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Comparing Major Targets of DBS in Individuals with Treatment-Refractory OCD: A Systematic Review

Hala Mahdi, BHSc Student [1], Vritti Vashi, BSc Student [2]*

[1] Department of Health Sciences, McMaster University, Hamilton, Ontario, Canada. L8S 4L8
[2] Department of Integrated Science, McMaster University, Hamilton, Ontario, Canada. L8S 4L8

*Corresponding Author: vashiv@mcmaster.ca

Abstract

Introduction: Individuals with obsessive-compulsive disorder experience lasting impairments that significantly lower their quality of life. Many neurostimulation procedures have formed a part of OCD treatment, including deep brain stimulation (DBS) - an established neurosurgical technique first introduced for treatment-refractory OCD (TROCD) involving implanting electrodes to send impulses to targeted brain regions. This paper aims to provide a systematic review of the current literature on DBS for TROCD, comparing six brain regions as potential targets.

Methods: The systematic review consisted of a literature search of primary research articles on PubMed, Google Scholar, MEDLINE, and Web of Science. The databases were assessed based on an inclusion and exclusion criteria which included patient health, comorbidities, diagnosis criteria, and age. In total, 17 articles were included.

Results: The stria terminalis, ventral capsule, and nucleus accumbens were identified as key areas targeted in the current literature for TROCD DBS. The inferior thalamic peduncle, medial forebrain bundle, and subthalamic nucleus were lesser studied regions, but presented with promising outcomes. Improvements in symptom severity for each target ranged from 35%- 54% in all six regions. Through this, scientists were able to speak upon the efficacy of the treatment and can now combine past knowledge to create tests with even better functioning outcomes. Moreover, connections between neuronal pathways can now be made to help in better understanding complexities of TROCD.

Discussion: Improvements in OCD symptoms were most promising for DBS to the ventral capsule and inferior thalamic peduncle. Common secondary outcomes included reduced anxiety and depression, and select studies also reported on improved quality of life and daily functional ability. Common adverse effects across the different targets were hypomania mood and anxiety-related events, with a large variety of adverse events across targets.

Conclusion: The ideal target for TROCD DBS is unclear due to the large variability of Y-BOCS scores, secondary outcomes, and adverse effects reported. Future directions include personalized targets within the regions, stimulating multiple targets in the same patient, further investigating the potential of targeting the medial forebrain bundle, and studying the effects of DBS on long-term quality of life.

Keywords: treatment refractory obsessive compulsive disorder (TROCD); deep brain stimulation (DBS); nucleus accumbens; ventral capsule (VC); stria terminalis

Introduction

Obsessive Compulsive Disorder (OCD) is a chronic disorder that is characterized by persistent anxious and intrusive thoughts with repeated, time-consuming compulsions that may provide temporary relief [1]. OCD has a lifetime prevalence of 2.3%, with 25-40% of individuals with OCD experiencing persistent symptoms and lasting impairments [2,3]. OCD is associated with significantly lower quality of life (QoL) and increased functional impairment compared to healthy controls in areas of family life [4]. Individuals with OCD who do not respond to traditional treatment methods such as Cognitive Behavioural Therapy (CBT), selective serotonin reuptake inhibitor (SSRI) treatments, antipsychotics, or other antidepressant agents are considered to have Treatment-Refractory Obsessive-Compulsive Disorder (TROCD) [5]. CBT in particular can be both a first-line therapy along with SSRIs and an augmentation therapy in individuals with OCD who have had SSRI treatments but are still symptomatic [5]. However, 40-60% of individuals with OCD either do not respond or only partially respond to these initial treatments involving CBT, SSRIs, or a combination [6]. Often, in cases of TROCD, CBT is consistently integrated with the other treatments and therapies at the various levels of nonresponse [5]. Further, two common traditional neurosurgical interventions for OCD are cingulotomy and capsulotomy, which involve the irreversible bilateral lesioning of the XYZ [7]. In a review of ten studies involving 193 participants with OCD who have

either undergone capsulotomy or cingulotomy, the average full response rate to capsulotomy was 54% and to cingulotomy was 41% [8]. TROCD is often characterized by differing criteria, but some general trends found in the literature is the use of the latest edition of the DSM or ICD available, as well as assessing severity with the Yale Brown Obsessive Compulsive Scale (Y-BOCS) [9–11]. The Y-BOCS scale has scores ranging from 0-40, with scores increasing as the severity of symptoms increase and categorized as follows: 0–7 = subclinical; 8–15 = mild; 16–23 = moderate; 24–31 = severe; 32–40 = extreme [9,10]. A Y-BOCS score reduction of ≥35% (calculated from changes in baseline and post-treatment Y-BOCS scores) is a common criterion for OCD treatment response, as seen in many of the reviewed studies that implemented this as the threshold for responders regardless of their target for DBS [9–11,13,14,18,19,24,25].

Deep brain stimulation (DBS), first introduced by Nuttin et al. in 1999, is an established neurosurgical treatment for movement disorders and involves surgically implanting electrodes to send impulses to targeted brain regions [12,13]. DBS offers key advantages over traditional surgical TROCD treatments such as cingulotomy and capsulotomy, with the most significant advantage being that DBS does not result in irreversible lesions while still achieving a clinical effect [7]. Additionally, DBS is also minimally invasive and reversible, as the stimulator can be turned on and off, allowing researchers to deliver stimulations either continuously or intermittently and gauge placebo effects by performing sham stimulations [7]. While DBS has shown promise in individuals with TROCD, the optimal DBS stimulation targets in this context are unclear. There are several brain regions that have been targeted for DBS, including the nucleus accumbens, stria terminalis, ventral striatum/ventral capsule, medial forebrain bundle, the subthalamic nucleus, and inferior thalamic peduncle [9–11,14,15]. The former three targets have been some of the most studied DBS target sites for TROCD, while the latter three are more recent targets for investigation. Our aim with this review is to comprehensively analyze these major targets of DBS in individuals with TROCD through comparing their efficacies, short- and long-term effects, limitations, and opportunities for future research.

Methods

The systematic review consisted of a comprehensive literature search of primary articles to study DBS as a treatment for TROCD. The databases used to search for relevant primary papers include PubMed, Google Scholar, MEDLINE, and Web of Science. The databases were assessed based on an inclusion and exclusion criteria which included patient health, comorbidities, diagnosing criteria, and age. Patient health was assessed to ensure the participants were not pregnant, did not have a substance abuse disorder, and did not show suicidality in the past 12 months leading up to the study. Individuals who have comorbidities with bipolar disorder and other personality disorders were excluded while other mental illness comorbidities were included. The diagnosing criteria primarily followed the Y-BOCS, in which participants had to test with a mean score of 24-28 to be included. Additionally, there must be a minimum two-year OCD diagnosis along with at least one trial of serotonin reuptake inhibitor treatment and a trial of CBT adding up to a minimum of 10 years. Lastly, it was pertinent that the participants were above the age of 18 as pediatric results showed great variation in outcomes making it difficult for studies to draw a clear consensus. The primary literature search returned a total of 25 studies. This was then followed by the abstract screening (n=21), and lastly, ending with a full-text screening (n=17). For each study, changes in means and SDs in Y-BOCS score, as well as percent improvement, were examined. Figure 1 depicts a visual schematic of the screening process.

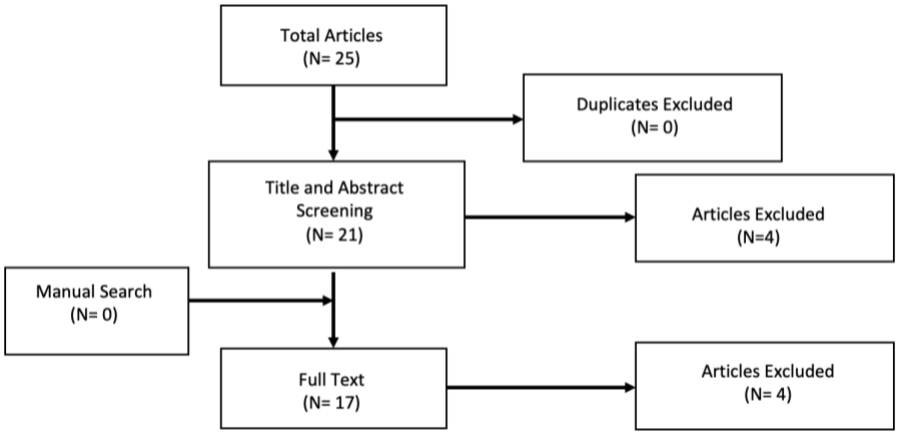

Figure 1. Methodological steps used to determine the pool size of studies used in the systematic review. The process comprises two main steps: the first being an abstract screening, and the second being a full text screening. Lastly, a manual search was conducted to ensure all eligible papers were found.

Results

Stria Terminalis

The stria terminalis is a white matter tract between the amygdala and thalamus that plays a crucial role in emotional and behavioural responses. As a result, targeting it with DBS is expected to reduce the OCD symptoms that are associated with these responses [11]. All studies combined had an average of 6.3 patients with an average one-year DBS, mean ± SD Y-BOCS score of 23.55 showing significant improvement. The study by Islam et al., had a total of eight patients with four undergoing DBS at the stria terminalis [16]. They were able to conclude that, of the four patients, the presence of comorbidities such as depression, bipolar disorder, and compulsive disorder were seen having minimal effects on the results of the study. Additionally, the study noted two patients undergoing severe side effects of bacterial infections, namely *S. epidermidis.* Though no long-term effects and mortalities were reported due to side effects, this finding warrants further research prior to the treatment becoming a standard practice. Overall, the mean improvement of Y-BOCS scores was 35% [16]. Next, a study by Winter et al., looked at targeting the internal capsule and stria terminalis simultaneously to determine the success rate of DBS [17]. They used varying voltages and were able to conclude that a 2V stimulation was ideal for the stria terminalis. Though short-term success was seen in Islam et al., Naesström et al., and Mosely et al., however, it is still pertinent that long term effects be examined in future studies [17]. Moreover, a comprehensive study conducted by Naesström et al. shows a one-year follow up after DBS was conducted on the bed nucleus of the stria terminalis where results showed a 38% improvement in Y-BOCS scores [13]. They concluded that the study aligns with previous studies (including the ones mentioned above) in which DBS shows promising treatment of TROCD. The authors placed a greater emphasis on the safety measures that took part in their procedure. Lastly, a study by Mosely et al. took a combined approach in which DBS was paired with rounds of CBT [11]. The process of including CBT was used as a secondary method of measuring success in which no serious psychiatric adverse effects of the simulation were noted. The combination approach significantly improved symptoms with Y-BOCS scores of 35%. A summary of the findings on Y-BOCS scores of participants who underwent DBS in the stria terminalis can be found in Table 1. Overall, the stria terminalis is a promising region for treatment of TROCD through DBS.

Table 1. Mean baseline and post-DBS Y-BOCS scores and mean improvement for studies targeting the stria terminalis

Study	Baseline Y-BOCS Score	Post-DBS Y-BOCS Score	Y-BOCS Improvement
Islam et al. [16]	34.75*	NA*	43.75%
Naesström et al. [13]	33 ± 3.0	20 ± 4.8	38%
Mosely et al. [11]	32.7 ± 2.6	17.4 ± 2.0	35%

*Table note: Standard deviation for baseline Y-BOCS scores and average post DBS Y-BOCS scores of patients in the Islam et al. study were not available due to the participants having different follow-up times. Y-BOCS improvements for each participant were reported however, and we reported on the mean improvement.

Ventral Capsule

The ventral capsule found within the limbic system plays a crucial role in reward regulation, and is another brain region pertaining to potential treatment of TROCD through DBS (Bouwens van der Vlis et al., Greenberg et al., and Tyagi et al.). It is believed that the excitatory connections formed by the ventral capsule in the orbitofrontal cortex can be manipulated through DBS to decrease activity thereby decreasing the magnitude and frequency of TROCD symptoms experienced [10,17]. A summary of findings related to Y-BOCS scores on DBS in the ventral capsule can be found in Table 2. Tyagi et al. studied six patients over a course of 12 weeks of treatment and were able to conclude significant findings in the ability of ventral capsule stimulation to improve TROCD symptoms in a sample of participants with an initial baseline score of 36.17 ± 0.75 and a 53% improvement after one year [10]. The study records improvements in mood regulation as noted by qualitative observations of the study. However, after DBS was conducted, the study noted a ceiling effect in which future CBT was no longer viable/effective options. The study by Greenburg et al., had similar results to those by Tyagi et al., in terms of benefits of DBS on ventral capsule showing improvements in a sample of participants with a baseline of 34.0±0.5 and an overall improvement of 38% [18]. However surgical side effects including hemorrhages, seizures, and infections were observed. This raises concerns on the short-term efficacy and comorbidities that may arise from the treatment. Looking at positive primary findings on the success of targeting the ventral capsule as a potential treatment for TROCD in 63% of patients contributes to the overall success and potential for DBS to become implemented as a standard practice.

Table 2. Mean baseline and post-DBS Y-BOCS scores and mean improvement for studies targeting the ventral capsule

Study	Baseline Y-BOCS Score	Post-DBS Y-BOCS Score	Y-BOCS Improvement
Bouwens van der Vlis et al. [19]	33.12 ±3.34	22.63±7.91	63%
Greenberg et al. [18]	34.0±0.5	21.0±1.8	38%
Tyagi et al. [10]	36.17 ± 0.75	17.00 ± 3.57	53%

Nucleus Accumbens

The nucleus accumbens is a component of the ventral striatum of the basal ganglia, located where the putamen and head of the caudate meet [18]. Its functions range from regulating goal-directed behaviors, addiction, and reward processing. As there is evidence of dysfunction and hyperactivity of the reward circuitry in individuals with OCD, the nucleus accumbens is a promising target for DBS [19]. A summary of findings on DBS in the nucleus accumbens can be found in Table 3. In particular, Figee et al. found that compared with healthy controls, individuals with OCD showed reduced reward anticipation activity in the nucleus accumbens [20]. In terms of efficacy, Denys et al. found that nine out of 16 patients treated with bilateral DBS in the nucleus accumbens responded to the treatment, and overall, the mean improvement of Y-BOCS scores was 52% [9]. In this study, responders were classified as patients who show at least a 35% decrease in their Y-BOCS score. The most common transient adverse effect reported was mild hypomania that lasted for two days, and permanent adverse effects included mild memory impairment reported by five patients and word-finding difficulties reported by three patients. Another study by Sturm et al. found that bilateral stimulation did not improve outcomes compared to unilateral stimulation [21]. Sturm et al. observed nearly complete recovery from both OCD and anxiety symptoms after unilateral DBS of the right nucleus accumbens in three out of four patients, with no side effects during the follow up periods of 24-30 months. Huff et al. investigated unilateral stimulation of the right nucleus accumbens and found that Y-BOCS scores decreased from a mean of 32.2 at baseline to 25.4 at one year after stimulation [22]. Additionally, it was reported that Global Assessment of Functioning Scale (GAF) scores drastically improved from a mean of 36.6 at baseline to 53 at the one-year follow up. No adverse events were reported during the implantation, but several patients experienced transient hypomania or agitation and anxiety after an increase in voltage; however, this was reversed when voltage was adjusted. In terms of long-term effects, Ooms et al. conducted a study from 2005 to 2011 to analyze the long-term QoL of the patients who underwent DBS at the nucleus accumbens for the Denys et al. study [23]. In terms of OCD symptoms, mean Y-BOCS improvement between one month prior to implantation to after three to five years of stimulation was 46.7%. The average duration of post-surgery follow-up was four years and three months, and QoL was measured using the WHO Quality of Life Scale-Brief Version that included one general score and four domain scores (physical, psychological, social, and environmental). The study reported that the QoL of the patients showed a mean improvement of 90% in the general score, 39.5% in the physical and psychological domains, and 16% in the environmental domain after a minimum of three years of active stimulation.

Table 3. Mean baseline and post-DBS Y-BOCS scores and mean improvement for studies targeting the NA

Study	Baseline Y-BOCS Score	Post-DBS Y-BOCS Score	Y-BOCS Improvement
Denys et al. [9]	33.7±3.6	16.2±8.6	52%
Ooms et al. [25]	33.75±3.62	18±9.2	46.7%
Huff et al. [24]	32.2 ± 4.0	25.4±6.7	21%

Inferior thalamic peduncle, subthalamic nucleus, medial forebrain bundle

In addition to the three regions previously discussed, there have also been numerous other investigated targets of DBS for TROCD. These include the inferior thalamic peduncle, subthalamic nucleus, and the medial forebrain bundle. A summary of the findings on DBS in these regions with respect to Y-BOCS scores can be found in Table 4.

The inferior thalamic peduncle is a bundle of fibers linking the intralaminar, paralaminar, and midline thalamic nuclei with the orbitofrontal cortex [15]. The inferior thalamic peduncle initially showed promising outcomes as a

DBS target for major depressive disorder (MDD), and as MDD and OCD pathology are believed to be involve similar neurotransmitters and show metabolic hyperactivity in the same regions, this region began to be investigated as a DBS target for TROCD [15,24]. In Jiménez-Ponce et al., five patients were implanted with bilateral tetrapolar electrodes aimed at the inferior thalamic peduncle, and subsequently followed up with every three months for a year after treatment. Improvement in the patients' OCD symptoms was seen with a mean 49.1% improvement in the Y-BOCS score, and their QoL was improved as seen in a 53% above baseline GAF score [24]. Jiménez et al. (2013) and Lee et al. (2018), yielded similar results in terms of OCD symptoms with decreased Y-BOCS scores by 51% and 54%, respectively [25,26]. There were no adverse events reported in either Jiménez-Ponce et al. or Jiménez et al. However, Lee et al. reported serious adverse effects in two patients, one who was hospitalized twice in the 51-month period after implantation due to substance abuse and overdose, and another who requested removal of the DBS device as it became an object of obsession and caused severe distress.

The subthalamic nucleus is an important structure in the basal ganglia, which acts as an intersection where different components of behaviour are processed through motor, limbic, and cognitive projections coming together [27]. The subthalamic nucleus became a potential DBS target for OCD after it was observed that targeting it with DBS for Parkinson's disease patients with comorbid OCD not only improved Parkinson's symptoms, but also resulted in a significant decrease of OCD symptoms [27]. In a double-blinded crossover study by Mallet et al., eight TROCD patients underwent stimulation of the subthalamic nucleus with two separate follow up periods of 3 months for the sham and active stimulations [28]. By the end of the study, the mean Y-BOCS score improvement from baseline to the end of active stimulation was 36.7%, and 62% of participants had improved GAF scores, with response criterions of a 25% decrease in Y-BOCS scores and a minimum GAF score of 51 corresponding with "moderate symptoms or moderate difficulty in social or occupational functioning" [28]. However, there were significant side effects, with 15 serious adverse events reported in 11 patients out of 47, with one permanent finger palsy resulting from a parenchymal brain hemorrhage, two infections leading to the removal of the electrode, and seven related to the stimulation that were transient [28]. Additionally, the effects of subthalamic nucleus DBS on risk-taking for rewards and avoiding losses were investigated in Voon et al [29]. It was reported that targeting the subthalamic nucleus has a variety of effects, as participants who underwent subthalamic nucleus DBS showed reduced sensitivity to magnitude during loss anticipation, and a decreased risk-taking to reward prospects to similar levels as those of healthy controls [29].

The medial forebrain bundle stemmmming from the basal olfactory regions is a relatively newer target for DBS, and similar to other targets, it is being investigated for OCD due to the fact that it has been shown to have promising outcomes when targeted for MDD [30]. As this is a newer target, the trials testing the region are very limited, with the primary study being that of Coenen et al., published in 2016 [14]. This paper presented two patients who were bilaterally implanted with DBS systems in the supero-lateral branch of the medial forebrain bundle with a follow up time of a year. Their average Y-BOCS improvement from baseline to one year follow-up was 40.6%. The first patient experienced a 35% in his Y-BOCS score when evaluated at the one year follow up, and the other reached a Y-BOCS score associated with remission [14] at three months after surgery and his final one year follow up score was just above that threshold. Further, no adverse events were reported for either patient, but as this work was a case report, it is unclear whether targeting the medial forebrain bundle in general consistently yields no adverse events.

Table 4. Mean baseline and post-DBS Y-BOCS scores and mean improvement for studies targeting the inferior thalamic peduncle, subthalamic nucleus, and medial forebrain bundle

Study	Target	Baseline Y-BOCS Score	Post-DBS Y-BOCS Score	Y-BOCS Improvement
Jiménez -Ponce et al. [33]	Inferior thalamic peduncle	35± 3.75	17.8 ± 2	49.1%
Jiménez et al. [27]	Inferior thalamic peduncle	35.8 ± 5.87	17.5 ± 3.6	51.1%
Lee et al. [28]	Inferior thalamic peduncle	35 ± 1.25	16.8*	52%
Mallet et al. [30]	Subthalamic nucleus	32.29± 2.25	19± 8	41.2%
Coenen et al. [14]	Medial forebrain bundle	34.5*	20.5*	40.6%

*Table note: Standard deviation for post-DBS Y-BOCS scores in the Lee et al. study were not reported. Standard deviation was also not reported for the Coenen et al. study as the data was taken from only two participants.

Discussion

The improvement of OCD symptoms as a result of DBS at the various targets was measured through Y-BOCS scores in the majority of the reviewed studies, with the exception of Ooms et al., that analyzed long-term QoL, and Winter et al. that assessed the perceived symptoms and emotional states of participants through visual analog scales [17,25]. The most substantial Y-BOCS improvements were seen from investigating the ventral capsule [10,18,19] and the inferior thalamic peduncle [26,27,28], with Y-BOCS improvements for each target ranged from 35% - 38% for the stria terminalis [11,13,16], 38%-63% for the ventral capsule [10,18,19], 21%-52% for the NA [9,16,24], and 49%-54% for the inferior thalamic peduncle. Only one paper for the subthalamic nucleus and medial forebrain bundle reported on Y-BOCS scores, and the improvements were 36.7% for the subthalamic nucleus and 40.6% for the medial forebrain bundle (Tables 1-4) [14,30]. The improvement in Y-BOCS scores at baseline and after DBS treatment were reported to gauge response levels. As mentioned prior, a Y-BOCS score reduction of ≥35% is commonly used as the threshold for 'response' to OCD treatment, but there were also several studies that did not set a specific threshold for response, and instead reported the improvement in YBOCS scores without a comparison to a target score. For example, Jiménez et al., Lee et al., (both targeted the inferior thalamic peduncle), Coenen et al. (targeted the medial forebrain bundle), and Islam et al. (targeted the stria terminalis) all reported Y-BOCS scores of individual participants at baseline and after treatment without comparing them to a set criterion [16,27,28]. The differences in the use of a set Y-BOCS score response threshold are likely due to the variation of response levels in the participants, both within the same study and across different studies, as seen in the results. Overall, the presence of a reference threshold was not critical when comparing efficacies of targeting the different regions, since we were able to directly compare the Y-BOCS score improvements that were reported for most studies.

Secondary outcomes, on the other hand, were measured using a wide variety of methods. These outcomes included anxiety, depression, QoL, and daily functional ability. The most common secondary outcomes measured were anxiety and depression, with most studies having reported on at least one, if not both. Depression as a secondary outcome was measured by three studies targeting the stria terminalis [11,13,16], three targeting the NA [9,16,24], three targeting the ventral capsule/ventral striatum [10,18,19], two targeting the subthalamic nucleus [25,30], one targeting the medial forebrain bundle [14], and one targeting the inferior thalamic peduncle [28]. An example is seen in the study by Bouwens van der Vlis et al., obtained a critical finding by measuring secondary factors such as depressive symptoms, anxiety, and QoL caused by DBS in the ventral capsule [19]. The study was able to conclude significant improvements in depressive symptoms (as measured by the BDI-II) with patients showing clinically improvement from severe depression to moderate depression. In addition, anxiety scores decreased in patients by 35% or more at the time of their last follow-up. However, the QoL was not affected by DBS to the ventral capsule which alludes to the idea that although DBS alleviated anxiety, the results were not enough to translate to day-to-day functioning. Overall, three different scales were used to measure depression across the different studies: the Hamilton Depression Rating Scale, the Beck Depression Inventory, and the Montgomery-Asberg Depression Rating Scale. Anxiety was reported as a secondary outcome measure by two studies targeting the nucleus accumbens [9,16], two studies targeting the ventral capsule/ventral striatum [18,19], and one study targeting the subthalamic nucleus [30]. Anxiety, like depression, was often measured using different methods, and these include: the Hamilton Anxiety Rating Scale, the State-Trait Anxiety Inventory, and the Brief Scale for Anxiety. Daily functional ability was measured through the GAF and/or the Sheehan Disability Scale (SDS).

GAF scores were measured by two inferior thalamic peduncle studies [27,33], one stria terminalis study [13], and one ventral capsule/ventral striatum study [19]. nucleus accumbens study used the SDS, and one subthalamic nucleus study used both GAF and the SDS [9,30]. Lastly, QoL was only explicitly measured as a secondary outcome in two studies, one targeting the inferior thalamic peduncle and one targeting the nucleus accumbens [25,28]. The inferior thalamic peduncle study used the SF-36 Quality of Life Assessment, while the nucleus accumbens study used the WHO Quality of Life Scale-Brief Version [25,28]. As seen, the large variability in both types of secondary outcomes measured and the methods used to measure them makes it difficult to reliably compare the effectiveness of different DBS targets on this basis. Further, because we were unable to find literature reporting on certain secondary outcomes for some targets (e.g., ventral capsule/ventral striatum and QoL), research remains mixed regarding the impact of DBS at these targets on the aforementioned outcomes.

Additionally, a new development in the field of DBS for TROCD is the stimulation of multiple targets at once to gauge the potential synergistic benefit of the different sites. Dual approach methods are becoming more popular and were not seen as much in the past due to the lack of technology supporting a dual system. In this type of system, the electrodes are connected to one another even though they are placed on different brain regions. This allows clinicians to manipulate voltages to an area individually, or simultaneously and record both qualitative and quantitative observations. In particular, Tyagi et al. conducted a recent study that was the first to compare the efficacy of DBS at two sites in the same participants [10]. The ventral capsule/ventral striatum and subthalamic nucleus were stimulated, and it was reported that while DBS at each site

was successful in reducing OCD symptoms as measured by the Y-BOCS scale, symptom severity did not significantly change following combined stimulation. However, DBS at the subthalamic nucleus was more effective at improving cognitive flexibility (the ability to shift the focus of attention to adapt to changing circumstances) while ventral capsule/ventral striatum DBS was able to elicit a greater improvement in mood as measured by the MADRS. Additionally, there were no common serious adverse effects associated with the stimulation of either target or combined stimulation [10]. Stimulation-induced hypomania was reported as the main adverse event, but this is frequently reported in other studies and no longer presented as an issue after adjustment. This study highlights the importance of understanding the involvement of different neural circuits implicated in OCD, as while the Y-BOCS efficacies did not differ between the two sites, there was clear variability in mood and cognitive flexibility improvement. The ventral capsule as stated above is responsible for mediating the reward centre and cognitive processing, and when this target is stimulated, the reward centre is activated reducing mood-related symptoms that individuals with TROCD commonly experience [10]. When combined with the subthalamic nucleus which is responsible for memory and learning, cognitive flexibility can also be improved [10]. In this study, the lack of negative adverse effects and similar Y-BOCS efficacy of the combined stimulation when compared to the individual targets implicates a potential direction of research where multiple sites can be stimulated to leverage the different circuitries and improve secondary outcomes in addition to the primary Y-BOCS score [10].

Another interesting new direction in the field of DBS for TROCD is individualizing the implantation lead locations within each target. Barcia et al. proposed a new mechanism that highlights an individualized approach to DBS as a potential treatment for TROCD, providing an alternative to using a standardized approach for all patients [34]. The study was a double-blinded and randomized trial targeting four points within the nucleus accumbens. They noted that six out of the seven participants showed varying levels of improvement to each stimulation point. In the future, this can be used to determine the most effective stimulation site for every individual, thereby increasing the success rate of the overall treatment [34].

In terms of adverse effects, the most common event across most studies reviewed was transient hypomania for several days after stimulation, which was resolved with adjustment. This was reported by studies targeting the stria terminalis, ventral capsule/ventral striatum, nucleus accumbens, and the subthalamic nucleus. However, as the hypomania typically was resolved either naturally or with adjustment to the stimulation voltage, it was not considered as a serious adverse event by any of the studies. Islam et al. and Greenburg et al., who targeted the stria terminalis and ventral capsule/ventral striatum respectively, both reported occurrences of seizures [16,19]. Infections at the implantation site were another adverse event observed at multiple targets, namely Greenburg et al. (ventral capsule/ventral striatum), Moseley et al. (stria terminalis), Naesström et al. (stria terminalis), and Mallet et al. (subthalamic nucleus) [11,13,19,30]. Transient mood and anxiety-related side effects were observed in the studies conducted by Naesström et al., Greenburg et al., Mallet et al., and Huff et al. (nucleus accumbens), and all of these effects were reversed within minutes, hours, or days at the most [13,19,24,30]. The studies with the greatest number of side effects were Mallet et al. (15 serious and 23 non-serious adverse events out of 45), Greenburg et al. (three implantation related, 11 stimulation related, and several that were categorized as "mood elevation/hypomania" out of 26), Naesström et al. (three serious events and five non-serious out of 11), Denys et al., (targeted the nucleus accumbens, six surgery related, three device related, 21 stimulation related out of 70), and Huff et al. (six stimulation related, one after implantation, and five long-term out of 11) [9,13,19,24,30]. The large variety of adverse events occurring at different targets implies that there is likely no one 'perfect' site for DBS implantation, and one can expect certain transient side effects with DBS for TROCD at any site such as hypomania and other mood and anxiety-related effects. From the comparison of adverse events, it seems as though there are minimal adverse events observed with targets such as the medial forebrain bundle and inferior thalamic peduncle, but this can be attributed to the low number of studies done on these sites and the small sample sizes of the currently available studies. Similarly, the large number of side effects reported from the studies mentioned above can potentially be attributed to larger sample sizes, more extensive follow-up, or a lower threshold for reporting. Additionally, it was observed that studies targeting the same region often did not present similar side effects, and in some cases there were studies reporting multiple adverse events while others reported none for the same site [9,13,17–19,23]. Examples of this include Greenburg et al. and Bowens van der Vlis et al. for the ventral capsule/ventral striatum, Naesström et al. and Winter et al. for the stria terminalis, and Denys et al. and Sturm et al. for the nucleus accumbens. Overall, it is evident that further research is required to form definitive conclusions on which regions are associated with better outcomes with respect to adverse events.

A common observation noted was the variable number of studies targeting each region. For example, the nucleus accumbens and ventral striatum was seen to have the most research participants and studies, while the medial forebrain bundle was seen with the least number of participants and studies. This division can be attributed to the two neural pathways and their relationship with TROCD in current scientific investigations. Both the nucleus accumbens and the ventral capsule regulate reward, cognition, and reinforcement of behaviours. It is postulated that stimulating the reward and cognition of the brain deviates

symptoms consistent with OCD. The first paper published on DBS at the ventral striatum/nucleus accumbens regions with regards to TROCD was in 2003 [23]. Nonetheless, the medial forebrain bundle is also noted to be associated with reward and pleasure centres but is supported with only one study published in 2017 [14].

Future research is expected to focus more on the medial forebrain bundle and its possible multi-targeted approach with other regions that show great promise [14]. The differing number of participants is the result of how rare TROCD is, appearing in 2.3% of individuals out of the 40-50% who have OCD [2,3]. The varying number of individuals was therefore taken into account by reporting mean and SD scores to avoid data inconsistencies. Moreover, the process of inserting electrodes into the brain is complex and difficult making it unlikely for studies to conduct mass trials. The results of smaller trials like those by Winter et al. showed numerous complications with seizures and infections. Prior to doing a mass trial it is important to mitigate such risks. The limitations of this review are similar to the limitations of the field of DBS for TROCD, namely the lack of comprehensive literature with consistent results and the small sample sizes that make replicating findings and making definitive conclusions difficult.

Conclusion

Overall, the targets with the most promising Y-BOCS improvements, as previously mentioned, were the ventral capsule and the inferior thalamic peduncle [18,28]. However, due to the limited number of studies on DBS for TROCD and small sample sizes used, an ideal target for TROCD DBS remains elusive. This is further supported by the wide variety of secondary outcomes measured and adverse events reported for each region. There are several promising areas for future research in this field, with targeting multiple regions in single individuals similar to Tyagi et al., being a significant one [10]. Additionally, stimulating personalized targets within each region (such as in Barcia et al.), further investigating the medial forebrain bundle, and implementing a focus on adverse events and their impact on long-term QoL for different targets are all also promising future directions of research for TROCD DBS [34].

List of Abbreviations Used

CBT: cognitive behavioral therapy
DBS: deep brain stimulation
Y-BOCS: Yale Brown Obsessive Compulsive Scale
GAF: global assessment of functioning
MDD: major depressive disorder
TROCD: treatment refractory obsessive compulsive disorder
SSRI: selective serotonin reuptake inhibitor
QoL: Quality of Life
SDS: Sheehan disability scale

Conflicts of Interest

The authors declare no conflicts of interest.

Ethics Approval and/or Participant Consent

As this paper is a systematic review, no ethics approval was required.

Authors' Contributions

HM: made equal contributions in this manuscript including the design and research of the work and can be held equally as accountable for all aspects of this study. Specifically including drafting of the manuscript, quality, content, and collectively approving the final version to be submitted.
VV: made equal contributions in this manuscript including the design and research of the work and can be held equally as accountable for all aspects of this study. Specifically including drafting of the manuscript, quality, content, and collectively approving the final version to be submitted.

Acknowledgements

We would like to thank and convey our heartfelt appreciation to Yu Bin Tan for her support and expertise throughout this process.

Funding

This paper was not funded.

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Article Information
Managing Editor: Jeremy Y. Ng
Peer Reviewers: Yu Bin Tan, Ricky Chow
Article Dates: Received Dec 12 21; Accepted Mar 03 22; Published May 11 22

Citation
Please cite this article as follows:
Mahdi H, Vashi V. Comparing major targets of DBS in individuals with treatment-refractory OCD: A systematic review. URNCST Journal. 2022 May 11: 6(5). https://urncst.com/index.php/urncst/article/view/347
DOI Link: https://doi.org/10.26685/urncst.347
