Moving the brain: Neuroimaging motivational changes of deep brain stimulation in obsessive-compulsive disorder
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Citation for published version (APA):

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In the introduction we presented Mrs. D., suffering from typical OCD symptoms with severe contamination obsessions and cleaning compulsions, as well as from smoking addiction and chronic overeating. We observed analogies between these behaviors, and more important, they all appeared to respond to DBS treatment. The main aim of this thesis was to understand how DBS is able to alleviate obsessive-compulsive and addictive behaviors together. To answer this question we have considered the behavioral addiction paradigm with its associated circuits that are involved in motivation. We used functional and nuclear imaging (fMRI en SPECT), electroencephalography (EEG) and peripheral dopamine measures to investigate if OCD patients have abnormalities in these pathways, and if they can be reversed with DBS.

Summary of findings

**OCD is related to frontostriatal reward dysfunction**

In the first part of this thesis we confirmed that OCD is related to dysfunction of the motivational network. OCD patients with cleaning or checking compulsions displayed blunted activity of the nucleus accumbens (NAc) and insula when they were anticipating monetary rewards, which was most pronounced in
treatment-resistant OCD patients who subsequently were successfully treated with DBS. Blunted anticipatory reward activation in the NAc is also found in addiction, and this finding thus supports the conceptualization of OCD as a disorder of behavioral addiction. In chapter 3 we examined risk-attitude and the neural correlates of risk processing in OCD. Patients with doubt and checking symptoms were more risk averse than patients with other OCD symptoms. Risk-related activity in the insula was higher in risk averse patients, whereas it was higher in risk seeking controls, suggesting that the insula signals value in healthy controls but signals risk in patients with OCD. These neuroimaging findings suggest that patients with OCD may not be able to recruit the NAc and insula properly for the processing of healthy rewards because of excessive recruitment related to a dependence on precautionary obsessive-compulsive behaviors.

DBS restores frontostriatal network activity

Next, we examined if DBS for OCD is able to reverse these patterns of aberrant activity in the motivational network. In chapter 4 we first reviewed PET imaging studies of DBS in OCD and other mental disorders. This review indicates that DBS of the ventral striatum or internal capsule is able to modulate activity in the frontostriatal network, especially activity in the nucleus accumbens and prefrontal cortex, but also in the amygdala, insula and thalamus. These frontostriatal-limbic changes may be therapeutic for both OCD and major depressive disorder by restoring goal-directed behavior and improving emotional, cognitive and behavioral control. In chapter 5 we report how we developed the first application of fMRI in DBS implanted patients to enable us to examine local and network changes more precisely. In chapters 6 and 7 we measured frontostriatal brain activity with functional MRI and EEG in OCD patients when they were stably treated with DBS and after 8 days of DBS discontinuation. We found that effective DBS for OCD restored NAc reward responses and normalized connectivity between the NAc and frontal cortex. In addition, DBS normalized frontostriatal and insula activity related to inhibitory control. Finally, DBS reduced excessive EEG activity in the frontal cortex when patients were viewing OCD-provoking pictures. DBS induced an average symptomatic change of 50% that was strongly correlated to frontostriatal network changes.
These results suggest that DBS interrupts a pathological frontostriatal loop allowing a shift from excessive processing of disease-related towards behaviorally relevant stimuli and restoration of goal-directed behavior.

**DBS induces striatal dopamine release**
Given the role of dopamine in frontostriatal reward processing and inhibitory control, restoration of these circuits by DBS suggests that it may also reverse dopaminergic abnormalities in OCD. Our review of neuroreceptor imaging studies in chapter 8 confirmed dopaminergic abnormalities in OCD, in combination with serotonergic and glutaminergic abnormalities. Dopaminergic changes were most prominent in the ventral striatum and corresponded with SRI-induced symptom improvement. Consistently, in chapter 9 we found that effective DBS in the ventral striatum corresponded with dopaminergic changes as well. Patients on active stimulation compared to DBS discontinuation for 8 days, had improved symptom scores along with lower availability of the SPECT radiotracer \([^{123}\text{I}]\text{IBZM}\) that binds to striatal D\(_{2/3}\) receptors. DBS was also related to increased blood levels of the dopamine/noradrenaline metabolite HVA. These central and peripheral measures suggest that effective DBS for OCD induces striatal dopamine release.

**In search of new targets for compulsivity**
In the final part of thesis we explored the most optimal DBS target for OCD. A review of all published efficacy studies (chapter 10) revealed that 62% of 94 OCD patients could be considered responders to DBS, with variable results depending on the target that was used. It appears that targets within the ventral striatum are effective for obsessions, compulsions, depression and anxiety, whereas DBS at the subthalamic nucleus predominantly affects compulsions. In the final chapter of this thesis we explored new potential DBS targets by distracting neuroanatomical information from published case-reports of obsessive-compulsive symptoms related to circumscribed brain injuries. We searched for brain circuits related to a broader manifestation of repetitive, habitual or stereotyped behaviors, which we defined as compulsivity. This search supported our previous findings of frontostriatal involvement in compulsivity, specifically the basal ganglia, frontal cortex and connecting...
internal capsule. Brain lesions were related to prototypical OCD, but also to symptoms within the broader compulsivity spectrum such as Tourette syndrome, hoarding, compulsive eating, and impulse control disorders. In some cases, symptoms resolved after lesions in the dorsal striatum and internal capsule, suggesting these may be effective DBS targets for compulsivity.

General discussion and future directions

Dysfunction of motivational network in OCD: evidence for behavioral addiction?

In this thesis we found evidence in support of the behavioral addiction model for OCD. Patients with OCD showed greatly attenuated reward anticipation activity in the ventral striatum (bilateral NAc) compared to controls (chapter 2), which matches up remarkably with findings in drug and non-drug addiction. Blunted reactivity of the ventral striatum in anticipation to monetary gain has been related to addiction of alcohol (Wrase et al., 2007), nicotine (Martin-Soelch et al., 2003; Bühler et al., 2009) cannabis (van Hell et al., 2010), and to non-drug addictions, e.g. pathological gambling (Reuter et al., 2005; de Greck et al., 2010; Balodis et al., 2012) and binge-eating disorder (Balodis et al., 2013). Conversely, disorder-specific stimuli increase activity of the ventral striatum in drug addiction (Diekhof et al., 2008), pathological gambling (Hollander et al., 2005) and food addiction (Stice et al., 2010). Likewise, blunted striatal responsiveness in our study is paralleled with increased activity in response to OCD-provoking stimuli in previous studies (reviewed in: Menzies et al., 2008).

In healthy humans, the ventral striatum is activated particularly in anticipation of a reward, and in proportion with its expected value (Knutson et al., 2001). This suggests that the ventral striatum is less responsive when recruited for healthy (monetary) reward processing due to its bias toward drugs in addiction, and due to its bias to disease-specific stimuli in OCD and other behavioral addictions.

Our second finding that links OCD with dysfunction of the motivational network is the involvement of the insula. OCD patients displayed diminished reward anticipatory activity in the left insula, especially patients
with contamination fear OCD (chapter 2). The insula is implicated in reward processing by integrating reward and motivation with autonomic and visceral information (Naqvi and Bechara, 2009). The insula is activated during processing of negative rewards in healthy individuals (Liu et al., 2011), during negative feelings of craving in addiction (Koob and Volkow, 2010) but also during anticipation of food, especially in obese individuals (Del Parigi et al., 2002). We revealed exaggerated insula recruitment during risky choices in risk-averse OCD patients, which contrasted with similar patterns in healthy risk-seeking participants (chapter 3). Previous fMRI studies found increased activation of the left insula in OCD patients when viewing aversive pictures (Schienle et al., 2005) and in OCD patients with contamination fear when viewing pictures depicting washing or contamination (Philips et al., 2000). The insula may thus be excessively activated during obsessive-compulsive symptoms, due to a bias to disgust-related stimuli and aversion of risk and negative outcomes, compromising its recruitment for healthy rewards.

It must be noted that some of our neuroimaging findings in OCD diverge from those in drug and non-drug addictions. During reward receipt we found similar frontostriatal activation between patients and controls (chapter 2). In contrast, a more generalized pattern of diminished frontostriatal reward processing is usually found in drug addiction and other behavioral addictions during both anticipatory and outcome phases (Hommer et al., 2011; Balodis et al., 2013). This suggests that OCD patients have primarily difficulties in estimating the value of a potential rewarding situation, whereas in other forms of addiction consummatory reward processing is also impaired.

Finally, the motivational network may be differentially affected depending on the subtype of OCD. Our results suggest that patients with doubt and checking compulsions are more risk-aversive than other subtypes (chapter 3) and have less blunting of insula and NAc activity during reward anticipation than patients with cleaning compulsions (chapter 2).

**Does effective DBS for OCD modulate the frontostriatal reward circuitry?**

In our DBS imaging experiments (chapters 6 and 7) we demonstrated that effective DBS for OCD restored healthy responses in reward and inhibitory control networks, normalized frontostriatal communication and reduced
excessive frontal responses to aversive OCD-stimuli. Also previous PET imaging studies indicate specific modulation of striatal and prefrontal regions cortex with DBS for OCD (chapter 4). In our study, DBS-related frontostriatal modulation specifically correlated with changes in obsessive-compulsive symptoms suggesting that this may reflect a direct therapeutic mechanism. In agreement, pathological frontostriatal hyperconnectivity in OCD has consistently been replicated in resting-state imaging studies, which correlated with OCD severity (Sakai et al., 2010; Harrison et al., 2009 and 2012). Further studies should examine whether frontostriatal connectivity patterns in OCD patients can predict response to DBS or even guide effective targeting.

Our studies also suggest that DBS for OCD restores insula activity. In chapter 8, we show that effective NAc DBS for OCD normalizes inferior frontal/insula activity during inhibitory control. One previous study has found changes in insula metabolism after internal capsule DBS for OCD (van Laere et al., 2006). In addition, NAc DBS in animals evoked BOLD activity changes in the insula (Knight et al., 2013). Future research should focus more on insula changes of DBS for OCD, for instance by using tasks from previous imaging findings of insula dysfunction in OCD related to abnormal processing of disgust (Schienle, et al., 2005) or risk aversion (chapter 3).

We did not explicitly examine DBS effects on networks involved in the regulation of mood and anxiety. Although we clearly observed that DBS improved mood and anxiety during our experiments, frontostriatal changes were statistically not directly correlated with changes on anxiety and depression scales. In previous DBS imaging studies, changes of the limbic-prefrontal anxiety pathways have been reported after NAc DBS for major depressive disorder (Bewernick et al., 2010) but not for OCD (chapter 4). Future EEG and fMRI studies should also use paradigms that probe affective changes to examine if an improved frontostriatal function in OCD is accompanied by alterations in mood and anxiety networks.

Although brain responses in patients normalized to patterns measured in healthy controls, these changes also occurred in three non-responders to DBS (less then 25% improvement on the YBOCS). We could therefore speculate that restored activity in motivational and inhibitory control networks enables most patients to overcome their OCD symptoms, but some patients fail to profit
from these neural changes. New studies may focus more on how frontostriatal changes enable patients to overcome compulsive responding. For example, it has been suggested that obsessive-compulsive symptoms are mediated by a disrupted balance between flexible, goal-directed action in the ventral striatum and habitual control in the dorsal striatum (Gillan et al., 2012), similar to addiction (Koob and Volkow, 2010). Future studies could therefore include paradigms that probe habitual versus goal directed responding, to test whether these measures correlate with frontostriatal changes of DBS and mediate its anti-compulsive and anti-addictive effects.

**How does DBS change frontostriatal function?**

We may be able to infer from our imaging results some further speculations on the mechanism of action of DBS. DBS applied to the ventral striatum induced changes both locally and more widespread in frontal cortical regions (chapters 6 and 7). How could we explain these widespread changes and what does this mean for the optimal OCD target? Symptom improvement in our OCD patients was most prominent when we stimulated at the border of the NAc core and the anterior limb of the internal capsule (Denys et al., 2010). This part of the internal capsule contains white matter fibers that connect the NAc and prefrontal cortex and stimulation of these fibers may thus explain the combination of local and prefrontal changes. Animal models support this mechanism, suggesting that DBS preferentially modulates white matter network fibers (Schmuckermair et al., 2013; McIntyre et al., 2004 and 2010) and that most effective DBS targets involve stimulation of these fibers (Lehman et al., 2011; Van Dijk et al., 2013). Stimulation of the internal capsule may have led to afferent modulation of the NAc and to frontal changes via antidromic or efferent thalamo-cortical modulation. An alternative mechanism of action that could be inferred from our studies is that local stimulation of the ventral striatum modulates network communication. In chapter 6 we demonstrate with resting-state fMRI that effective DBS in OCD results in a reduction of pathological hyperconnectivity within the frontostriatal network. In the same patient group we recently confirmed this finding with a resting-state EEG experiment that suggested DBS restores normal communication from the cortex to the striatum (Smolders et al., 2013).
In summary, effective DBS for OCD appears to depend on stimulation of fronto-striatal white matter fibers that restores accumbal and frontal cortical function and restore network communication from cortex to striatum. These proposed mechanisms support the internal capsule as an effective DBS target for OCD.

**How does DBS modulate dopamine release?**

In the last experiments of this thesis we showed that effective DBS for OCD induced striatal dopamine release, as was demonstrated by lower availability of dopaminergic D_{2/3} receptors in the putamen and increased blood levels of HVA (chapter 9). It is not possible to validate these findings against existing human data because neurotransmitter changes of striatal stimulation have only been investigated in animals. Following DBS of the NAc shell in rats, postmortem tissue concentrations of dopamine were increased in the stimulated region (Sesia et al., 2010), and decreased in the prefrontal cortex (Falowski et al., 2011). However, in our study we did not stimulate the NAc shell, but rather the NAc core and adjacent internal capsule. Stimulation of this target in rats was associated with dopamine release in the OFC but not in the stimulated area (van Dijk et al., 2011 and 2012). Although it is still difficult to reliably measure dopamine receptors in the human frontal cortex, it would be of interest for future studies to explore cortical effects of DBS using extrastriatal neurotracers, such as \(^{[18}F\)fallypride or \(^{11}C\)FLB.

We used a dopaminergic neurotracer with affinity to D_{2} receptors, so our results likely reflect DBS effects on indirect striatal D_{2} expressing pathways only. In these indirect D_{2} pathways, excitatory glutaminergic cortical input into the striatum is assumed to result in net GABA-ergic inhibition of output structures, whereas on the contrary, this will cause net output excitation in direct D_{1} pathways. Our findings of DBS-induced dopamine release in indirect D_{2} pathways may thus reflect inhibitory striatal output on excessive cortical activity, resulting in improved control of obsessive-compulsive symptoms. It would be interesting for future studies to investigate if DBS-induced dopamine release in indirect D_{2} pathways is accompanied by decreases in direct D_{1} expressing pathways, e.g. using the D_{1} receptor tracer \(^{11}C\)-SCH23390. Moreover, further studies are needed to discern whether this inhibitory output caused by dopamine release, is accompanied by GABA-ergic increases and glutamin-
ergic decreases. GABA-ergic and glutaminergic changes could be measured with $^1$H magnetic resonance spectroscopy (chapter 8), though it is currently unknown if this technique can be safely applied in implanted patients. Finally, imaging studies should also apply serotonergic neurotracers to clarify whether stimulatory dopamine release in this group of therapy-refractory OCD patients primarily compensates dopaminergic or serotonergic deficits.

**Compulsivity due to brain injuries: potential new DBS targets?**

In chapter 11 we provide additional neuroanatomical information from case reports of acquired brain lesions, supporting that compulsive behaviors most often originate from basal ganglia pathology, predominantly the head of the caudate and putamen. Frontal cortical lesions were more often related to compulsivity combined with personality changes and severe cognitive decline, and we found no case reports describing exclusive involvement of the anxiety-related limbic system. Moreover, most patients with newly acquired OCD did not experience anxiety. Rather, they often experienced other forms of compulsive and repetitive behaviors, like tics, compulsive grooming, hoarding, eating or impulse control disorders. These neuroanatomical data thus support the concept of compulsivity that can be defined as the propensity to habitual and repetitive behaviors and seems primarily related to basal ganglia dysfunction. The National Institute of Mental Health (NIMH) has recently urged researchers to develop new ways of classifying mental disorders based on observable behaviors that can be linked to brain circuits rather than starting with an illness definition (www.nimh.nih.gov/research-priorities). Our neuroanatomical data might support the concept of compulsivity, linked to basal ganglia dysfunction, as one of these potential classifications.

Resolution of compulsivity with lesions in the putamen and internal capsule supports the notion that striatal areas would be the most likely candidates for DBS treatment of compulsivity. In agreement, specifically compulsions resolved after putamen infarction (Fujii et al., 2005) and DBS of the subthalamic nucleus was found to primarily affect compulsions (Mallet et al., 2008). Induction or resolution of compulsivity after putamen and caudate pathology matches neuroimaging findings of pathological hyperactivity and increased volumes of these basal ganglia structures in OCD (Radua et al., 2010, Whiteside et al., 2004,
Rotge et al., 2008). The head of the caudate and putamen may thus be effective DBS targets for treatment of OCD. Direct stimulation of the putamen has never been tried and would probably induce too many side effects. DBS of the caudate was tried in 57 epilepsy patients using low frequency stimulation for excitatory effects on the caudate, but higher inhibitory frequencies, that would also be needed to reduce caudate hyperactivity in OCD, induced seizures, bradykinesia, and sensory perception or autonomic changes (Chkhenkeli et al., 2004). Nonetheless, a case-report describes high-frequency caudate DBS in two OCD patients with positive effects on mood and OCD, but no explicit report of side effects (Aouizerate et al., 2009). Moreover, current striatal DBS targets for OCD are often located where the head of the caudate and the anterior portion of the putamen meet (Greenberg et al., 2010; Goodman et al., 2010).

**DBS for other disorders of frontostriatal dysfunction?**

Although not investigated explicitly in this thesis, we could speculate about the implication of our results for the understanding and treatment of compulsivity in other mental disorders. Similar to the findings of this thesis, compulsivity in addiction and eating disorders have been related to blunted ventral striatal activation in anticipation to rewards (Hommer et al., 2011), to altered frontostriatal connectivity (Volkow et al., 2011; Upadhyay et al., 2010; Stoeckel et al., 2009), and to increased frontal low-frequency oscillations (Knyazev, 2012). Normalization of frontostriatal dysfunction by DBS therefore suggests its potential for treatment of these other addiction-related disorders.

Our study of brain injury related case-reports, suggests that DBS may be explored for disorders within a broader compulsivity spectrum. Aberrant frontostriatal activation has been related to repetitive behaviors in autism (Dichter, 2012), and very recently DBS was tried for the first time in an autistic patient with self-injurious behaviors (Sturm et al., 2012). The exact neurocircuitry of compulsivity in autism however is still greatly unknown and before expanding the application of DBS to autistic patients, the effects of various stimulation targets should be tried in animal models of compulsive behaviors in autism (Lewis et al., 2007; Schwartz et al., 2013). Even more hypothetical, frontostriatal dysfunction may be tried to target with DBS in animal models of
compulsivity in schizophrenia (Klein et al., 2012).

Finally, in a cohort of 100 Parkinson’s patients visiting our neuropsychiatric DBS unit we have observed that DBS targeted at the STN may have beneficial effects on compulsivity in these patients (unpublished), which is supported by a recent prospective study in a cohort of 67 Parkinson’s patients (l’Hommée et al., 2012), and by a study showing beneficial effects of STN DBS on compulsive behaviors in OCD (Mallet et al., 2010). Although this thesis did not provide neuroanatomical evidence for direct STN involvement in OCD pathology, STN DBS may be effective for compulsivity by normalizing frontal hyperactivity through the indirect inhibitory frontostriatal pathway (chapter 5). The role of the STN in compulsivity could be further explored in future neuroimaging studies of STN DBS in Parkinson’s disease.

Methodological considerations

We must consider a few methodological issues when interpreting the results of our studies. The most important issues concern the relative small study populations, the acquisition and analysis of MR data, and our DBS ON/OFF study design.

The experimental design of our DBS imaging studies was extremely difficult for patients since we scanned them after 8 days of DBS discontinuation, which caused a full relapse of OCD, anxiety and depression in most patients (chapters 6, 7 and 9). Being confronted with this design, only 16 out of a total of 40 patients agreed to participate. Moreover, we had to exclude even more participants for each individual experiment when no second scan was available, when participants moved > 4 mm during scanning, when they executed less than 50% of the task trials of the experiments, and when deviating electrode placement disturbed the signal in the NAc ROI. The relatively small sample sizes that we were left with created some limitations. In our fMRI study in non-implanted OCD patients (chapter 2) we scanned 18 patients and found blunted NAc anticipatory reward responses compared to controls, which was more pronounced in contamination fear OCD patients relative to harm-avoidant patients. However, we were only able to repeat this experiment in 9 DBS implanted patients (chapter 6), which was too little to investigate differential
DBS effects on NAc reward processing in OCD subtypes, and neither could we investigate the contribution of symptom subtypes to our other imaging findings.

We primarily analyzed changes in pre-defined region of interests (ROIs), such as the ventral striatum (reward experiment chapter 6), the ventral striatum and frontal cortex (resting-state experiment chapter 6), the right striatum and right inferior frontal cortex/insula (inhibitory control experiment chapter 7) and putamen and caudate (SPECT experiment chapter 9). These ROIs were based on strong a-priori hypotheses regarding the expected frontostriatal effects of NAc DBS, and also on prior results in OCD from our own study (chapter 2) or others (Zandbelt and Vink, 2010; Martino et al., 2008). However, due to the small sample size, our studies were underpowered to perform whole-brain analyses with appropriate correction for multiple comparisons, although we did confirm DBS-related changes in the frontostriatal circuit using an exploratory whole-brain analysis with liberal statistical thresholds. Nevertheless, the effects of DBS on regions outside the frontostriatal network should still be investigated in future whole brain analyses using larger study populations.

A potential limitation related to scan-acquisition, is the fact that we had to use strict safety rules for imaging of implanted patients, in order to minimize exposure of the DBS device to the pulsed radio-frequency field of the scanner (chapter 5). This may have limited neuroanatomical precision of our scans, as we could not use a brain scanner with a stronger magnetic field than 1.5 Tesla, we were restricted in the optimization of our imaging parameters and the electrode caused some artifacts on our brain images. Finally, we had to turn the DBS system off just before patients entered the scanner. However, symptom recurrence usually takes several days after the modulator has been switched off and our scans therefore still reflect neuronal activity related to the effects of DBS. Additionally, we used EEG to measure brain activity changes during concurrent stimulation, as well as SPECT scans for measuring stimulation-related dopaminergic activity.

Counter balancing ON and OFF conditions would have been a good method to correct for potential experience or learning effects between the two scanning sessions. However, our purpose was to examine the mechanism of action of therapeutic DBS. We therefore performed our first scan when patients
showed stable clinical improvement on active DBS treatment for at least one year. If we would have performed the first scan in half of the subjects after they had been off for one week and the second scan just after having turned the device on, the latter situation would very much differ from the therapeutic settings of DBS ON for one year. Therefore we chose to correct for learning effects by including a healthy control group that we scanned twice as well.

Although the changes in \( ^{123}\text{I} \)IBZM receptor binding that we measured in our SPECT study (chapter 9) clearly reflect dopaminergic changes, there is a great variety of opinions in the literature regarding the origins of the peripheral HVA measures that we performed concurrently. There is evidence that plasma HVA is produced primarily by brain dopamine neurons but to a lesser extent also by peripheral dopamine or central noradrenergic neurons (Davis et al., 1991). However, animal experiments indicate that plasma HVA changes after dopamine receptor agonists are the result of central and not peripheral effects (Davidson et al., 1987). As we compare HVA changes related to a central (DBS) intervention, we argue that peripheral effects are likely to be minimal in our study as well. However, we cannot completely rule out the possibility that DBS-induced HVA changes have also been influenced by central noradrenergic changes.

Finally, the non-stimulation condition of 8 days DBS discontinuation that we used in all of our imaging studies may not be a true baseline pre-treatment measure for comparison with stimulation conditions. In fact, DBS discontinuation in this group could have even induced some rebound effects (Ooms et al., under review). Future studies should try to obtain baseline imaging measures before implantation.

**Conclusion**

Do we now understand the origins of Mrs. D’s compulsive cleaning, as well as her addiction to smoking and eating, and how DBS enabled her to overcome these different behaviors? Our results suggest that these behaviors are rooted in compulsivity that can be restored with DBS. Mrs. D may have been unable to switch to healthy goal directed behavior for over 20 years because her motivational brain network was chronically compromised by a dependence on addictive...
and compulsive behaviors. DBS targeted at the accumbal area restores normal activity and dopaminergic neurotransmission in the motivational network, allowing Mrs. D. to control her unwanted behaviors and refocus on healthy rewarding stimuli. This thesis also raises important questions for future work. Does DBS of the same target also affect brain networks involved in anxiety and depression? How are other neurotransmitters involved in the effects of DBS, e.g. serotonin, glutamate and GABA? Does DBS induce similar changes in addiction or other disorders of compulsivity? This thesis may provide a platform for exploring these questions and for developing new potential therapeutic targets for treatment of OCD and other disorders of compulsivity.