** wordt het experiment beschreven waarin we een 3-groeps vergelijking maken; we vergeleken de uitkomsten van de' reversal learning' taak tijdens fMRI bij 20 patiënten met OCS, 20 patiënten met depressie, en 27 gezonde vrijwilligers. Opnieuw was het gebruik van psychoactieve medicatie een exclusiecriterium voor de patiëntgroepen. De uitkomsten van deze studie waren als volgt: patiënten met OCS en patiënten met depressie lieten tragere reactietijden zien tijdens het uitvoeren van de 'reversal learning' taak dan gezonde vrijwilligers, en beide patiëntgroepen vertoonden differentiële activiteit van onder andere OFC-striatale gebieden op straf, beloning en affectief switchen, ten opzichte van gezonde vrijwilligers. De patiëntgroepen verschilden onderling eveneens in de activaties van diverse prefrontale, striatale en posterieure hersengebieden. De conclusie van dit experiment is dat OCS en depressie gekenmerkt worden door verschillende neurale disfuncties tijdens 'reversal learning', ondanks het feit dat er op fenomenologisch en neuropsychologisch niveau talrijke overeenkomsten zijn (zie boven).

De experimenten uit hoofdstuk 3, 4 en 5 werden verricht met de 'reversal learning' taak, die cognitieve flexibiliteit binnen een motivationele context meet. Om na te gaan in hoeverre de gevonden groepsverschillen eventueel verklaard konden worden door de motivationele context in plaats van door cognitieve (in)flexibiliteit op zich, verrichten wij een 3-groepsvergelijking (18 patiënten met OCS versus 19 patiënten met depressie versus 29 gezonde vrijwilligers) met de 'task switching' taak. Dit experiment is beschreven in **hoofdstuk 6**. 'Task switching' meet – zoals eerder uiteengezet – cognitieve flexibiliteit buiten een motivationele context. We onderzochten zowel groepsverschillen in gedrag (dat wil zeggen in neuropsychologische uitkomstmaten op de 'task switching' taak) als in hersenactiviteit - op switchen. De resultaten laten zien dat er subtiele gedragsverschillen werden gevonden tussen de groepen met OCS en depressie, geassocieerd met differentiële prefrontale-striatale activaties op neuraal niveau. De betekenis van deze resultaten is dat cognitieve flexibiliteit dus afwijkend is in en tussen patiëntgroepen met OCS en met depressie - ook buiten een motivationele context.

De bovenbeschreven experimenten in hoofdstuk 3, 4, 5 en 6 zijn alle verricht met behulp van *functionele* MRI die hersen*activiteit* in kaart brengt. Met MRI kunnen evenwel ook vergelijkingen gemaakt worden tussen hersengebieden op *structureel* niveau, dat wil zeggen verschillen in *volumina* van hersengebieden kunnen worden gemeten. **Hoofdstuk 7** beschrijft

een studie waarin een groot aantal (N=55) medicatievrije patiënten met OCS vergeleken werd met een groot aantal gezonde vrijwilligers (N=50) op verschillen in volumina van diverse hersengebieden in zowel de witte als grijze stof. De specifieke gebruikte analysetechniek hiervoor heet 'voxel-based morphometry' (VBM). Patiënten met OCS bleken verminderde volumina in diverse hersengebieden te hebben, vergeleken met de gezonde controlegroep. Bovendien werden er associaties gevonden tussen abnormale volumina in bepaalde hersengebieden en specifieke symptoomdimensies (zie eerder) binnen de OCS groep. Interessant daarbij was dat het in veel gevallen ging om OCS-gerelateerde afwijkingen in dezelfde hersengebieden, als die in de fMRI experimenten met de OCD groep waren gevonden – zoals de OFC, andere PFC gebieden, posterieure gebieden en het striatum.

Hoofdstuk 8 van dit proefschrift behelst de samenvatting en de algemene discussie, waarin de gevonden resultaten uit onze experimenten besproken en geïnterpreteerd worden. De resultaten van dit proefschrift hebben namelijk implicaties voor verdere theorievorming omtrent OCS, depressie, en omtrent de co-morbiditeit van OCS en depressie. Inmiddels zijn er in de literatuur nieuwe pathofysiologische modellen voor OCS en depressie gepresenteerd, waaraan de resultaten van onze experimenten al hebben bijgedragen. Tot slot worden in hoofdstuk 8 sterke en zwakke methodologische aspecten van onze studies besproken, en worden aanbevelingen voor toekomstig onderzoek gedaan.

Conclusies

Op basis van de resultaten van de experimenten beschreven in dit proefschrift, kunnen de volgende conclusies worden getrokken: **1.** PFC-striatale hersengebieden vormen – zoals gehypothetiseerd – het neurale substraat van de door ons geïntroduceerde 'reversal learning' taak, **2.** patiënten met OCS vertonen gedragsafwijkingen evenals verminderde OFC-striatale activiteit tijdens 'reversal learning', **3.** OCS en depressie worden gekenmerkt door differentiële neurale disfuncties tijdens 'reversal learning', **4.** patiënten met OCS en depressie vertonen disfunctionele en differentiële PFC-striatale activiteit tijdens 'task switching', **5.** OCS wordt gekenmerkt door symptoomdimensies-specifieke afwijkingen in volumina van hersengebieden en **6.** de gevonden resultaten bij patiënten met OCS en depressie wat betreft gedrag en hersenactiviteit tijdens cognitieve flexibiliteit dragen bij aan nieuwe theorievorming over het neurale substraat van deze psychiatrische stoornissen.

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Curriculum Vitae

Peter Lorin Remijnse werd geboren op 3 februari 1972 te Den Haag. Hij bezocht het 's Gravenhaags Christelijk Gymnasium 'Sorghvliet' tussen 1984 en 1990. Hierna studeerde hij geneeskunde aan de Vrije Universiteit te Amsterdam. Het doctoraalexamen behaalde hij in 1995, het artsexamen in 1998 ('cum laude'). Vervolgens werkte hij enkele jaren als assistent-geneeskundige-niet-in-opleiding (agnio) op de afdelingen Cardiologie en Interne Geneeskunde van Ziekenhuis Amstelveen, en op de afdeling Interne Geneeskunde van het VU Medisch Centrum te Amsterdam. Na een kort agnio-schap in de psychiatrie, startte hij in 2001 met de specialisatie psychiatrie bij GGZ Buitenamstel in Amsterdam (respectievelijke opleiders: prof. W. van Tilburg, prof. A.T. F. Beekman en prof. A.J.L.M. van Balkom). Tijdens dit specialisatie-traject verrichtte hij promotie-onderzoek, waarvan het resultaat voor u ligt. In 2008 registreerde hij zich als psychiater. Op dit moment werkt hij als psychiater bij de polikliniek 'Psychosomatiek' van GGZ inGeest te Amsterdam, en bij Psyon – samenwerkingsverband voor psychiatrische expertise en rapportage. Hij deelt zijn leven met Andrea Ruissen.

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