Deep Brain Stimulation in the Cortico-Striato-Thalamo-Cortical Pathway and its Effect on Obsessive-Compulsive Disorder

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***Abstract*- Obsessive-compulsive disorder (OCD) is a neuropsychiatric disorder in which repetitive behaviors are done to relieve anxiety caused by repeated and intrusive thoughts. About 20% of OCD patients remain resistant to therapies and medications and are linked to suicidal behavior and lack of social functioning. Deep brain stimulation (DBS) has been considered as a last-resort solution for these patients. Recently, neuroimaging techniques have shown significant differences in the activity of the cortico-striato-thalamo-cortical (CSTC) pathway in OCD patients, supporting the first studies of DBS in the anterior limb of the internal capsule (ALIC), which is a part of this pathway. Since then, studies have expanded DBS into other locations of the CSTC pathway. With all these different regions being studied, many patterns have been found. However, as each location has a different degree of efficiency in each trial, the final goal should be to be able to determine which location will be most beneficial for patients. The purpose of this paper is to compare the studies and effects of DBS on OCD patients in varying parts of the CSTC pathway and discuss the goals and experimental setups of future studies to determine the best combination of stimulation parameters and DBS locations for patients.**

I. INTRODUCTION

Obsessive-compulsive disorder (OCD) is a disabling neuropsychiatric disorder that has a lifetime prevalence of approximately 2.3% within our population.[7] It is characterized by the presence of obsessions, which are persistent and uncontrollable thoughts or impulses, and compulsions, repetitive behaviors done to diminish the anxiety and discomfort associated with the obsessions. Effective treatments for OCD include cognitive behavioral therapy (primarily exposure and ritual prevention) and medications (mainly antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and clomipramine, as well as antipsychotics that manipulate the transmission of monoaminergic neurotransmitters). Unfortunately, despite this assortment of treatment options, 40-60% of patients do not respond to SSRIs and 10-20% of patients remain resistant to all therapies.[3] These patients are diagnosed with treatment-resistant OCD and it is in these cases that deep brain stimulation (DBS) can be considered as a last resort treatment option.

DBS is a neurosurgical technique that uses electrical current delivered to specific locations of the brain through the means of implanted electrodes to regulate abnormal neural activity.[22] While the precise mechanism of DBS is unknown, there is evidence that shows DBS exerts its effect through both the activation and inhibition of brain areas by stimulating positive and negative feedback loops.[7] Via a pulse generator embedded in the chest and a connecting cable that runs under the skin, the electrodes are supplied power. Clinicians then set parameters that determine how strong of an impulse is generated, how long it lasts, and how many times per second it is delivered. The adjustability and reversibility of DBS allows neuromodulation to be done without serious side effects. DBS has been used since the mid-1980s to treat movement disorders such as Parkinson's disease and was first used for the treatment of OCD in 1999.[13] DBS has so far only been tested in those with severe OCD which is characterized by a 32-40 on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). The Y-BOCS scale is a test that is used to determine the severity of OCD by asking the patient a series of questions related to the impact of the symptoms on their lives. Since then, following multiple studies, DBS has been approved by the Food and Drug Administration in the United States.[5]

This review covers the regions of the cortico-striato-thalamo-cortical (CSTC) pathway that have been tested for OCD, their overall effectiveness, and their shortcomings. By discussing the differences and results of studies, a better action plan is formulated to determine the best treatment parameters for OCD patients using DBS.

II. CSTC PATHWAY

The regions targeted in most DBS studies are a part of the cortico-striato-thalamo-cortical (CSTC) pathway which is a brain circuit that controls movement execution, habit formation, and reward.[19] Recent studies and analysis using neuroimaging show abnormal activity and anatomical differences in the CSTC circuits of patients with OCD. The affected regions include the orbitofrontal cortex (OFC), the anterior cingulate gyrus (ACC), the prefrontal cortex (PFC), and the ventral striatum.[7] The current leading hypothesis is that OCD is associated with hyperactivity of the CSTC loop, and while the precise mechanism of DBS is unknown, its effects on patients with OCD could be explained by an inhibition of the CSTC network.[15] The CSTC network projects from the frontal cortex to specific targets in the striatum. It then goes through the basal ganglia, through direct and indirect pathways, to the thalamus and back to where it started in the frontal cortex. Neuroimaging findings that relate the involvement of the CSTC pathway in the pathophysiology of OCD show elevated activity in the nodes of this circuit in OCD patients at rest, which are accentuated during symptom provocation and attenuated toward normal with successful treatment.[15, 18] There are two widely studied stimulation areas of the CSTC pathway for OCD patients.[7] The first is the striatal region, which includes the anterior limb of the internal capsule (ALIC), the ventral striatum/ventral capsule (VS/VC), the ventral caudate nucleus, the nucleus accumbens (NAc), the bed nucleus of the striata terminalis (BST), and the medial forebrain. The second is the subthalamic nucleus (STN).[19]

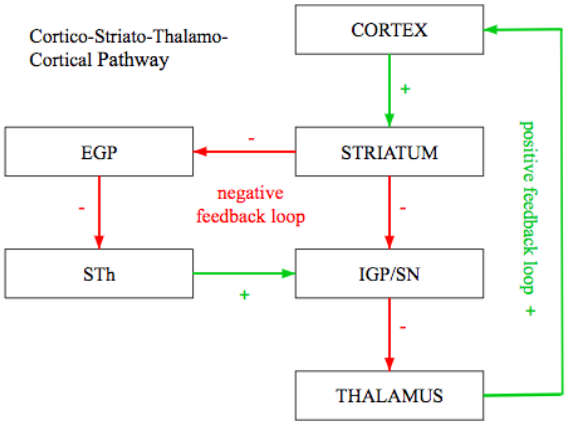

Figure 1 - Feedback loops within the CSTC pathway
The CSTC pathway uses both positive and negative feedback loops in regions of the brain to influence habit formation and reward.

III. STRIATAL REGION

A. Anterior limb of the internal capsule (ALIC)

The ALIC is a bundle of fibers that connects the thalamus to the frontal lobe, caudate nucleus and putamen. It is known to be linked with the processing of emotion, cognition, decision making, and motivation, and abnormalities in its white matter are often found in psychiatric illnesses such as OCD.[17]

The first case study of DBS for the treatment of OCD that was done in 1999, targeting the ALIC. In this study, four patients were implanted with bilateral DBS, and three were reported to have beneficial effects (Nuttin et al. 1999).[13] Since a definition for improvement is not given, it cannot be said to which degree the patients got better. However, more detailed data was given for one patient who reportedly had a 90% Y-BOCS reduction. Similar to this study, there have been many more that propose beneficial effects of DBS in the ALIC for OCD. In another study done with 6 patients, a blinded double random crossover design was used to choose four of those patients who were given continuous stimulation. All four of the patients were shown to have a 61.3% decrease in the Y-BOCS scale from postoperative off to stimulation-on.[16] Unfortunately, during the stimulation-off period, all four patients' symptoms severity approached the baseline levels.[16] An open-label study with 20 patients showed a 33% reduction on the Y-BOCS scale in the 40% responders one year after surgery.[20] In an open label study, both the patients and the researchers know which treatment is being administered. Therefore, the fact that it is an open label study introduces positive bias, which is the overestimation of the positive effects, into the results. It also enhances the placebo effect among patients especially considering that the results are based on self-reports, making the data from this study subjective. According to the data, DBS did not show an improvement in anxiety and depression. In fact, 35% of patients reported a sudden increase in anxiety after stimulation was stopped. Adverse events were limited to one case due to hardware infection.[20] Effects due to changes in DBS settings, such as hypomania, disinhibition, lack of concentration, transient loss of energy, sleep disturbances, and >20% weight gain also occurred. These side-effects were temporary. All of the studies above, however, had many varying factors among patients such as stimulation parameters and follow-up periods which makes it difficult to compare the data directly. Since there are so many variable factors, it is hard to determine whether it was stimulation parameters, the location, or the follow-up time that caused the improvement of the patients. For future studies, researchers should decide on only one varying factor, whether it be stimulation time, parameters, or DBS location.

The inconsistent conclusions in YBOCS reduction and response rates between studies in individual clinical trials show that they cannot predict the response towards DBS in a large group. A study done by Hartman et al. used neuroimaging techniques to follow the progress of ALIC-DBS.[25] It showed that the two best responder target locations within the ALIC had stronger connectivity between the right middle frontal gyrus (MFG), which is known to be associated with executive functions and adapting in response to changing task requests. On the other hand, the two non-responder targets had stronger connectivity with the right thalamus and the orbital part of the right inferior frontal gyrus, which is implicated in task-switching and maintenance of compulsive behavior. This shows that beneficial ALIC-DBS relies on the adaptation of the brain and particular executive functions and that the effectiveness of ALIC-DBS is largely based on which fiber pathways it influences within the active DBS site. However, since each patient's body reacts in a different way, in order for the stimulation parameters to be optimized, each patient had a different set of stimulation parameters. This means that while the location of DBS stimulation and the follow-up period were the same, the parameters among patients being tested were not. Therefore studies from different locations cannot be compared because then there are two changing variables, the location and the stimulation parameters. While ALIC-DBS results may not be consistent now, further investigation into influencing specific fiber pathways may yield patterns and responses that are more applicable to the general public of OCD patients.

B. Ventral striatum/ventral capsule (VS/VC)

The junction of the ventral capsule/ventral striatum is referred to as the 'VC/VS' and is now one of the most popular targets for OCD. However, one of the first randomized studies done for VC/VS failed to establish the difference between "on" and "off" stimulation patients. The result of the study could be explained by the short follow up time of only two months for active stimulation.[4] After one year though, out of those same patients, 66.7% were responders showing a more than 35% decrease on the Y-BOCS scale. However, the reduction in symptoms and criteria for responders is unknown so the true efficiency cannot be determined. Most studies show an average response rate of 50% within a year after the surgery.[4] Greenberg et al. did a double-blind crossover study with 26 patients and implanted them with electrodes in the VS/VC. After a follow-up period of 3-36 months, 10 patients (38.5%) were responders and had a Y-BOCS reduction from 0-62.5%. Since the time before the follow-up influences the effectiveness of DBS, the varying time of

follow-ups between patients may explain the drastic range of Y-BOCS reductions found in the trial.[10] However, almost all of the patients had a secondary anxiety disorder; 82% of patients had major depressive disorder. These disorders often have similar symptoms as OCD since it is also a mental anxiety disorder that can cause anxiety and frustration. It is possible that the big reduction in Y-BOCS scores could be due to a response the DBS exerted on the comorbidity, and not on OCD itself. While this does not mean that DBS had no effect on OCD as there still were patients with no comorbidities who improved, it does mean that the extent to which it helps is uncertain and may not be as positive as it appears. Still, compared to other forms, VS/VC-DBS, shows a higher response rate.

Similar to ALIC-DBS, it was also associated with transient cognitive side-effects that were mainly related to changes within links to the reward and motivational system. Certain patients experienced stimulation-induced symptoms and temporary hypomania.[10] A study by Tyagi et al. compared the effectiveness of VS/VC and anteromedial subthalamic nucleus (amSTN) DBS in the same patients and looked for differences in mood, cognitive flexibility and associated neural circuitry.[1] They found that the patients with VS/VC stimulation had a greater improvement in mood.[1] Their implant site was within the VC and connected mainly to the medial orbitofrontal cortex (medial OFC). This improvement in mood can be explained by previous abnormal functional connectivity found by functional MRI (fMRI) in OCD patients. The MRI scans showed the medial OFC to be hyperresponsive to threat stimuli.

C. *Nucleus accumbens (NAcc)*

While many case reports have been documented investigating NAcc-DBS, there are only a small handful of larger studies. In the open-label design study conducted by Kohl et al., 18 patients were implanted with electrodes with the bilateral NAcc. In a double-blind study, neither the researchers nor the patients know which treatment is being administered. Hence, compared to a double-blind study, open-label studies added positive bias into their conclusions. After one year, there were around 50% responders and 16.7% partial responders.[12] In a second study, 16 patients also received bilateral NAcc stimulation and after a follow-up period of eight months, 9 (56.25%) patients were responders. Responders showed a mean decrease of 46% on the Y-BOCS scale. After the eight months and a double-blind crossover study with a two-week period, the difference in Y-BOCS score between active and sham stimulation was a notable 25%.[8] Sham stimulation is used in research for a placebo effect and indicates an inactive or weak form of stimulation. This is different from off-stimulation in which there is no stimulation at all. The time for off-stimulation was different for each patient and so were the stimulation parameters. The varying off-stimulation period may result in different effects in patients as the patients with lower off-stimulation may experience a higher Y-BOCS reduction. There was also no control group who had sham stimulation for the whole period of the study. This means that the effectiveness and numbers from the study are not fully reliable because the placebo group is altered throughout the experiment and no longer provides an accurate baseline for comparison. Aside from mild forgetfulness and word-finding problems, depression and anxiety were decreased significantly within patients.

Resting-state fMRI scans in 16 NAcc-DBS responders showed reduced frontostriatal connectivity between NAcc, lateral prefrontal cortex (LPFC), and the medial PFC before the treatment when compared to afterwards.[6] NAcc-DBS also reduced excessive frontal low-frequency oscillations caused by symptom-provoking events. These oscillations are known to be linked to the severity of OCD symptoms.[11] By decreasing the excessive frontostriatal connectivity and allowing the natural processing of stimuli to return, targeting regions of the NAcc with the strongest connectivity to the LPFC and medial PFC might further enhance the beneficial effects of NAcc-DBS.

D. *Bed nucleus of the striata terminalis (BST)*

Although the BST is not typically cited in OCD pathology, it is known to have a role in emotional learning and there has been evidence relating it to anxiety responses.[14] While not many DBS studies have been done in the BST for OCD, the few that have been done look promising. One study conducted by Luyten et al. monitored patients with electrodes planted in BST and patients with electrodes in the bilateral ALIC simultaneously.[14] After a follow-up period of 48 months, 80% of the BTS stimulated patients were responders and had an average Y-BOCS reduction of 50%. The patients with ALIC implanted electrodes had a 16.7% response rate and demonstrated a 22% Y-BOCS reduction. Since they were a part of the same experiment, many varying factors were the same. ALIC-DBS patients seem to show a notably lower response rate and Y-BOCS reduction than BST-DBS. Compared to past ALIC-DBS experiments however, the success and improvement shown are rather low. This may be because this study has patients with implants in both the BST and ALIC and therefore may not have many factors that directly boost the performance of the ALIC-DBS like the solely ALIC-DBS focused studies. It is also possible that the exact region within the ALIC that the electrodes were implanted was not very beneficial as the precise location of the DBS activity has been proven to influence the benefits of DBS. Regardless, BST-DBS shows great promise for the future as its responder rate and Y-BOCS reduction are high and while not enough studies have been done in order to predict its effects on a larger population, hopefully future studies focus more on this region.

IV. SUBTHALAMIC NUCLEUS

The anteromedial subthalamic nucleus (amSTN) is another targeted region for DBS in OCD patients. Since stimulation of the subthalamic nucleus with DBS was previously used for Parkinson's patients, the concept of stimulating this region was known for improving motor symptoms.[2] However, after studies were conducted, it was found that the stimulation of the dorsolateral STN affects primarily motor networks while stimulation of the anteromedial STN (amSTN-DBS) affects limbic and

associative functions.[9] The first double-blind crossover study of amSTN-DBS with 16 OCD patients had a 75% responders after a mere 3 month follow up period. The patients had a decrease in OCD severity by 39%.[1] A meta-analysis reported that 44% of patients could be considered responders to STN-DBS.[3] While the responding rate and severity decrease are not extraordinary compared to the other DBS techniques, the small follow-up period to obtain those similar results is. Most other locations used for DBS require at least one-year post-surgery to obtain the same results, as shown in Goodman et al.

Authors	Target	Patients	Design	Stimulation Parameters	Follow up (months)	Y-BOCS Reduction
Luyten et al, 2015[14]	Bilateral ALIC and BST	6 - ALIC; 15 - BST;	Double-blind, random crossover	F: 85-130 Hz, PW: 90-450 µs, A: 3-10.5 V	48	22% - ALIC 50% - BST
Nuttin et al, 1999[13]	ALIC	1	Case study	F: 100 Hz, PW: 210 µs, A: 5-7 V	--	90%
Nuttin et al, 2003[16]	ALIC	4	Double-blinded random crossover	F: 100 Hz, PW: 210-450 µs, A: 4-10 V	21	61.3%
Huys et al, 2019[20]	ALIC	20	Open-label	F: 100-135 Hz, PW: 210 µs, A: 4-7 V	12	33%
Greenburg et al, 2010[10]	VS/VC	26	Double-blind crossover trial	F: 100-130 Hz, PW: 90-450 µs, A: 2-8 V	3-36	0 - 62.1%
Goodman et al, 2010[4]	VS/VC	6	Double-blind crossover	F: 130-135 Hz, PW: 90-210 µs, A: 2-5 V	12	>35%
Kohl et al, (2015)[12]	NAcc	18	Open-label	F: 120-130 Hz, PW: 90-150 µs, A: 3.8-7 V	12	--
Denys et al, 2010[6]	Bilateral NAcc	16	Double-blind crossover	F: 130 Hz, PW: 90 µs, A: <= 5 V	8	46%
Mallet et al, 2002[2]	amSTN	16	Double-blind crossover	F: 130 Hz, PW: 90 µs, A: 3 V	3	39%

Figure 2 - **Summary of DBS Studies for OCD treatment**
This table lists the researchers, target region, design, stimulation parameters, follow-up period, and Y-BOCS reduction, of different studies that have tested DBS for the treatment of OCD.

V. CONCLUSION

DBS in the CSTC pathway improves OCD symptoms through a variety of different locations, each having its own benefits. Each DBS target influences through its own specific pathway and electrodes implanted in different areas within the same region have been shown to have varying outcomes. Future studies should focus more on optimizing the targets chosen as it has already been shown that certain fiber pathways are more effective than others. By experimenting more in specific regions, more precise patterns and pathways that are more beneficial can be found. Plus, since stimulation parameters are easy to adjust after surgery, it is highly critical that the location of the implant is best suited towards each patient to decrease their symptoms to the highest degree. In order to find this, studies should make sure that there is only one varying factor, and that factor should be the location. By keeping all other variables, such as stimulation parameters, the same, the location can be best optimized. Since placing the electrodes is the most invasive and difficult part of DBS, it will be easier to optimize other variables afterwards and create a better understanding and treatment plan for patients with OCD using DBS if the location is ideal.

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