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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