Behavioral effects of deep brain stimulation of the subthalamic nucleus in obsessive compulsive disorder

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Abstract/Summary

Obsessive compulsive disorder (OCD) is one of the most disabling psychiatric disorder. About 10% of patients with OCD do not respond to pharmacological treatment. However, deep brain stimulation (DBS) has advanced as an alternative treatment. In 2002, two patients who suffered from co-morbidity of Parkinson’s disease (PD) and OCD were treated with DBS for their PD, with DBS-electrodes placed in the subthalamic nucleus (STN). Surprisingly, not only PD symptoms but also OCD symptoms were improved. This was the first time that patients with OCD were treated with DBS in STN and it was found to markedly improve their symptoms. When performing DBS in patients with OCD, as well as for treating PD, several side-effects have been observed. The side-effects can be both physical and psychological. In this project, the aim is to investigate the efficiency and side-effects of DBS in OCD, correlated with the position of the electrode in, or near, the STN. To address the aim, 10 published reports were analysed. It was found that all electrode positions reported resulted in great improvement of OCD symptoms. In fact, 88% of patients had significant improvement. There was no clear correlation between position of the electrode and number or type of side-effect. However, there was a trend that patients with the electrode placed in associative/limbic STN suffered from more side-effects. In conclusion, this project demonstrates that there might be a correlation between target for electrode stimulation and side-effects. It would be interesting analyse this closer, including additional electrode target areas, but also consider other possible explanations for the variety of side-effects caused by DBS for OCD.
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1. Introduction

Deep brain stimulation (DBS) has long been used as a treatment for Parkinson’s disease (PD). In 2002, Mallet et al treated two patients who suffered from both PD and obsessive-compulsive disorder (OCD) with DBS in the subthalamic nucleus (STN). What is interesting about the patients Mallet treated is, that except from the improvement for their PD, they had significant improvement in their OCD symptoms. Note that they were treated for PD, and the improvement of OCD symptoms was unexpected and not planned for. Both these patients suffered from severe OCD which they suffered from for 33 versus 16 years (Mallet et al. 2002). After this finding, DBS in STN for patients with severe treatment resistant OCD, has become more common. When DBS has been performed in patients with OCD, but also PD, it has become clear that there are several side-effects. Examples of these side-effects are depression, mood changes, hypomania, impulse control disorder, weight gain etc. These side-effects seem to vary depending on which part of the STN that is stimulated (Nassery et al. 2016). Since 2002, it has not only become more common with DBS in the STN as a treatment for OCD, but there have also been several trials with other targets often located close to the STN.

2. Aim

In this project the aim is to find out how the efficiency and side-effects of DBS are correlated with position of the stimulating electrode in, or near, the STN. For this to be addressed, the research field of DBS, mainly on OCD but also PD, of clinical assessments of patient material will be reviewed and results analysed.

3. Background

3.1. The basal ganglia function

The basal ganglia are a group of subcortical nuclei for which the main function is to control movements. Apart from motor control, the basal ganglia are also involved in behaviours, emotions, executive functions, and motor learning. The primary structures of the basal ganglia are located deep in the brain hemisphere and are known as the striatum and globus pallidus. The striatum includes the caudate and putamen. Additional structures important for the function of the basal ganglia are the STN located in the diencephalon, substantia nigra located in the mesencephalon, and the pedunculopontine nucleus in the pons (Lanciego et al. 2012). All basal ganglia structures have a limbic, motor, associative division. However, these divisions are not always possible to determine by specific anatomical boundaries (Nambu 2007).

3.1.1 The motor loop

The motor loop is the most studied of the three loops. The motor loop has three pathways, the direct which facilitates movement, and the indirect and hyperdirect which inhibit movement. The striatum receives glutamatergic input from the cerebral cortex and modulating dopaminergic input from the substantia nigra pars compacta (SNC). The input from SNC can be
both excitatory (direct pathway) or inhibitory (indirect pathway) depending on which receptor in striatum that receives the input. The dopamine receptor type mostly found in neurons of the direct pathway is called D1, and for the indirect pathway, it is called D2. In the direct pathway, the striatum sends GABAergic projections to the substantia nigra pars reticula (SNr) and globus pallidus interna (GPI). The inhibition of these two basal ganglia output structures results in disinhibition of ventro-lateral thalamus. When the thalamus no longer is inhibited, it can facilitate movement. Because neurotransmission from the GPI and SNr is tonic, this means that ventro-lateral thalamus is inhibited in the absence of input from the direct pathway. This inhibition of the thalamus needs to be overcome to initiate movement by activation of motor cortex. In the indirect pathway, the striatum inhibits the globus pallidus externa (GPe) via GABAergic projections, which result in disinhibition of the STN. The STN is a glutamatergic structure, and its disinhibition leads to excitation of the SNr and GPI. The hyperdirect pathway instead works by excitatory projections directly from the cerebral cortex to the STN, and have the same effect as the indirect pathway (Benzina et al. 2016, O’Callaghan & Lewis 2017). See figure 1.

Figure 1. Basic circuitry of the basal ganglia. The direct pathway contains the cortico-striato-GPi/SNr nerve tract, the indirect pathway, the cortico-striato-GPe-STN-GPIi/SNr pathway, and the hyperdirect pathway contains the cortico-STN-GPIi/SNr pathway. Filled arrows represent GABAergic projections and open arrows represent glutamatergic projections. Ctx = cerebral cortex, GPe = globus pallidus externa, GPI = globus pallidus interna, SNr = substantia nigra pars reticula, STN subthalamic nucleus, Str = striatum, Thal = thalamus (Nambu 2007).

3.1.2 The limbic loop
The limbic loop is not as well studied as the motor loop. However, similar structures are involved. For example, the ventral aspect of the striatum, called the nucleus accumbens (NAc) is active in the limbic loop. The dopaminergic input comes from the ventral tegmental area (VTA) instead of the SNc, while the GABAergic input comes from the ventral pallidum instead of the globus pallidus. In addition, the part of the STN that is of interest to the limbic loop is more ventro-medial than for the motor loop, and is called the limbic tip of the STN. The output structures project to the medio-dorsal thalamus rather than ventro-lateral which is more typical for the motor loop. The limbic functions of STN are important for reward and motivation (Benzina et al. 2016, O’Callaghan & Lewis 2017).
3.1.3 The cognitive/associative loop
The cognitive/associative loop differs anatomically from the other two loops. It is more well-known than the limbic loop. The cognitive/associative loop is proven to be important for directed behaviours, decision-making, and attention. Also, impulsivity is a feature of this loop. The cognitive/associative loop receives projections from the cerebral cortex to the anterior caudate in the striatum. The anterior caudate then projects via GABAergic neurons to the GPi and SNr, and these in turn inhibit the dorsal and ventral anterior nuclei of thalamus (Benzina et al. 2016, O’Callaghan & Lewis 2017).

3.2 Description of OCD
OCD a psychiatric disorder characterized by uncontrolled, unreasonable thoughts known as obsessions, and behaviours acting out these thoughts, known as compulsions (Rapinesi et al. 2019). Around 10% (Nuttin BJ et al. 2003, Ooms et al. 2014) of patient with OCD do not respond at all to cognitive behavioural therapy or medication and have a refractory version of the disorder. Approximately 40% to 60% of OCD patients respond to treatment but still have some persistent symptoms (Bout et al, 2020). The annual prevalence of OCD varies from 0.00065% (Taiwan) to 3.3% (southern India). Changes in diagnostic manuals might affect the diagnostic prevalence (Rapinesi et al. 2019).

3.2.1. Symptoms
Obsessions are thoughts that are unwanted, persistent, and anxious. The thoughts are also experienced as intrusive and not in line with what the person might want to think or is feeling at the moment. It can be said that the obsessions are random and impossible to stop from coming. The compulsions are often an attempt to manage the anxiety induced from the obsessive thoughts. Compulsions can be repetitive acts, mental or behavioural, that often are very time consuming (Rapinesi et al. 2019). There are different subtypes of OCD symptoms, for example aggressive, ordering, checking, washing, and more (Chabardès et al. 2013). OCD is often associated with impairment in motor impulsivity especially impaired ability to stop a movement when it is initiated (Voon et al. 2017).

These compulsions and obsessions can cause much anxiety and be so time consuming that it is debilitating. OCD is associated with both personal and professional disability, and affects societal and economic factors (Rapinesi et al. 2019). OCD tends to be chronic and is ranked one of the ten most disabling disorders. In a study on risk for suicide in patients with OCD, the results showed that with up to six years follow-up 13 of 218 patient attempted suicide (5.91%) and 18 patients displayed persistent suicidal thoughts (8.2%). Other studies have indicated higher frequencies of attempted suicide from 12.2% to 27%. The rate attempted suicidal in the general population in the US are 2%, as a compresence (Alonso et al. 2010).

3.2.2. Pathophysiology
The neurological mechanisms that cause OCD is not fully understood. What is known, however, is that there is some disruption of the orbito-fronto-striato-thalamo-cortical circuit engaging the basal ganglia. Studies has also found that there is increased activity in orbitofrontal cortex,
anterior cingulate cortex, caudate and thalamus (Lee et al. 2019b). The neurons in STN behave differently in people with OCD: STN neurons in patients with OCD tend to fire at a lower rate and display a bursting pattern. Patients with PD have a similar burst pattern in the STN to patients with OCD, both has burst activity in about 70% of the STN neurons. Different for OCD is that the bursts are more common in the STN in the left hemisphere (Piallat et al. 2011).

3.2.3. Treatment

As OCD can be very severe and disabling, treatment includes different types of medication as well as cognitive behavioural therapy. Recommended medication for OCD is different types on selective serotonin reuptake inhibitors, commonly referred to as SSRI’s, or the antidepressant clomipramine, which affects serotonin transporters. According to guidelines, the medication for OCD should be high dose and consistently taken for a long period of time. Sometimes antipsychotics are used as treatment for severe OCD (Rapinesi et al. 2019). Still about 40% to 60% of OCD patients do not respond fully to these treatments and still have an impaired quality of life (Alonso et al. 2010). Therefore, cingulotomy or capsulotomy has previously been used as additional treatment when medication and cognitive behavioural therapy has not given effect. As cingulotomy and capsulotomy are not reversible, DBS is a more favourable option (Goodman et al. 2010).

3.3 Deep brain stimulation (DBS)

DBS is a method that has been used since the 1950s and it is an established method for PD. There have also been several studies on DBS on different psychiatric disorders like Tourette syndrome, major depression and OCD (Blomstedt et al. 2013). DBS in a patient with OCD was first performed in 1999, where the anterior limb of the internal capsule was the target for electrode placement (Nuttin B et al. 1999). After that, the NAc, ventral capsule/ ventral striatum, bed nucleus of the stria terminalis, inferior thalamic peduncle (ITP) and STN has been studied as options for electrode positioning in DBS for OCD patients. The targets that have been proven to improve OCD symptoms are usually the same targets that are used for major depression and Tourette syndrome (Blomstedt et al. 2013).

When performing DBS, the brain target area is first identified with the stereotactic frame and magnetic resonance imaging. When the target has been identified, a burr is made a few centimetres from the midline in the precalculated trajectory. The electrode, which is transferred though the burr hole to the target area, has four contacts that is 1.5 to 3 mm in length, separated with 0.5, 1.5 or 4 mm. The diameter of the electrode is 1.27 mm (Blomstedt et al. 2013). Subsequently, a pulse generator connected to the electrode is placed under the collarbone to allow control of the electrical activity that is to be sent from the implanted electrode (Lee et al. 2019b). When inserting an electrode into the brain through deep surgery, there is always a risk of intracerebral haemorrhages. Large cohort studies have estimated the risk to 1% to 2% (Blomstedt et al. 2013).
3.4 DBS for OCD

The brain target areas for DBS electrode positions included in this project are the STN or structures close to STN. Close to STN will include the zona incerta (ZI), fields of Forel, and ITP. STN and areas nearby is not the only electrode target for DBS in OCD. Other common electrode targets are NAc ventral capsule/ventral striatum (Rapinesi et al. 2019) and anterior limb of the internal capsule (Guzick et al. 2020). The STN is, unlike the other electrode targets of DBS, familiar to surgeons because it has long been used for treating PD patients. In addition to the familiarity of the STN from PD studies, the non-motor aspect of the STN can be determined with MRI and biomarkers can be obtained during surgery with intraoperative MRI. The voltage for stimulations is lower in STN than for anterior capsule and striatum (Chabardès et al. 2013).

3.4.1. DBS electrode target areas

3.4.1.1. The subthalamic nucleus (STN)

The STN is located posterior to the entopeduncular nucleus, ventral to the cerebral peduncle and dorsally to the ZI (see figure 3). Most projections from the STN are glutamatergic (Guillaumin, 2020). The volume of the STN is about 138mm$^3$ (Lau et al. 2020), compared to the whole brain which is approximately 1100 cm$^3$ (Hanlon et al. 2016). STN is an important structure for the indirect and hyperdirect pathways of the basal ganglia, through which it exert powerful impact on regulation of motor, limbic and associative functions (Alexander et al. 1991).

3.4.1.1.1. Tripartite model

A major question is how the anatomy of the STN is correlated with its diverse functions. There are two major hypotheses aiming to explain this. One hypothesis claims that STN neurons engaged in the different loops are intermingled in the STN, while the other hypothesis claims that there are anatomical and functional subdivisions within the STN. The last model is referred to as the tripartite model (Janssen et al. 2017). In the tripartite model, the suggestion is three domains, the anterior-medial domain, which is associated with the limbic loop, dorso-lateral which is involved in the motor loop, and the ventro-lateral domain involved in the associative/cognitive loop (see figure 2). It has been proposed could be that the STN structure is more “intermingled” in rodent than in humans (Lambert et al. 2012, Alkemade et al. 2015). Studies on humans seem to give contradictive results when investigating proteins and mRNAs in the different domain, which has led to a difficulty in finding molecularly distinct domains in the human STN (Parent et al. 1996, Augood et al. 1999).
Figure 2. Schematic representation of the two main models of the anatomical-functional structure of the STN. Left, the tripartite model; Right, the intermingled hypothesis. In the tripartite model, the dorso-lateral division is the largest part and is associated with the motor loop. The smallest medioventral part is associated with the limbic loop and the ventral part is associated with the associative loop. In the intermingled model the neurons corresponding to the different functions are mixed.

The anteromedial part of the STN is probably the associative limbic part of STN according to Mallet et al, 2008. Based on functional studies and clinical results observed upon STN-DBS in patients, there is consensus about the tripartite model existing in humans even if some scientists imply more research is needed (Alkemade & Forstmann 2014). For example, in a review, the scientists conclude that there is more likely to be a regional specialisation without any direct borders in the STN (van Wijk et al. 2020). In this degree project, most of the articles studied assume that there is an anatomical-functional division of the STN that corresponds to the tripartite model.

3.4.1.2. Zona incerta (ZI)

The ZI is a small collection of grey matter in the deep brain, first discovered in 1877 by Auguste Forel, who described it as “an immensely confusing area about which nothing can be said” (Forel 1877). Now, more is known about ZI and its surroundings. The ZI is about 252 mm$^3$ and lies on the superior border of the STN but extending longer both caudally and rostrally. More specifically, the ZI lies imbedded in several white matter fibres, and is located ventral of the thalamus between the STN and the red nucleus. The white matter areas surrounding the ZI are still called the fields of Forel. Nowadays the fields are divided into; the H1 field of Forel which is the fasciculus thalamicus, the H2 field of Forel also known as fasciculus lenticularis and lastly the H field of Forel, a convergence for the ansa lenticularis and the fasciculus thalamicus. Except for the fields of Forel surrounding the ZI, there are several other white matter pathways, as it is encircled by a complex junction of fibres. Examples of these other pathways are cerebellothalamic, pallidothalamic, medial lemniscal and corticospinal tracts (Lau et al. 2020).

The major outputs from the ZI project to the thalamus, brainstem, spinal cord, and hypothalamus. Projections to thalamus are both inhibitory (GABAergic) and excitatory (glutamatergic). Projections to the basal ganglia, specifically substantia nigra, pedunculopontine tegmental nucleus and entopeduncular nucleus, are mostly glutamatergic and
hence excitatory. Some of the main inputs to the ZI come from the cingulate, frontal and parietal cortex, brainstem, and spinal cord. Input from the brainstem comes from several different nuclei. ZI also projects back to all nuclei in the brainstem that it receives input from, so called reciprocal projections. Further, the ZI receives and projects back to spinal cord, but not necessarily to the exact same area in the spinal cord. The ZI has a role in functions like arousal, shifting attention, posture and locomotion, and, in general the structure is involved in visceral activity (Mitrofanis 2005).

3.4.1.3. Inferior thalamic peduncle (ITP)
The ITP is a fibre bundle that connects the amygdala and the anterior temporal cortex with the medial thalamic nucleus. The fibre bundle is also known as the amygdalothalamic pathway or the extracapsular thalamic peduncle. It is one out of four fibre bundles in the ansa penduncularis. The other three fibre bundles included in the ansa penduncularis is the ansa lenticularis (globus pallidus to thalamus, subthalamus, red nucleus, and substantia nigra), amygdalohypothalamic fibres (amygdala to hypothalamus) and amygdoseptal fibres (amygdala and anterior temporal cortex to septal region). The ansa penduncularis enfolds around the cerebral peduncle where the four fibres tracts fuse together. The more exact location is superior to the anterior perforated substance and inferior and posterior to the anterior commissure. After the fibres fuse at the cerebral peduncle, the tract continues towards the amygdala going superior to the optic tract. The fibre tract then continues inferior to the putamen and globus pallidus and then partly crossing the anterior perforated substance nucleus accumbens and substantia innominate (see figure 3). The ansa peduncularis connections influence memory, decision-making, social abilities and learning (Li et al. 2020). The ITP is supposedly involved in selective attention. It has been found that the ITP is a promising DBS target for depression (Lee et al. 2019a).

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Figure 3. A schematic representation of the brain and some structures important for the understanding of DBS. STN = subthalamic nucleus, the zona incerta is located just anterior of the STN, ITP = inferior thalamic peduncle, NAc = Nucleus accumbens, VC/VS = ventral capsule/ ventral striatum, GPi = Globus pallidus interna, LHb = lateral habenula (Drobisz & Damborská 2019).
3.4.2. Side-effects upon treatment with DBS in OCD
Side-effects for DBS vary but common side-effects for DBS for OCD are emotional lability, anxiety, depression, and hypomania. Cases of suicidal thoughts have been observed after DBS treatment. When stimulation parameters are changed, or the battery runs low, irritability and anxiety have been observed. Transient hypomania appears to be the most common side-effect, for stimulation in the STN. About 4-5% of the patients get hypomania (Váquez-Bourgon et al. 2019). Mania has also been described as a side-effect (Mallet et al. 2008). The definition of mania is when a person is extremely irritable or exuberant and has more energy than usual. A manic person might also feel less need for sleep, speak much faster, have racing thoughts and ideas, and/or often change the subject while talking, distractibility/carelessness, increased risk-taking behaviour and hyperactivity. For it to be considered a manic episode, the person needs at least three of these changes in behaviour. The manic episode also must last for minimum one week. If the episode lasts for shorter time than a week and/or the symptoms are less severe it is called hypomania (Howland & El Sehamy 2021). STN-DBS has also been found to increase impulsivity. STN is supposed to delay thalamic input and act as a brake in conflicted situations. This function could be disrupted with DBS in STN and lead to more impulsive reactions (Kibleur et al. 2016).

3.5 Scales for determining psychological state
There are several rating scales for determining a person's psychological state. There are several scales for depressive symptoms, anxiety, level of disability and so on.

3.5.1. Yale-Brown Obsessive Compulsive Scale (Y-BOCS)
Y-BOCS is commonly used to determine severity of symptoms in patients with OCD. The scale is designed so it can be used on all different types of obsessions. The scale has ten items with each a rating from no symptoms (0) to extreme symptoms (4), the total range is accordingly 0 to 40. The total score can be divided into the subtotals obsessions and compulsions (Goodman 1989).

3.5.2. Other scales
In table 1, are examples of some scales that are used for determining psychological state.
Table 1. Scales used to determine different types of physiological state, sorted on name and what symptoms they measure.

<table>
<thead>
<tr>
<th>Name of scale</th>
<th>Symptom it measures</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montgomery Åsberg Depression Rating Scale (MADRS)</td>
<td>Depression</td>
<td>(Chabardès et al. 2013)</td>
</tr>
<tr>
<td>Hospital Anxiety and Depression Scale (HADS)</td>
<td>Depression and Anxiety</td>
<td>(Mallet et al. 2019)</td>
</tr>
<tr>
<td>Global Assessment of Functioning (GAF)</td>
<td>Level of disability</td>
<td>(Mallet et al. 2019)</td>
</tr>
<tr>
<td>Sheehan Disability Scale (SDS)</td>
<td>Level of disability in work/school, social life, and family life.</td>
<td>(Mallet et al. 2019)</td>
</tr>
<tr>
<td>Clinical Global Impression (CGI)</td>
<td>Symptom severity and treatment response</td>
<td>(Mallet et al. 2019)</td>
</tr>
<tr>
<td>SF-36</td>
<td>Quality of life. Physical and mental health</td>
<td>(Lee et al. 2019a)</td>
</tr>
<tr>
<td>Oxford Happiness Questionnaire (OHQ)</td>
<td>Happiness</td>
<td>(Lee et al. 2019a)</td>
</tr>
<tr>
<td>Warwick-Edinburgh Mental Well-Being Scale (WEMWBS)</td>
<td>Well-Being</td>
<td>(Lee et al. 2019a)</td>
</tr>
</tbody>
</table>

4. Methods

Due to the ongoing pandemic with restrictions in possibility to work in a laboratory, this project is a literature study. This degree project was conducted by comparative analysis of current literature paralleled by statistical analysis on data obtained by Serra/Mackenzie in a previous experimental study.

On April 21, a search on PubMed with the syntax: trial AND ("obsessive compulsive disorder") OR OCD) AND ("Deep brain stimulation") OR DBS) AND human, was conducted. There was restriction. The search yielded 140 records, and 19 additional articles were found through reviews, systematic reviews or other overview articles.

In a first quick scan, a total of 119 were excluded for the following reasons: 3 used another method than DBS, 6 had duplicates of all or some patients, in 9 of the articles the patients did not suffer from OCD, 1 tested only rodents, 4 did not have a follow-up, 22 had a different angle on the matter (eg. neuroimaging of DBS target, investigation of prefrontal metabolism after DBS, gene therapy etcetera) and at last, 74 articles were reviews, systematic reviews or other overview articles. After this screening, 40 articles were included for further analysis. These 40 articles were sieved with the criteria that the target for DBS had to be STN, ITP or ZI. 24 records had other electrode targets and were excluded, and additionally 6 records were excluded because they had a different angle on the matter. Finally, 10 records were included, see figure 4.
From each article, the following information was collected: the target for DBS, number of patients who completed the study, proportion of patients who had 25% improvement or more according to Y-BOCS. From the articles that contained the requested information, the following data was also collected: proportion who developed hypomania or impulsivity, proportion who had an improvement on depressive symptoms or anxiety, and lastly other behavioural side-effects.

If the article had more than one follow-up, the data analysis is conducted from the latest one. All patients included in this project had a Y-BOCS higher than 23, a minimum disease duration of five years, and all were unresponsive or mostly unresponsive to medication and cognitive behavioural therapy.

Behavioural side-effects that were described as transient, permanent, serious, and nonserious are mixed in the results. The side-effects that are included are only the ones during active stimulation. No motor symptoms or side-effects due to surgery complications have been included.

In this project, an improvement with 25% on the scale will be considered a significant improvement. The standard is to call 35% a significant improvement, but some of the articles included has used 25% as their limit and therefore the same limit was chosen for this project.
5. Result

5.1. Patients with PD and OCD

5.1.1. Electrode position at anteromedial STN, between anteromedial STN and ZI and motor STN

One study and one case report included patients with both OCD and PD (Mallet et al. 2002, Fontaine et al. 2004). The first study (Mallet et al. 2002) included two patients and the purpose of the DBS was to treat their PD. The stimulation electrodes were placed between anteromedial part of STN (amSTN) and ZI, bilaterally, in the first patient, and in the second anteromedial part of STN, and between amSTN and ZI. After six months of stimulation, both patients had significant improvement of their OCD. Likewise, both had significant improvement in depressive symptoms and anxiety. The behavioural effects were proposed to be caused by the stimulation of the ZI because it is a structure where many fibre bundles from different areas of the brain cross (Mallet et al. 2002). The case report included only one patient, the stimulation target was the motor-STN. After a twelve-month follow-up, all OCD symptoms had disappeared and there was a slight improvement in anxiety. No changes in depressive symptoms were detected and no other side-effects (Fontaine et al. 2004).

5.2. Patients with OCD

5.2.1. Electrode position at anteromedial STN

In one study, the efficiency of DBS in the ventral capsule/ventral striatum was compared to the amSTN. The stimulation period with electrodes turned on (ON) only in the amSTN was 12 weeks long, and the study was conducted on six patients. All patients had one period with only amSTN stimulation, one period with only VC/VS stimulation and one with both. The results are taken only when patients had stimulation setting ON. When stimulation was on only in amSTN, four of the six patients had significant improvement in their OCD. There was a general improvement in depressive symptoms as well as cognitive flexibility. The improvement in depressive symptoms was better for VC/VS as electrode target, but there was no improvement in cognitive flexibility. Two of the six patients experienced hypomania when the amSTN stimulation was turned ON, but this could be reversed by adjusting the stimulation frequency, and the symptoms disappeared within hours. (Tyagi et al. 2019).

5.2.2. Electrode position in limbic/associative STN (a/l STN)

One study tested 16 patients with refractory OCD. The target for electrode position was the a/l STN defined as 2 mm anterior to and 1 mm medial to the target that is used in patients with PD. See figure 5 for electrode position in this study.
Figure 5. Panel A and B are MRI atlas-based alignment of the basal ganglia. Panel C shows the target of stimulation, in a/l STN, from a superior view. Panel D shows the STN in an oblique view at the axis of the electrode. The four contacts on the electrode can be seen, the contact coloured in yellow is the active one. Green represent the motor STN, purpure the associative and the yellow is the limbic STN. pu = putamen, th = thalamus, cd = caudate nucleus, ot = optic tract, cp = cerebral peduncle, STN = subthalamic nucleus, ZI = zona incerta, rn = red nucleus (Mallet et al. 2008).

The study had a crossover design with phases of three months, ON and OFF stimulation, with a one-month washout in-between. From evaluation from the period where DBS was ON, the average improvement in OCD symptoms, measured with the Y-BOCS, was 31%. No change in depressive symptoms or anxiety was observed (on a group level). However, all patients showed an improvement in level of functioning, measured with the GAF scale. There were several behavioural side-effects. Five patients experienced hypomania that disappeared when stimulation frequency was adjusted. Besides hypomania, one patient developed mania, one displayed depressive symptom and three displayed anxiety. Apart from behavioural side-effects, there was also several serious adverse events, including intracerebral haemorrhage and infections. During sham stimulation, two patients had depressive symptoms with suicidal ideas (Mallet et al. 2008).

A later study included two of the patients from the study reported by Mallet et al, 2008, and added two patients. The DBS electrode position was the same as in the previous two patients. The patients were followed up three, six and eighteen months after surgery. Both new patients (that had not previously been described) showed a significant improvement in their OCD symptoms. One of the two patients developed increased impulsivity and two of all four patients showed weight (Chabardès et al. 2013).

Three follow-up studies have been conducted on the 18 patients described above.
5.2.2.1. Follow-up 1
In a long-term follow-up (34 - 46 months), twelve of the eighteen patients were re-evaluated. Eleven patients had 25% or more improvement in their Y-BOCS score, compared to before surgery. The results also showed that there had been a general significant improvement in Y-BOCS scores from 16 months after surgery to the long-term follow-up. Apart from the improvements in OCD symptoms, four experienced hypomania, four experienced impulsivity, three experienced anxiety, three attempted suicide and six of the twelve displayed depressive symptoms. The study also demonstrated a general improvement of global functioning, improvement of depressive symptoms, less anxiety and lower level of disability in work/school, social life, and family life (Mallet *et al.* 2019).

5.2.2.2. Follow-up 2
In the second follow-up, eleven patients were included. The study focused on decisional impulsivity. The patient’s decisional impulsivity was tested with a test called Beads in a Jar task (Beads task). They performed the test with DBS stimulation ON and again but with stimulation turned OFF. The study also included a control group consisting of 154 healthy voluntaries. The results show that when DBS phases was turned OFF patients gathered less evidence than healthy controls before making their decision. When comparing results from patients with OCD ON and OFF DBS, patients with DBS ON had a higher decisional impulsivity as well as impulsive choice. In conclusion, STN DBS in patients with OCD improves reflection impulsivity closer to healthy controls (Voon *et al.* 2017).

5.2.2.3. Follow-up 3
In another follow-up, eleven patients were tested for risky reward prospects. The eleven patients preformed the tests after minimum 5 months (5-71 months) after their DBS surgery. The purpose of the test was to determine if the DBS affected risk taking to rewards. The results showed that when the DBS stimulation was ON, the patients took less risk to acquire the reward and they had a decreased ability to weighting the loss of magnitude (Voon *et al.* 2018).

5.2.3. Electrode position at inferior thalamic peduncle (ITP)
The ITP has also been used as electrode target for DBS when treating patients with OCD, see figure 6. One study implanted DBS targeting the ITP in six patients and did a twelve-month follow-up. All patients had significant improvement of their OCD symptoms. The six patients also had a 68% improvement on the GAF scale. Three of six patients had such improvement in OCD that they could return to work. One of the patients suffered from a former drug addiction and continued using drugs still after his OCD symptoms improved, he took a cocaine overdose and died (Jiménez *et al.* 2013).
One more study used the ITP as target for DBS on five patients with OCD. The follow-up was done four to six weeks, twelve months and 21-56 months after surgery. All five patients had more than a 25% improvement on Y-BOCS after twelve months. Four patients had a reduction in depressive symptoms, that was significant at the two years follow-up. The fifth patient had little depressive symptoms before surgery, therefore no reduction in depressive symptoms could be seen. There was no improvement in quality of life or happiness, a trend of improvement in mental wellbeing and a significant improvement on social and family subscale when measuring disability. Two patients managed to start working and one patient started volunteer work. Behavioural side-effects included one patient being hospitalized two times because of drug overdose and one patients DBS had to be removed because it became the focus of his obsession (Lee et al. 2019a).

5.3. Summary

With the a/l STN as target for DBS, 92% of the patients had 25% or more improvement on Y-BOCS after 34-46 months follow-up (n=12). AmSTN as target resulted in 67% of the patients significantly improving on Y-BOCS (n=6). The patient with stimulation in the anteromedial STN and between STN and ZI and the patient with bilateral stimulation between STN and ZI both (100%) had significant improvement of OCD symptoms (n=2). With the motor-STN as target, 100% significantly improved on Y-BOCS (n=1). When ITP was the target for stimulation 91% of the patients had significant improvement in OCD symptoms (n=11). See table 2.

Impulsivity, increase in depressive symptoms and anxiety, weight gain, mania and suicide attempt were only reported in patients with the a/l STN as electrode target. ITP as a target let to such improvement that patients could return to work. However, one patient who suffered from drug addiction died from overdose following drug overdose. Cases of hypomania only occurred for patients with electrode positioned in the amSTN (33% experienced hypomania) and in the a/l STN (31% experienced hypomania). No patients with the other target experienced hypomania. See table 2. The table includes in total 38 patients.
<table>
<thead>
<tr>
<th>Electrode position</th>
<th>&gt;25% improvement on Y-BOCS</th>
<th>Depressive symptoms +/-</th>
<th>Hypomania</th>
<th>Anxiety +/-</th>
<th>Impulsivity</th>
<th>Other</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boundary of associative/limbic STN</td>
<td>Average improvement with 31%</td>
<td>+ (1/16)</td>
<td>5/16</td>
<td>- (3/16)</td>
<td>×</td>
<td>16/16 improvement on GAF</td>
<td>Mallet et al., 2019</td>
</tr>
<tr>
<td>Boundary of associative/limbic STN</td>
<td>-</td>
<td></td>
<td>2/2</td>
<td>- (2/2)</td>
<td>0/2</td>
<td>×</td>
<td>1/16 manic</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>2/4 weight gain</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>× = no reported cases/information, - = same target and patients as to the left</td>
</tr>
<tr>
<td>Motor STN</td>
<td>1/1</td>
<td>×</td>
<td>11/12</td>
<td>- (6/12)</td>
<td>3/12</td>
<td>×</td>
<td>Voon et al., 2017</td>
</tr>
<tr>
<td>ITP</td>
<td>6/6</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>Voon et al., 2018</td>
</tr>
<tr>
<td>ITP</td>
<td>4/5</td>
<td>- (4/5)</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>Mallet et al., 2019</td>
</tr>
<tr>
<td>Anterior medial STN</td>
<td>4/6</td>
<td>- (general)</td>
<td>2/6 ×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>Fontaine et al., 2004</td>
</tr>
<tr>
<td>Anterior medial STN + between STN and zona incerta</td>
<td>1/1</td>
<td>- (1/1)</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>Jimenez et al., 2013</td>
</tr>
<tr>
<td>Between STN and zona incerta</td>
<td>1/1</td>
<td>- (1/1)</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>Lee et al., 2019</td>
</tr>
</tbody>
</table>

Table 2: Improvement of OCD symptoms, depressive symptoms, anxiety, number of cases with hypomania, impulsivity, and other behavioral side-effects sorted on electrode target of stimulation.
6. Conclusion

DBS in all subdivisions of STN, ITP and ZI generally has very good effect on treating OCD symptoms. All electrode targets seem to be equally effective for improving OCD symptoms, the efficiency differs only slightly between studies. Of all patients \((n=38)\) 88% had 25% or more improvement in the OCD symptoms. When it comes to side-effects, they were most frequent in patients with the electrode positioned in the a/l STN. Many studies did not have any cases with patients that experienced impulsivity or did not address impulsivity as a side-effect. The only electrode target where impulsivity was reported was for the a/l STN. During one study two patients with sham stimulation had depressive symptoms with suicidal ideas. Thus, behavioural depressive symptoms do not always have to be due to DBS stimulation.

7. Discussion

7.1. Improvement in OCD and level of disability

To get back to the aim of the project, the efficiency of DBS in or near STN for treating OCD is beneficial. It also seems that OCD symptoms get better and better over time. In the follow-up study (Mallet et al. 2019) it was found that the patient’s OCD symptoms had improved from 16 months after surgery to the follow-up at 34-46 months after surgery. This shows that DBS for OCD is not just a short-term effect, it rather seems to give more effect with time. These long-term improvements could be due to plasticity of the brain, the CBT therapy might work better or maybe the fact patients had a greater ability to improve other parts of their life when the worst symptoms disappear. For example, they might for the first time get a job, start exercising or make more social contact which in turn might help improve their symptoms. A support for this idea is that together with the improvement in OCD symptoms patients often show improvement in level of disability including global functioning and some even returned to work.

7.1.2. Side-effects correlated with target of stimulation

There are several behavioural side-effects, most observed for electrode stimulation in the a/l STN. The a/l STN also had several side-effects that were not observed for any other electrode target. However, the studies with this target had most patients included, long follow-ups, three separate follow-up studies and looked specifically at many behavioural side-effects, which other studies did not have. For example, anxiety increased for two patients with the electrode in the a/l STN, but there was still a general decrease in that same group. No studies with other targets have looked specifically on anxiety, probably because it is so closely related to the disease.

Nonetheless, the studies with the a/l STN as electrode target include the highest number of patients \((n=18)\). Studies with the electrode placed at the ITP also had many patients \((n=11)\) but not as many side-effects, and the improvement in OCD symptoms was as good as for the a/l STN. But then again, the studies with ITP as electrode target were not as meticulous in their evaluation of behavioural side-effects. Because the studies with the a/l STN did have the most
patients and most careful evaluation it is still only 18 patients in two studies. Therefore, more studies will be needed to eliminate the possibility of coincidence. It would also be interesting with studies comparing side-effects of other electrode targets, like and NAc ventral capsule/ventral striatum.

7.1.3. Impulsivity
Regarding impulsivity, the results are contradictory. Impulsivity is only closely investigated in the follow-ups on the studies that used the a/l STN as electrode target. One follow-up observed one case of impulsivity that was viewed as a side-effect. Another follow-up’s focus was on impulsivity, they found that the DBS led to higher decisional impulsivity and reflection impulsivity closer to healthy controls. The third follow-up investigated a (little) different angle and found that DBS led to less risk-taking to award and less ability of weighting loss of magnitude. Certain types of impulsivities can also be desirable to gain, because it can improve OCD symptoms, while other types of impulsivities might worsen OCD symptoms. Patients with OCD is known for having impairment in motor-impulsivity, meaning they have a hard time stopping a movement especially if it has already been initiated. At the same time impulsivity is seen as a side-effect for DBS. Hypomania is a side-effect that also include impulsivity and therefore those two might be hard to separate in evaluation of behavioural side-effects. In conclusion, some aspects of impulsivity are increased, and some are decreased with DBS for OCD. This makes it difficult to determine when impulsivity is a side-effect and when it is a desirable effect to decrease OCD symptoms. How impulsivity manifests itself in OCD and what types of impulsivities that are to be viewed as side-effects upon DBS is in other words quite complicated and probably need to be analysed by a psychiatrist.

7.1.4. Intermingled hypothesis vs tripartite model
The majority of studies included has assumed that there is an anatomical division of the STN. For instance, terminology like the limbic or associative parts of the STN has been used in most articles. One study (Fontaine et al. 2004) included here, had the motor-STN as target for electrode stimulation. After twelve months of stimulation all OCD symptoms had disappeared. This rise the question of how that would work if the electrode were not in the limbic or associative areas of STN.

7.1.5. Other parameters than area of stimulation causing side-effects
During this project I have come across many other possible explanations for the differing efficiency and side-effects for DBS in OCD. For instance, some patients might get different result from stimulation depending on what subtype of OCD they have (e.g., washing, aggressive, checking) or stimulation frequency. Both in the study by Mallet et al, 2008 and Tyagi et al, 2019, hypomanic symptoms disappeared after stimulation frequency was adjusted. However, one patient, in the Mallet et al, 2008 study, with manic symptoms was not helped by changes in stimulation frequency. These parameters (stimulation frequency and OCD subtype) would also be interesting to consider in further investigations of how and why there are so many side-effects for DBS.
7.1.6. DBS may not always be trigger for side-effects
Even if there are several side-effects from DBS, one study (Mallet et al. 2008) could clearly show that depressive symptoms can occur without DBS. This could apply to other side-effects as well. This means that all side-effects do not have to be connected to the DBS stimulation.

7.1.7. Not only behavioural side-effects
It is common with severe side-effects from DBS stimulation. For example, in the study by Mallet et al, 2008 there were 15 events categorized as severe adverse events, unwanted side-effects. This project’s focus has been behavioural side-effects, yet it is important to mention that there are physical side-effects as well. For instance, paralysis of body parts and infections including intracerebral haemorrhage. A larger project could examine both behavioural and physical side-effects for all different targets being used for DBS in patients with OCD.

7.8. Limitations
There is not yet one way of evaluating phycological state which makes the studies more complicated to compare. Except from Y-BOCS, a variety of different scales have been used in different studies. When using Y-BOCS there are also different requirement for what is a significant improvement, some use 25% and others use 35%. Therefore, patients with 25-35% improvement in studies that use 35% as their limit might be missed in projects like this, or in summarizing or comparative reviews. The different studies also address many different side-effects, and there is no consensus on which effects that are important to address. Not all articles included seem to have considered behavioural side-effects, and therefore the number of patients with different side-effects reported might not be the actual number of patients that suffered from them. For example, the category of “people who returned to work” might be difficult to fully address because most of the studies did assess this parameter. Same for impulsivity and cognitive flexibility. However, these results give a hint on how common the different behavioural effects could be.

One study (Mallet, 2008) included what the actual location of the electrode was after surgery using MRI scanning. The electrode target was the a/l STN, but out of 33 contacts, 4 were in the ZI, 4 in the internal capsule, 3 in the substantia nigra and 2 in fields H2 of Forel. It does not say which patients that had electrode outside the STN and therefore no conclusions can be drawn about side-effects in relation to area of stimulation. In other words, one limitation of this project is the difficulty in knowing what the actual area of stimulation is, which makes the connection of stimulation target and side-effects slightly more uncertain. Because in (Mallet et al, 2008) 13 of 33 contacts were misplaced, this could mean that the limitation does not play a big role. Even if it is with certainty found which target is most efficient and has the least side-effect, it is as likely that the electrode is slightly misplaced when using that target for treating OCD. This could mean that when looking at side-effects and efficiency, we should look at what the intended electrode position is and not the actual positing. Because, hypothetically, what if all electrodes placed in ZI causes hypomania? The risk of putting the electrode in ZI when targeting STN is very big, then the risk of hypomania when using STN as target, even if its not stimulation
in STN causing the hypomania, is still present. At the same time, for future studies investigating the mechanisms behind DBS in patients with OCD, could be important.

7.9. Summary

Lastly, less side-effects were observed when amSTN, motor-STN, ZI or ITP was the target for stimulation. There is also a general major improvement in OCD symptoms for all electrode positions. More studies, and studies with more patients, are needed to with certainty draw conclusions. As well as more overview studies comparing all electrode position brain target areas that are used for DBS in patients with OCD. However, this project implies that there could be a higher risk of negative side-effects with the electrode position at the a/l STN.

For future studies, it would be interesting to compare all areas that are being used for DBS in patients with OCD. It would also be of interest to consider more parameters, for instance frequency of stimulation, OCD type, or individual differences in physiology.

8. Acknowledgements

I wish to express my sincerest thanks to my supervisor Åsa Mackenzie for providing me guidance, great constructive advice as well as help finding the aim for the project. Furthermore, I would like to thank my supervisor Gian Pietro Serra for providing an exercise for statistical analysis. I also want to thank Marina Balerio and Aubree Stephens for useful feedback.
9. References


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10. Supplementary data analysis

**Background:** The structure subthalamic nucleus (STN) is known to be important for movement. STN is well-studied regarding its involvement in Parkinson's disease (PD). For example, it is known that STN neurons is hyperactive in patients with PD, and degradation of STN is associated with Huntington's disease. In other words, excitation of STN results in inhibition of movement and inhibition of STN leads to more movement. The function of STN and the circuits it is connected to is, accordingly important for the understanding of movement disorders like Huntington's or PD. However, these mechanisms are not entirely understood.

**Aim:** To examine if the activation of STN in mice affects the total distance they move.

**Aim of data analysis:** To gain experience in data analysis.

**Method:** Experiments were conducted by (Guillaumin et al, 2021). I received data and did an analysis. The mice in the experiment had a stereotaxic virus injection with Cre-dependent channelrhodopsin (ChR2) or a control virus. After virus injection there was optic cannual implantation, so the experimenter manually can activate the STN with light stimulation. The open filed experiment was in five-minute phases, starting with light stimulation OFF and then ON for total 4 phases. The total distance moved for each face, and each mouse was recorded automatically. The statistical analysis was done in excel with a ANOVA for the groups; control ON, control OFF, ChR2 ON and ChR2 OFF.

**Result:** There was no significant difference between the four groups (treatment or stimulation), and neither for the interaction between groups. See figure 1.

![Figure 1](image)

Figure 1. Diagram of the total distance moved sorted on mice with virus implantation (ChR2) ON and OFF STN activation, and the control groups ON and OFF STN activation.