Moving the brain: Neuroimaging motivational changes of deep brain stimulation in obsessive-compulsive disorder
Figee, M.

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Since its introduction for treatment of therapy refractory obsessive-compulsive disorder (OCD) in 1998, it is estimated that deep brain stimulation (DBS) has been applied to 100 OCD patients worldwide using various brain targets. This paper reviews the effects of five different targets in OCD. The combined preliminary results suggest a 40 to 60% symptom decrease in at least half the patients. The efficacy, the time to response and the type of symptoms that improve depend on the target of choice. Although side effects occur, most of these are transitory and linked to specific stimulation parameters that may be changed. DBS research has opened up the opportunity to investigate how various symptom layers of OCD, such as anxiety, obsessions, compulsions, and depressed mood are related to brain activities within the frontostriatal network.

**Introduction**

Obsessive-compulsive disorder (OCD) is a chronic psychiatric disorder characterized by obsessions and compulsions. Obsessions are recurrent and disturbing thoughts causing anxiety or unease, such as the fear to be contaminated or to hurt someone, and the need for symmetry or perfectionism. Compulsions are acts with a ritual character that are performed to neutralize the anxiety
caused by the obsessions, such as cleaning, washing, checking, classifying or counting. Approximately two percent of the general population suffers from OCD (Fullana et al., 2009; Ruscio et al., 2010). Though three out of four patients experience an average symptom decrease of 35% with selective serotonin reuptake inhibitors or behavioral therapy, eventually, one out of ten patients cannot be helped with these regular treatments (Denys, 2006).

In case of severe treatment-refractory OCD that is incapacitating in all aspects of daily life, an OCD patient might be candidate for neurosurgical treatment. For decades, neurosurgeons have made lesions in the anterior limb of the internal capsule (ALIC) and the basal ganglia by means of classic, ablative neurosurgery (Lipsman et al., 2007). During the past two decades, a shift has occurred in the field of stereotactic neurosurgery since deep brain stimulation (DBS) became an established reversible and adjustable method for the alleviation of movement disorders. For the first deep brain stimulation to be performed, it was plausible to choose selective stimulation of the ALIC in order to imitate the effects of earlier capsulotomies. Since then more targets have been explored, and as OCD is one of the few diseases in psychiatry in which more functional data on neuroanatomical correlates are becoming available linking specific brain areas to its pathophysiology, DBS can nowadays be applied in OCD with a more rational approach. This article presents a review of various DBS targets in treatment refractory OCD.

**Efficacy of DBS in OCD**

At present (2010), approximately 100 patients with treatment refractory OCD have received experimental DBS treatment. Efficacy of DBS has been reported in eight double-blind controlled studies (Abelson et al., 2005; Nuttin et al., 1999; Nuttin et al., 2003; Greenberg et al., 2006; Okun et al., 2007; Mallet et al., 2008; Huff et al., 2010; Goodman et al., 2010; Denys et al., 2010) and six case studies (Mallet et al., 2002; Anderson et al., 2003; Fontaine et al., 2004; Aouizerate et al., 2004; Aouizerate et al., 2005; Franzini et al., 2010). Five targets have been used for DBS in OCD: the anterior limb of the internal capsule (ALIC), the ventral capsule/ventral striatum (VC/CS), the nucleus accumbens (NAc), the subthalamic nucleus (STN) and the inferior thalamic peduncle (ITP) (Fig. 1). Efficacy results are summarized in **table 1**.
Fig. 1. Deep brain stimulation targets in OCD

a, Coronal T2- weighted MRI at 3 mm anterior of the anterior commissure (AC) showing the nucleus accumbens (NAc), anterior limb of the internal capsule (ALIC), and ventral striatum (VS) or ventral caudate. b, Axial T2 MRI at the level of the AC showing the ALIC, VS, bed nucleus of the stria terminalis (BST), and inferior thalamic peduncle (ITP). c, Axial T2 MRI at 4 mm below the AC showing the subthalamic nucleus (STN) (Adapted from: de Koning et al., 2011)

**ALIC**

DBS in OCD was initiated in 1998 at the Karolinska institute in Stockholm where two patients received bilateral implantation in the ALIC, but the results were never published (personal communication S. Andreewitch). In 1999, the Leuven Group reported on bilateral ALIC DBS in four patients (Nuttin et al., 1999). In a subsequent paper, these four patients and two others were followed-up for a period of 21 months (Nuttin et al., 2003). Three out of four patients who completed the study experienced a ≥35% decrease of symptoms. An average symptom change of 40% was observed in the double-blind controlled part of the study in which the stimulator was put on and off. In 2005, the Michigan Group reported another study of implantation of electrodes in the ALIC of four patients. Patients were stimulated in a double blind way in a phase of four times three weeks with the stimulator on or off, followed by an open phase (Greenberg et al., 2006). Only one patient had a decrease of more than 35% in the double-blind phase. In the open phase, this patient progressed from severe disability to relatively normal life with 73% improvement over baseline in 8 months. Another patient who experienced only a 17% decline in the double-blind phase, showed improvement in the open phase with a final reduction
of 44% after completing an intensive behavioral treatment program. In the two patients who were considered responders, PET scans showed decreased activity of the orbitofrontal cortex. In another case study of ALIC DBS, a patient experienced 79% reduction of symptoms at three-month follow up (Anderson et al., 2003). At 10-month follow-up, the patient was able to return to work with compulsions in complete remission. These first studies show that the ALIC is a potential effective target for the treatment of therapy refractory OCD. However, the effects are modest and subsequent targets were localized in a more ventral position.

**VC/VS**

In 2006, an American-Belgian group published the results of ten patients with bilateral stimulation of the VC/VS (Greenberg et al., 2006). Eight of them were followed during three years after bilateral implantation. Over these three years, OCD symptoms improved from severe to moderate with a 30% decrease on average. Four of eight patients were considered responders with a symptom reduction of at least 35%. The Leuven Group, the American-Belgian Group and a group from the university of Florida published the combined results of VC/VS DBS in 26 patients (Greenberg et al., 2010). During this period, targeting within the VC/VS evolved from anterior to a more posterior area. The percentage of responders was 62% at 36 months with more effective stimulation at lower currents at the more posterior targets. A recent pilot study reported on VC/VS in six treatment refractory OCD patients (Goodman et al., 2010). Patients were stimulated at either 30 or 60 days post-surgery under blinded conditions. Four of six patients (67%) were responders with a decrease of at least 35% of symptoms. Interestingly, depressive symptoms improved significantly in all patients.

**NAc**

A German Group aimed at the right NAc as stimulation target in four OCD patients (Sturm et al, 2003). In three out of four patients, open stimulation resulted in nearly total recovery from both anxiety- and OCD symptoms at 24 to 30 months. The lack of effect in the fourth patient appeared to be caused by a displacement of the electrode in the caudo-ventral direction thereby missing
the target area. The same group subsequently published a double-blind study on unilateral right-sided NAc DBS in 10 OCD patients (Huff et al., 2010). A modest improvement of merely 10% was observed in the double-blind part of the study, which was initiated six months after the stimulator had been implanted. At one-year follow-up, five out of ten patients showed symptom decreases of more than 25%, and one patient more than 35%. Depression scores improved within one year, but anxiety failed to respond. Denys et al. published a study on 16 patients with NAc DBS for OCD in 2010. This study consisted of an open 8-month treatment phase, followed by a double-blind, crossover phase with randomly assigned 2-week periods of active or sham stimulation. It ended with an open 12-month maintenance phase. This resulted in an average 46% symptom decrease after 8 months. Nine of 16 patients were responders during follow-up. These nine individuals had a mean Y-BOCS score decrease of 72% (23.7 points). The average symptom decrease at 21 months’ follow-up for all 16 individuals was 48% (17.5 points). In the double-blind, sham-controlled phase (n=14), the mean Y-BOCS difference between active and sham stimulation was 25% (8.3 points).

A case study on one patient with OCD and depression reported a marked but delayed reduction of symptoms up to 52% at 15 months follow up (Aouizerate et al., 2004). An Italian group recently reported delayed effects of NAc stimulation in two OCD patients (Franzini et al., 2010). On average, symptoms improved by 38% after one year of stimulation in the first patient and after two years in the second patient with depression scores improving concomitantly.

**STN**

The STN was long known as an effective target for DBS in Parkinson treatment, and in some patients positive effects of STN stimulation on OCD symptoms were reported (Fontaine et al., 2004; Mallet et al., 2002). In 2008, the French Group reported on the efficacy of bilateral STN stimulation in 18 OCD patients (Mallet et al., 2010). STN DBS resulted in positive effects on compulsive behavior but appeared to have no effect on mood and global functioning within the first six months.
**Thalamic Peduncle**

In 2007, a case report in patients with OCD and major depression was published targeting the inferior thalamic peduncle (ITP) (Jimenez *et al.*, 2007). ITP stimulation showed a significant reduction of obsessive and compulsive symptoms. This finding was substantiated by the same Mexican group that described a 49% reduction of symptoms following open stimulation of the bilateral ITP in five patients with OCD (Jimenez-Ponce *et al.*, 2009).

In conclusion, DBS in ALIC, VC/VS, NAc, STN and ITP has shown to be effective in therapy-refractory OCD. Fifty-eight of 94 reported patients experienced a ≥35% reduction of obsessive-compulsive symptoms. Sixty-two percent of the patients are thus considered responders making DBS a promising technique. However, efficacy varied strongly, not only between different brain targets but also among patients targeted at the same area. Moreover, DBS at different targets appears to modulate different symptoms of OCD: VC/VS DBS improved mood, obsessions and compulsions whereas STN DBS predominantly improved compulsions. Another significant difference was the time to response between the different studies. In the earlier studies, Mallet *et al.* (2002) and Nuttin *et al.* (1999) reported an acute relief of anxiety and obsessions whereas in the later studies of Nuttin *et al.*, reduction of obsessions and compulsions was not observed until a week of stimulation (Nuttin *et al.*, 2003). Sturm *et al.* (2003) reported onset of clinical improvement a few days to several weeks after the beginning of the stimulation. In the study from Abelson *et al.* (2005), beneficial effects were seen within the three-week blinded study-period, whereas Mallet *et al.* (2008) reported improvement of symptoms after three months, Aouizerate *et al.* (2004) after nine months, and Franzini *et al.* (2010) only after one year up to two years.
<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Side</th>
<th>Target</th>
<th>(n)</th>
<th>Diagnosis</th>
<th>Mean Y-BOCS pre-operative</th>
<th>Mean Y-BOCS post-operative</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>Nuttin et al</td>
<td>Bilateral</td>
<td>Anterior limb of internal capsule</td>
<td>4</td>
<td>OCD</td>
<td></td>
<td>In 3 of 4 patients effects were found.</td>
</tr>
<tr>
<td>2003</td>
<td>Nuttin et al</td>
<td>Bilateral</td>
<td>Anterior limb of internal capsule</td>
<td>6</td>
<td>OCD</td>
<td></td>
<td>Cross-over phase: stimulation off: 32.3 ± 3.9; stimulation on: 19.8 ± 8</td>
</tr>
<tr>
<td>2003</td>
<td>Anderson et al</td>
<td>Bilateral</td>
<td>Anterior limb of internal capsule</td>
<td>1</td>
<td>OCD</td>
<td>34</td>
<td>7</td>
</tr>
<tr>
<td>2005</td>
<td>Abelson et al</td>
<td>Bilateral</td>
<td>Anterior limb of internal capsule</td>
<td>4</td>
<td>OCD</td>
<td>32.8</td>
<td>Open stimulation: 23; Double blind phase: 1 patient: at least 53% decrease, 1 patient: 17%, 2 patients: non-responders.</td>
</tr>
<tr>
<td>2006</td>
<td>Greenberg et al</td>
<td>Bilateral</td>
<td>Anterior limb of internal capsule</td>
<td>10</td>
<td>OCD</td>
<td>34.6 ± 0.6</td>
<td>Open stimulation: after 3 months: 25 ± 1.6; after 36 months (8 patients): 22.3 ± 2.1</td>
</tr>
<tr>
<td>2008</td>
<td>Greenberg et al</td>
<td>Bilateral</td>
<td>Internal capsule / ventral striatum</td>
<td>26</td>
<td>OCD</td>
<td>34.0 ± 0.6</td>
<td>Open stimulation: after 3 months: 21.0 ± 1.8; after 36 months: 20.9 ± 2.4</td>
</tr>
<tr>
<td>2010</td>
<td>Goodman et al</td>
<td>Bilateral</td>
<td>Internal capsule/ventral striatum</td>
<td>6</td>
<td>OCD</td>
<td>33.7</td>
<td>After 12 months: 18 ± 4.1</td>
</tr>
<tr>
<td>2003</td>
<td>Sturm et al</td>
<td>Unilateral</td>
<td>Nucleus accumbens (right)</td>
<td>4</td>
<td>OCD</td>
<td></td>
<td>3 of 4 patients almost complete remission of anxiety and OCD symptoms.</td>
</tr>
<tr>
<td>2009</td>
<td>Hoff et al</td>
<td>Unilateral</td>
<td>Nucleus accumbens (right)</td>
<td>10</td>
<td>OCD</td>
<td>32.2 ± 4</td>
<td>Open stimulation: after 12 months: 25.4 ± 6.7; Cross-over phase: stimulation on: 25.9 ± 6.4; stimulation off: 31.2 ± 5.0</td>
</tr>
<tr>
<td>2010</td>
<td>Denys et al</td>
<td>Bilateral</td>
<td>Nucleus accumbens</td>
<td>16</td>
<td>OCD</td>
<td>33.7 ± 3.6</td>
<td>Open stimulation: after 8 months: 18 ± 11.4; after 21 months: 16.2 ± 8.6; Double blind cross-over phase: stimulation on: 25.8 ± 9.3; stimulation off: 30.7 ± 4.5; stimulation off: 29.5 ± 11.4; stimulation on: 17.6 ± 10.1</td>
</tr>
<tr>
<td>2004</td>
<td>Aouizerate et al</td>
<td>Bilateral</td>
<td>Nucleus accumbens + caudate nucleus</td>
<td>1</td>
<td>OCD + depressive disorder</td>
<td>25</td>
<td>Open stimulation: after 12 months: 10; after 15 months: 14; after 27 months: 12</td>
</tr>
<tr>
<td>2010</td>
<td>Franzini et al</td>
<td>Bilateral</td>
<td>Nucleus accumbens</td>
<td>2</td>
<td>OCD</td>
<td>34</td>
<td>Follow up after 24-27 months: 21</td>
</tr>
<tr>
<td>2002</td>
<td>Mallet et al</td>
<td>Bilateral</td>
<td>Subthalamic nucleus</td>
<td>2</td>
<td>OCD + Parkinson</td>
<td>No Y-BOCS scores reported.</td>
<td>Patient 1: 58% improvement; patient 2: 64% improvement</td>
</tr>
<tr>
<td>2004</td>
<td>Fontaine et al</td>
<td>Bilateral</td>
<td>Subthalamic nucleus</td>
<td>1</td>
<td>OCD + Parkinson</td>
<td>32</td>
<td>Follow up after 1 year: 1</td>
</tr>
<tr>
<td>2008</td>
<td>Mallet et al</td>
<td>Bilateral</td>
<td>Subthalamic nucleus</td>
<td>18</td>
<td>OCD</td>
<td>32.3</td>
<td>Cross-over phase: stimulation on: 19 ± 8; stimulation off: 28 ± 7</td>
</tr>
<tr>
<td>2009</td>
<td>Jiménez et al</td>
<td>Bilateral</td>
<td>Inferior thalamic peduncle</td>
<td>5</td>
<td>OCD</td>
<td>35</td>
<td>At 12 months follow-up: 17.8</td>
</tr>
</tbody>
</table>

Table 1a: studies on deep brain stimulation in obsessive-compulsive disorder (OCD)
Mechanism of action of DBS in OCD

Since OCD has been associated with hyperactivity of the CSTC network (White-side et al., 2004), efficacy of DBS in OCD is most likely related to functional changes within this network. Electrical stimulation appears to be effective because it is assumed to induce a reset of network oscillatory patterns across the CSTC network (McIntyre and Hahn, 2009). Studies in OCD combining DBS treatment with neuroimaging methods have confirmed changes within the CSTC network (chapter 4). A positron emission tomography (PET) study in six OCD patients, which was carried out two weeks after implantation of electrodes in the VC/VS demonstrated DBS-induced activation of the orbito-frontal cortex (OFC), anterior cingulate cortex, striatum, pallidus and thalamus (Rauch et al., 2006). It is of note, however, that at that moment no clinical effects of DBS had been occurred. Post-operative functional magnetic resonance imaging (MRI) in one OCD patient with ALIC DBS showed increased activity in the frontal cortex and striatum compared to pre-operative brain activity (Nuttin et al., 2003). In the same study, clinical response after three months of continuous stimulation was related to a relative decrease of hyperactivity in the OFC as measured with PET imaging. A study by Abelson et al. (2005) showed decreased PET activity in the OFC after three to six weeks of ALIC DBS in two OCD responders, but not in the non-responders. In conclusion, sparse neuroimaging research suggests that DBS is effective in OCD because it induces functional changes, not limited to the target area, but observable in the complete CSTC network such as decreased activity in the OFC.

Side effects of DBS in OCD

Potential complications of DBS can arise (1) as a result of surgery (‘procedure related’), (2) due to the implanted device (‘device related’) or (3) due to stimulation or cessation of stimulation. A potential risk of surgery is intra-cerebral hemorrhage. This was reported in one out of ten patients by Greenberg et al. (2010), and in one patient in the sample of Mallet et al. (2008). One patient had a single intraoperative generalized tonic-clonic seizure following electrode implantation (Greenberg et al., 2006). Superficial surgical wound infection after implantation was reported in one of ten patients by Greenberg et al. (2010) and in two of sixteen patients by Mallet et al. (2008). In the latter study, the
implanted electrodes had to be removed. Other studies did not mention procedure-related complications. Device-related side effects were reported by Greenberg et al. (2010), where a break in the electrode and subcutaneous extension cable required a replacement in one patient. Also, patients have reported that they disturbingly feel the material within their body, to the extent that some patients wanted it to be removed (one out of four patients: Nuttin et al., 2003).

Side effects of stimulation can be divided in acute effects and effects of chronic stimulation. The latter can be subdivided in effects on mood, cognition and personality. Stimulation may cause various acute physical and mental side effects, most of which are transitory and disappear after adaptation of stimulation parameters. Okun et al. (2007) reported acute olfactory, gustatory and motor sensations which were strongly associated with the most ventral electrode positions, as well as physiological responses such as autonomic changes, increased breath rate, sweating, nausea, cold sensation, heat sensation, fear, and panic episodes. All effects reversed when DBS was stopped or parameters were changed. Acute mood changes during the first few days of stimulation of the ALIC and NAc have been reported by Okun et al. (2007), such as transient sadness, anxiety, euphoria or giddiness, sometimes to the extent of hypomanic symptoms (five of ten patients: Greenberg et al., 2006; two of ten patients: Huff et al., 2010; four of six patients: Goodman et al., 2010). Chronic mood improvement is an unintended but favorable side effect of DBS since most treatment refractory OCD patients suffer from comorbid major depression. Patients start to laugh, experience blissful feelings and describe that they can see the world more bright and clear within seconds after stimulation. Abelson et al. (2005) reported improvement of depression in one out of four patients while stimulating the ALIC. Decreased depression scores following VC/VS stimulation were found by Greenberg et al. (2006) and following NAc stimulation by Denys et al. (2010). Anti-depressive effects seem to be especially related to DBS of the ventral striatum (Greenberg et al, 2006; Denys et al, 2010; Goodman et al., 2010; Aouizerate et al., 2005; Franzini et al., 2010). No improvement of depression was found following STN stimulation (Mallet et al., 2008). Apart from transient diminished concentration and verbal perseverations (Greenberg et al., 2010), DBS has not been associated with cognitive decline. Some patients did complain about memory and language problems but this has not
been confirmed with neuropsychological tests. Gabriëls et al. (2003), Abelson et al. (2005), Aouizerate et al. (2005), Goodman et al. (2010) and Greenberg et al. (2006) reported no decline in cognitive and executive functioning. On the contrary, in the latter study, a group analysis revealed significant improvements in memory recall. Gabriëls et al. (2003) reported no major adverse or harmful personality changes after one year of DBS using the Minnesota Multiphasic Personality Inventory (MMPI). Neither patients nor family members did report changes in personality in the study of Abelson et al. (2005). Finally, remission of alcohol dependency (Kuhn et al., 2007) and unintended, effortless smoking cessation was observed following bilateral stimulation of the NAc (Kuhn et al., 2007; Mantione et al., 2010), supporting the idea of compulsivity with common circuitry in the processing of diverse rewards.

**Follow-up treatment**

Although studies indicate that DBS has the potential to significantly improve OCD symptoms in treatment refractory patients, they also show that complete remission rarely is achieved. In addition, patients often continue having problems in daily life functioning after DBS, even when most OCD symptoms have disappeared. Compulsions and avoidance behavior that have been around almost life-long in most therapy refractory OCD patients may have become habitual. Therefore, follow-up treatment with behavioral therapy may be essential to motivate patients implementing the effects of DBS in their daily lives (Abelson et al., 2005; Gabriëls et al., 2003; Mantione et al., under review). Studies are needed to investigate the additional efficacy of behavioral therapy following DBS.

**Conclusion**

DBS has been applied in therapy refractory OCD in an experimental setting for approximately a decade in approximately 100 patients. Stimulation of five different targets resulted in variable efficacy, from no response till almost complete remission of symptoms. Overall, DBS in OCD may effectuate a decrease of 40 to 60% of symptoms in at least half of patients. Stimulating the VC/VS improves mood, obsessions and compulsions, whereas STN stimulation only improves compulsions. Most side effects are transitory and reverse after
adaptation of stimulation parameters. The various stimulated brain areas, in many cases developed empirically, are still in agreement with recent theoretical findings on the neuroanatomy of OCD. DBS is probably effective in OCD because it modulates pathological activity within the CSTC network, resulting in a decrease of hyperactivity. DBS may be more effective when patients are followed up with behavioral therapy after surgery. DBS certainly has the potential of becoming preferential treatment for a specific group of seriously ill, therapy refractory OCD patients due to the small risk of the operation, the reversible nature of the technique, and the possibility to optimize treatment postoperatively.