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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Mrs. D., a 47-year-old married woman with refractory obsessive-compulsive disorder (OCD) was referred to the psychiatry department of the Academic Medical Center (AMC) for deep brain stimulation (DBS). For 26 years, she had been suffering from obsessions with dirt and compulsions consisting of cleaning her house. At the time of referral to our department, Mrs. D. would spend 22 hours per day vacuuming, sweeping and scrubbing her home, corresponding to a total of 38 points (extremely severe OCD) on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). Mrs. D’s obsessive-compulsive symptoms had never responded to standard psychotherapeutic or drug treatment strategies for OCD.

Secondly, Mrs. D. had a long history of smoking: for 22 years she smoked 35 cigarettes daily, which she tried to quit several times without success. Mrs. D. described parallels between her cleaning compulsions and smoking. Comparable to the satisfactory experience of smoking, she occasionally achieved a satisfactory feeling of having completed all of her cleaning compulsions perfectly which had become harder to achieve over time, and she experienced similar feelings of distress during abstinence of smoking and compulsions. A third problem was that Mrs. D. weighed 107 kg with a height of 170 cm, corresponding to a body mass index of 37 (obesity), due to excessive intake of high-calorie foods.
After extensive screening, Mrs D. was found eligible for experimental treatment of OCD with DBS. Two electrodes were implanted bilaterally in the nucleus accumbens and connected to a DBS stimulator. Three weeks after implantation, when stimulation of the electrode contacts was optimized, obsessive-compulsive symptoms started to improve. Mrs. D reported that she did not feel compelled to clean anymore and within 5 months she decreased the time spent on obsessions and compulsions from 20 hours to less than 1 hour a day, corresponding to a Y-BOCS score of 2 (subclinical OCD symptoms). She kept on cleaning her house daily, but now felt satisfied with only 30-60 minutes of cleaning and experienced that it was her own choice again.

Seven months after implantation, Mrs. D. realized that she wanted to be free of her unhealthy smoking habits as well, and that the smell and the taste of cigarettes had become unpleasant to her. She stopped smoking effortless without craving or experiencing withdrawal symptoms, despite the fact that her husband continued smoking 30 cigarettes a day. Two weeks after having quit smoking, Mrs. D. decided to also change her unhealthy eating habits. With the support of a dietitian, she started to lose one kg a week and lost 44 kg in ten months until she reached her goal of 71 kg (body mass index = 25). She reported that high calorie foods did no longer provide her any satisfaction and she developed a strong preference for healthy foods.

The 5-year follow-up evaluation (2013) shows that Mrs. D. now scores one point on the Y-BOCS, has never desired to smoke anymore, and has lost 55 kg since implantation (weight 61 kg, BMI 21). Mrs. D. attended the AMC three times during the past 5.5 years when she noticed being late for work due to the gradual return of former obsessions and compulsions, which each time turned out to be associated with a battery depletion and was rescued completely after replacement of the neurostimulator.

**How does DBS improve obsessive-compulsive and addictive symptoms?**

This prototypical case of DBS treatment for OCD raises an important problem related to our psychiatric diagnostic system. In the current version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR, American Psychiatric Association 2000), OCD is classified as an anxiety disorder because compulsive behaviors develop in response to anxiety. Mrs. D.’s smoking habits
can be classified in DSM-IV-TR as substance dependence, which is defined as persisting use of drugs despite problems, tolerance to the effect of the drug and withdrawal symptoms when use is reduced or stopped. Obesity due to chronic overeating is not considered as a mental disorder in DSM-IV-TR but bears addictive characteristics as well. How is DBS capable of changing behavior of three different disorders in one single patient?

Some researchers have proposed to view OCD as a disorder of behavioral addiction, with obsessions and compulsions being related to loss of voluntary control and a dependency on repetitious, self-defeating behavior (Holden, 2001; Denys, 2004). Based on analogies with addiction, several other non-drug related disorders have been proposed within this concept, for example pathological gambling, trichotillomania, skin-picking, compulsive eating, compulsive computer use, compulsive sexual behavior, and compulsive buying (Holden, 2001; Grant et al., 2006). When viewed as a behavioral addiction, patients may develop a dependency upon compulsive behaviors, because of their rewarding effects when performed perfectly or when compulsions reduce obsession-induced anxiety or distress. Similar to addiction, OCD patients develop a restricted behavioral repertoire at the cost of healthy rewarding actions and they are unable to switch to more adaptive, goal-directed behaviors. The concept of behavioral addiction may help to understand the profound behavioral changes across three different disorders following DBS treatment in our prototypical case. Though attractive, the behavioral addiction paradigm has never been tested thoroughly in OCD patients. As of yet, it has been suggested in literature a few times (Holden, 2001; Denys, 2004; Grant et al., 2006), but has not been adopted in DSM V, or being used as an experimental test paradigm.

In many other proposed disorders of behavioral addiction this concept is supported by substantial overlap in neuronal circuits with drug addiction. These include dysfunction of the motivational brain circuitry and abnormalities in the dopamine neurotransmitter system (Hollander et al., 2005; Grant et al., 2006; Belin & Everitt, 2008; Stoeckel et al., 2009; Upadhyay et al., 2010; Van Holst et al., 2010). The motivational brain network consists of neural pathways that connect frontal lobe regions with the basal ganglia (Alexander, 1986) or striatum (which can be defined as the part of the basal ganglia that receive
cortical input via the internal capsule). These frontostriatal pathways are involved in selecting adaptive behaviors that maximize rewarding outcomes and help avoiding negative ones. Within the frontostriatal network, dopaminergic neurons are important for detecting potential alerting and rewarding environmental stimuli that can be used for adaptive modulation of behavior (Schultz, 1998). Its ability to translate potential rewarding information into goal directed actions while inhibiting unwanted behaviors is why this network is critically linked to motivation (Frank, 2011).

Mrs. D. is engaged in a restricted set of obsessions and compulsions for 22 hours per day and she is unable to switch to more healthy goal-directed behavior, which may be reflected by dysfunctional motivational circuits. Could OCD then be regarded as a behavioral addiction with similar dysfunction of motivational brain circuits and does effective DBS for OCD modulate these circuits? Though frontostriatal abnormalities (Whiteside et al., 2004; Menzies et al., 2008; Radua et al., 2010), and alterations of the dopaminergic system (Figee et al., 2010) are indirect evidence for a dysfunctional motivational system in OCD, as of yet there is no direct evidence for altered reward or motivation proving the usefulness of behavioral addiction. Direct evidence would involve the manifestation of altered reward processes in OCD or in vivo demonstration of recruitment of different neuro-circuits that support these processes.

1. So, the first question we raised was whether we could discover disturbances in the motivational network in OCD. To that end, we tested two different paradigms in OCD patients and healthy controls. We adapted a monetary reward paradigm to evaluate reward-related motivation with functional magnetic resonance imaging (fMRI) (chapter 2), and a risk-decision making paradigm to assess how risk-attitude affects brain responses in OCD patients (chapter 3). We hypothesized that OCD patients would have impaired responses to monetary rewards in the motivational network, similar to drug and non-drug addictions. In addition we expected that OCD patients would be risk-aversive and have exaggerated brain responses to risk.

2. The second question we raised was whether we could change dysfunction of the motivational network with direct stimulation of the striatal-accumbal
area. We first reviewed previous DBS neuroimaging studies in OCD, addiction, Tourette’s syndrome and major depressive disorder (chapter 4). Only very few DBS imaging data exist and exploring results for different disorders may maximize our insight into brain changes underlying DBS. Unlike PET imaging used in these previous studies, fMRI would be able to detect rapid task-related and functional connectivity changes to probe motivational circuit function. However, fMRI was never applied in fully implanted patients because of safety issues. In chapter 5 we describe how we resolved these issues and developed the first application of fMRI in DBS. In chapter 6, we repeated the fMRI reward paradigm from chapter 2 but now in implanted patients, as a probe for local DBS effects on the nucleus accumbens (NAc). To probe motivational network changes, we also examined how DBS influenced resting-state patterns between the NAc and frontal cortex. In addition, we measured electro-encephalogram (EEG) activity in the frontal cortex when patients were viewing OCD symptom-eliciting pictures to evaluate DBS effects on frontal symptom regulation. Finally, in chapter 7 we used an inhibitory control paradigm to examine if DBS also affects pathways that are involved in the control of unwanted behaviors. We used these different imaging paradigms to test our hypothesis that effective DBS for OCD would be able to restore normal responses in the NAc and in the connected frontostriatal network.

3. The third question was whether we could observe adaptations of dopaminergic dysfunction in OCD following DBS in OCD patients. First, we reviewed molecular imaging studies to search for evidence of dopaminergic disturbances in OCD (chapter 8). Then, we examined dopaminergic changes of DBS in OCD using [¹²³I]iodobenzamide single photon emission computed tomography ([¹²³I]IBZM SPECT) and measurements of the dopamine/noradrenaline metabolite homovanillic acid (HVA) (chapter 9). We hypothesized that effective DBS would be associated with dopaminergic changes.

4. Finally, we explored new potential DBS targets for OCD. We first reviewed the efficacy of all current DBS targets for OCD (chapter 10). For our final chapter (chapter 11), we attempted to redefine OCD symptoms as compulsivity, which may better capture the manifestation of compulsive behaviors within
a broad range of psychiatric disorders. We used neuroanatomical information from published case reports of compulsivity linked to circumscribed brain injuries, to explore brain circuits of compulsivity that could be effectively modulated with DBS.