Changes in Cognitive Function from Baseline to 1-Year Follow-Up Post VC/VS Deep Brain Stimulation Treatment for Severe Obsessive-Compulsive Disorder

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Thesis

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Shout out to women in STEM! I'm proud to be the newest member of the squad.

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Code Directory

BL Y-BOCS: Baseline Y-BOCS
FU-YBOCS: Follow-Up Y-BOCS
WMS: Wechsler Memory Scale
WMS_DS: WMS Digit Span scaled score
WMS_LNS: WMS Letter-Numbering Sequence scaled score
WMS_SS: WMS Spatial Span scaled score
WMS_LMI: WMS Logical Memory I scaled score
WMS_LMII: WMS Logical Memory II scaled score
WMS_FI: WMS Faces I scaled score
WMS_FII: WMS Faces II scaled score
BVMT: Brief Visuospatial Memory Test-Revisited
BVMT_DR: BVMT Delayed Recall scaled score
BVMT_TR: BVMT Total Recall scaled score
BVMT_L: BVMT Learning scaled score
BVMT_DISC: BVMT Discrimination raw score
CVLT: California Verbal Learning Test
CVLT_SUM: CVLT Sum of T1-T5 raw score
CVLT_SDFR: CVLT Short Delayed Free Recall z-score
CVLT_SDC: CVLT Short Delayed Cued Recall z-score
CVLT_LDFR: CVLT Long Delayed Free Recall z-score
CVLT_CVLT_LDC: CVLT Long Delayed Cued Recall z-score
CVLT_SEM: CVLT Semantic Clustering z-score
CVLT_TLS: CVLT Total Learning Slope z-score
CVLT_TR: CVLT Total Repetitions z-score
CVLT_LB_IFR: CVLT List B Immediate Free Recall z-score
CVLT_TRD: CVLT Total Recognition Discriminability z-score
WCST: Wisconsin Card Sorting Test
WCST_PR: WCST Perseverative Responses scaled score
WCST_TC: WCST Total Correct raw score
IGT: Iowa Gambling Test
IGT_NT: IGT Net Total scaled score
WCST_C: WCST Categories raw score
WCST_LS: WCST Loss of Set raw score
DKEFS: Delis-Kaplan Executive Function System test
DKEFS_LF_C1_TC: DKEFS Letter Fluency Category 1 Total Correct scaled score
DKEFS_CF_TC: DKEFS Category Fluency Total Correct scaled score
DKFS_CS_TCR: DKEFS Category Switching Total Correct Responses scaled score
DKEFS_CS_SA: DKEFS Category Switching: Switching Accuracy scaled score
DKEFS_E_PSLE: DKEFS Errors Percent Set Loss Errors scaled score
DKEFS_E_PRE: DKEFS Errors Percent Repetition Errors scaled score
DKEFS_TM_C1: DKEFS Trail Making Category 1 scaled score
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DKEFS_TM_C4: DKEFS Trail Making Category 4 scaled score

DKEFS_TM_C4_E: DKEFS Trail Making Category 4 Errors scaled score
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DKEFS_TM_CSS: DKEFS Trail Making Combined scaled score
DKEFS_CWI_C1: DKEFS Color-Word Interference Category 1 scaled score
DKEFS_CWI_C2: DKEFS Color-Word Interference Category 2 scaled score
DKEFS_CWI_C3: DKEFS Color-Word Interference Category 3 scaled score
DKEFS_CWI_C4: DKEFS Color-Word Interference Category 4 scaled score
DEKFS_CWI_CCN: DKEFS Color-Word Interference Combined Color Naming and Word Reading scaled score
DKEFS_CWI_ITE: DKEFS Color-Word Interference Inhibition Total Errors scaled
DKEFS_CWI_ISTE: DKEFS Color-Word Interference Inhibition-Switching Total Errors scaled score
GPB: Grooved Peg Board
GPB_D: GPB Dominant Hand scaled score
GPB_ND: GPB Non-Dominant Hand scaled score
JLO: Judgment of Line Orientation
JLO_RS: JLO Raw Score
RCFT: Rey Complex Figure Test
RCFT_C: RCFT Copy raw score
RCFT_IR: RCFT Immediate Recall t-score
RCFT_DR: RCFT Delayed Recall t-score
BNT: Boston Naming test t-score

INTRODUCTION

Background

Obsessive-Compulsive Disorder (OCD), marked as a top 10 most debilitating disorder by the World Health Organization, affects 2-3% of the general population (Öst et al. 2015; Benzina et al. 2016). Its debilitating characteristics can be best described as intrusive and recurring thoughts, images, or urges known as obsessions and a person's conscious attempt to reduce or neutralize their discomfort through ritualized rules and time-consuming behaviors manifested through compulsions (Öst et al. 2015; Jacobson and Newman 2016; Benzina et al. 2016). The characteristics of the obsessions paired with repetitive behaviors or mental acts performed in response to distressing thoughts can become so consuming that OCD has been linked to a lower quality of life through distress and functional impairment at work, socially, or at home (Öst et al. 2015; Koning et al. 2013).

Diagnosis and Quality of Life

It is believed that those diagnosed with Obsessive-Compulsive Disorder have a genetic predisposition to the disorder (Veale 2014). Environmental factors such as psychosocial stressors, developmental factors, and trauma can additionally affect certain neural pathways leading to the prevalence of OCD (Pauls 2014).

Although early diagnosis and treatment can yield improved treatment outcomes, those with early onset diagnosis also have a higher chance of comorbidities (Jacobson and Newman 2016). Lifetime diagnoses of anxiety, depressive disorders, bipolar disorders, impulse disorders, and substance abuse are present in an estimated 80% of OCD patients (Jacobson and Newman

2016; Meier et al. 2016). Psychiatric comorbidities are decidedly a primary factor for worse outcomes; the risk of premature death is doubled, with the risk of suicide tripled, and the risk of an accidental death doubles when compared to the general population (Meier et al. 2016).

Currently there are no lab tests to confirm a diagnosis, symptoms are often noticed by family members or general practitioners and can be misdiagnosed as anxiety or depression, causing reduced substandard treatment outcomes (Veale 2014; Grant 2014). People are likely to be diagnosed either before age 10 or between the ages of 17 and 30, with 30-50% of individuals diagnosed before the age of 10 (Jacobson and Newman 2016; Grant 2014; Pauls 2014). Avoidance of fears and threats, such as the threat of the disorder itself, is a primary symptom of OCD. Due to this denial, some suffering from OCD often seek treatment 10 years after first experiencing symptoms (Veale 2014).

Delays in treatment lead to increased dysfunction and lowered quality of life compared to an early diagnosis and treatment plan (Grant 2014; Alonso et al. 2001). Surveys show that one-third of patients with OCD refuse treatment, leave treatment early, or do not show improvements. A formal diagnosis is determined after initial screening questions, followed by ICD-10 and DSM-IV examinations (Veale 2014). A diagnosis typically includes the presence of obsessive thoughts for more than one hour each day (Grant 2014). These thoughts often arise from an original dysfunctional belief; perceived threats stemming from the dysfunctional belief lead to compulsive actions aimed to lessen or nullify the perceived threat creating a self-reinforcing cycle of obsessions and compulsions (Veale 2014; Jacobson and Newman 2016).

Neurological Pathophysiology

Over time the following parts of the brain have had a confirmed role in OCD: cingulate, prefrontal (orbitofrontal and frontal), parietal, and temporal cortices; basal ganglia (striatum and amygdala), and cerebellum (Del Casale et al. 2011). Successful treatment of the corticostriatal pathophysiological model (referenced in the literature as the cortico-striato-thalamo-cortical (CSTC), cortico-basal ganglial circuit, orbital-striatal-thalamic loop, and frontal-basal ganglia-thalamic circuit), has led to the model's consensus among researchers (Lopes et al. 2009, Rasmussen, Eisen, Greenberg 2012; Haber and Heilbronner 2013; Harrison et al. 2009; Dougherty et al. 2002). Additionally, there is an emphasis on treating the affected *network* within the implicated region rather than a specific structure; this emphasis is owed to the amount of success researchers have had in their patients when stimulating multiple sites within the cortico striato thalamocortical circuit (Haber and Heilbronner 2013; Cleary et al. 2015). Primary differences between a healthy control and an OCD patient can be found within the prefrontal cortex's orbitofrontal cortex (OFC), caudate nucleus, thalamus, and striatum. Within the striatum, it is believed that "inefficient gating" at the thalamic level leads to hyperactivity within the OFC, corresponding to increases in intrusive thoughts and hyperactivity within the anterior cingulate cortex (ACC); the ACC's hyperactivity is believed to add to OCD's characteristics of non-specific anxiety (Del Casale et al. 2011). In an attempt to neutralize the dysfunction within the striatum, compulsions are manifested to alleviate the deficient thalamic gating (Del Casale et al. 2011).

The dysfunction between the ACC, OFC, and striatum leads to not only the increased visibility of OC symptoms, but also their initial development since the system's structures become increasingly abnormal in an attempt to compensate for the other's hyperactivity (Harrison et al. 2009; Rasmussen, Eisen, Greenberg 2012). The flaws within this network

explain the altered cognitive functions associated with the clinical expressions of the disorder (Benzina et al. 2016). Clinical manifestations such as impulsivity and a lack of cognitive flexibility further the evidence linking the frontal lobe and its subcortical structures (Grant 2014). The adversely altered network within the striatum has provided a way for abnormal activity within the hippocampus; a region similarly linked to PFC activity and associated with memory (Del Casale et al. 2011).

To confirm this neuropathophysiology PET, SPECT, and symptom provocation studies have all displayed increased activity within the OFC and ACC in patients with OCD (Rasmussen, Eisen, Greenberg 2012; Harrison et al. 2009). It was even found that the recorded abnormal activity of orbital-striatal function has a correlation to a patient's OCD severity (Rasmussen, Eisen, Greenberg 2012). The altered functions of someone with OCD have been likewise linked to the serotonin, dopamine, and glutamate systems. Due to these findings, successful treatments include the use of serotonin reuptake inhibitors ideally paired with cognitive behavioral therapy as well as neuromodulation and ablative therapies targeting the disruption of the dysfunctional corticostriatal pathophysiological model.

It should be stated that a singular model of regions in the brain responsible for OCD is not applicable to every patient (Del Casale et al. 2011). The subtype and severity of each case create distinct pathophysiologies and favorability in outcomes.

Treatment Methods

Pharmacotherapy

Pharmacotherapy for the treatment of OCD most commonly uses serotonin reuptake inhibitors (SRIs), serotonin-norepinephrine reuptake inhibitor (SNRIs), and clomipramine

(Romanelli et al. 2014). SRIs are chosen over clomipramine due to a more favorable safety profile. Results from head-to-head trials between different types of SRIs have shown no significant difference (Hirschritt, Bloch, Matthews 2017; Grant 2014). While SRIs are commonly used and known for depressive disorder treatment, in greater doses they have been shown to have a significant effect on patients with OCD compared to placebos (Öst et al. 2015; Veale 2014). Pharmacotherapy tends to have a positive response in patients with 40-65% experiencing an improvement in symptoms (Grant 2014). The optimal treatment plan for SRIs is the "maximal tolerated dose" for 8 to 12 weeks, continued for at least 6 to 12 months after response to treatment (Hirschritt, Bloch, Matthews 2017). Patients that have a positive response to pharmacotherapy treatment generally continue with this method for one to two years; however, symptom relapse is common in 25-40% of patients after medication is discontinued (Grant 2014).

Cognitive and Behavioral Therapy Treatments

Psychotherapy, including Cognitive and Behavioral therapy, is the most practiced approach to anxiety disorders such as OCD (Deacon and Abramowitz, 2004). Cognitive therapy (CT) is used for patients who "lack insight into their obsessions" and are unable to directly face their OCD's triggers (Hirschritt, Bloch, Matthews 2017). CT involves a cognitive restructuring through a focus on the identification of a patient's obsessions to correct and question the logic behind the patient's beliefs (Jacobson and Newman 2016; Grant 2014; Deacon and Abramowitz 2004). Through careful monitoring of a patient's obsessions and actions derived from these obsessions, clinicians encourage patients to reevaluate the consequences of "engaging in or refraining from compulsive behaviors" (Grant 2014). Without specifically focusing on the

anxiety stemming from unrealistic compulsions, beliefs, or exposure the patient's beliefs are identified and tested in a pragmatic manner to ultimately lessen their anxiety without the negative connotations drawing the total focus. Patients prematurely leave their cognitive therapy treatments at a rate of 20-30% (Grant 2014).

Behavior Therapy "involves procedures based on learning theory, such as exposure or relaxation" (Deacon and Abramowitz 2004). A key behavioral technique used in this form of therapy is Exposure and Response Prevention (ERP), which since 1966 has improved the prognosis for OCD patients as repeated exposure to stimuli reduces anxiety and compulsive actions due to a process called habituation (Deacon and Abramowitz 2004).

Cognitive Behavioral Therapy (CBT) utilizes both behavioral and cognitive therapeutic procedures, involving exposure to stimuli (Deacon and Abramowitz 2004). CBT bluntly exposes and provokes a patient to confront the anxieties and physical manifestations of OCD (Jacobson and Newman 2016; Öst et al. 2015). Utilizing Behavior Therapy's ERP approach is recommended for patients who are motivated to work with an emotionally and time demanding therapeutic schedule. Cognitive therapies that involve behavioral therapeutic exposures such as ERP are the optimal form of treatment (Deacon and Abramowitz 2004), yet 25% of patients refuse to experiment with ERP due to the continuous, direct exposure to the stimuli that "provoke obsessions and the accompanying anxiety and distress" (Öst et al. 2015; Veale 2014; Jacobson and Newman 2016; Hirschritt, Bloch, Matthews 2017).

The probability of a partial remission in symptoms is less than 50% following a full course CBT treatment (Alonso et al. 2001). Such remission includes the improvement of behavioral compulsions rather than the decrease in obsessive thoughts (Alonso et al. 2001). Seventy-five percent of patients demonstrate recurrent OCD symptoms post treatment (Jacobson

and Newman 2016). Barriers to the success of CBT include lack of availability of clinicians, patient-doctor relationships, substantial time requirements, high out-of-pocket expenses, and the need for motivation to engage in this intense confrontation of their disability (Hirschritt, Bloch, Matthews 2017; Deacon and Abramowitz 2004).

Combination Therapies

When directly compared, a slight benefit towards CBT with an emphasis on ERP as a treatment over pharmacotherapy is observed (Romanelli et al. 2014). When CBT as a monotherapeutic approach is unsatisfactory or a patient exhibits significant comorbidities, pharmacotherapy is often paired with CBT (Romanelli et al. 2014; Grant 2014). However, the significantly improved outcomes when employing combination therapy proved more beneficial to those who were only on SRIs compared to those only undergoing CBT (Romanelli et al. 2014; Grant 2014). Using both CBT and pharmacotherapy is recommended for patients who prefer to be less dependent on medication as the time spent in CBT can help offset symptom relapse once the medication's treatment course is finished (Grant 2014).

Neurosurgery

Although CBT and pharmacotherapy have higher success rates when combined, according to one study 36.7% of the participants were resistant to the combined treatment (Alonso et al. 2001). This study along with other meta-analyses results demonstrate the prevalence of residual symptoms due to ineffective therapeutic attempts (Alonso et al. 2001; Grant 2014; Romanelli et al. 2014). It is estimated that greater than 10% of OCD patients experience refractory illness and remain severely disabled post pharmacotherapy and cognitive

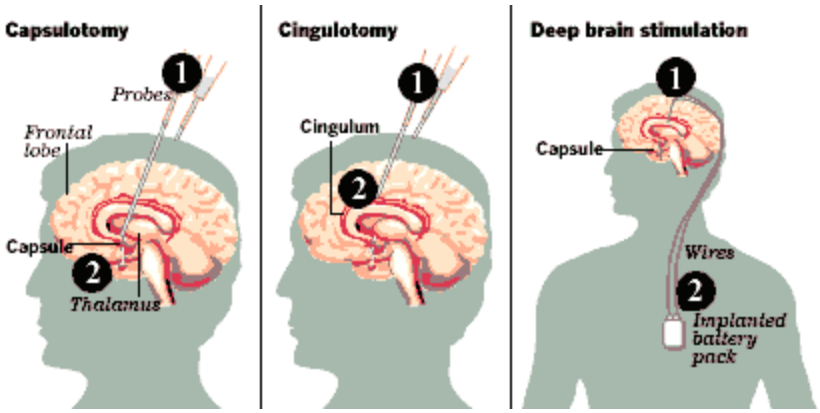
behavior therapy (Kim et al. 2003). Due to this lack of success, more invasive neurosurgical techniques have been developed to treat OCD in patients with "severe, treatment-refractory symptoms" (Hirschritt, Bloch, Matthews 2017). For years doctors have looked towards neurosurgery as a treatment option for mental disorders. Currently neuromodulation and ablative procedures are the two forms of neurosurgery available as options today.

Ablative Procedures

Treatment alternatives for patients with refractory OCD include four ablative procedures: anterior cingulotomy, anterior capsulotomy, subcaudate tractotomy, and limbic leucotomy. Each involves lesioning a section of the brain involved in the corticostriatal circuit (McLaughlin and Greenberg 2012; Dougherty et al. 2002). While studies show positive response rates ranging from 50-60%, the more an ablative procedure is repeated in a patient, the higher the risk for adverse effects; these procedures are thus reserved for the most severe patients as a final and intensive treatment option (Hirschritt, Bloch, Matthews 2017; McLaughlin and Greenberg 2012; Veale 2014; Alonso et al. 2015). Currently anterior capsulotomies and cingulotomies are most common in the United States with subcaudate tractotomies and limbic leucotomies not as often performed, yet useful from a historical perspective.

Figure 1: The locations for the 3 main locations for invasive treatment.

Anterior capsulotomy and anterior cingulotomy are known as ablative procedures for their irreversible, purposeful lesions. DBS qualifies as a neuromodulation as it does not make defined lesions within the brain tissues as treatment (Image taken from https://www.mentalhealthbookclub.com).



Anterior Capsulotomy

In an anterior capsulotomy, the fibers that connect the dorsomedial thalamus to the PFC and subgenual anterior cingulate are interrupted by the creation of neurosurgical lesions. This procedure is performed with either thermolesions through radio frequency, or stereotactic radiosurgery using gamma rays. Using a gamma knife approach has increased recently due to its non-invasive characteristic (McLaughlin and Greenberg 2012). In the more recently common procedure, "bilateral, double-shot capsulotomy lesions" are targeted in the ventral portions of the anterior limb and are made through beams of gamma radiation (Lopes et al. 2009). The area of the internal capsule was also used in beginning research experimenting with Deep Brain Stimulation for OCD (Pepper, Hariz, Zrinzo 2015). Gamma knife capsulotomies have been shown to produce an improvement in 55-70% of patients and presented a decreased activity in the PFC (Lopes et al. 2009). According to one study, not only did OCD severity improve at the one-year follow-up, there was a consistent decline displaying stable improvement with capsulotomy (Ruck et al. 2008). Improvement from capsulotomy procedures is believed to be caused by the direct interruption to the dysfunctional circuit implicated in the neuropathophysiology of this disorder (Lopes et al. 2009).

Performing anterior capsulotomy procedures with Laser Interstitial Thermal Therapy (LiTT) instead of a gamma knife involves risks such as hemorrhages, hematomas, and ipsilateral motor weakness (Hoppe et al. 2017). When looking at adverse effects of a gamma knife procedure, cysts have been found to develop after a three to five-year delay post-surgery, with one patient reported as developing cysts sooner (McLaughlin and Greenberg 2012; Rasmussen et al. 2018). In both procedures nausea, vomiting, discrete pain on the scalp from the stereotactic frame positioning, and headaches have been reported by patients postoperatively as neurological adverse effects (Rasmussen et al. 2018; Lopes et al. 2009; Hoppe et al. 2017). Other medical events such as weight and appetite changes, blurred vision, and an impaired emotional well-being have been reported over 36 months of follow-up by patients (Lopes et al. 2009; Hoppe et al. 2017). Necrosis from the gamma radiation is thought to unfavorably affect other systems adjacent to the targeted corticostriatal circuit (Lopes et al. 2009).

Anterior Cingulotomy

The approach to create lesions in the anterior cingulum was developed in 1947. Over time the technique has developed to incorporate thermocoagulation, using thermistor electrodes to lesion the cingulum (McLaughlin and Greenberg 2012). These lesions are placed within the dorsal anterior cingulate to decrease mass and activity within the ACC and fibers of the cingulum (Kim et al. 2003). It has become the most widely used neurosurgical method to treat OCD in the United States (McLaughlin and Greenberg 2012). Recently it was reported that more than 25% of patients who underwent anterior cingulotomy responded positively to the treatment, displaying a mean symptom severity improvement of 36% (Kim et al. 2003).

Anterior cingulotomy approaches to OCD have revealed adverse effects such as headaches, insomnia, and weight change (Kim et al. 2003; Jung et al. 2006). These were only temporary effects and resolved themselves within days to months. Other transient adverse events reported include urinary incontinence and seizures (Volpini et al. 2017). Longer lasting adverse events reported in studies include hemorrhages and suicide (Lopes et al. 2004). Patients that were reported to commit suicide had histories of suicidal ideations and attempts; the resulting suicide was not predictable from the procedure itself (Lopes et al. 2004).

Subcaudate Tractotomy

A subcaudate tractotomy places lesions in the substantia innominate to interrupt the activity between the OFC and subcortical limbic structures. The technology has evolved from using radioactive yttrium seeds to stereotactically controlled radiofrequency ablation. This surgery has found much success; in a 1994 review, it was determined that due to subcaudate tractotomy, 40-60% of 342 patients were able to live normal or near normal lives (McLaughlin and Greenberg 2012). The most frequently reported adverse events from a subcaudate tractotomy procedure include fatigue, suicide and convulsive crises; other adverse events include delirium, mania, and weight gain (Lopes et al. 2004).

Limbic Leucotomy

The fourth kind of ablative treatment procedure is a combination of subcaudate tractotomy with an anterior cingulotomy. Due to the combinatory nature of the procedure, 5 lesions are created in the patient (McLaughlin and Greenberg 2012). This procedure historically has exhibited high rates of success. These high rates continue as recently it was reported to

provide a marked improvement in approximately 68% of patients (Cho et al. 2008). Periods of confusion irregular menstrual periods have been reported as two main physiological adverse events from this procedure (Kelly and Mitchel-Heggs, 1973).

Neuromodulation

Deep Brain Stimulation

Deep Brain Stimulation (DBS) provides an option for a reversible neuromodulation therapy to affect activity in the aforementioned sites implicated in the neuropathophysiology of (Cleary et al 2015; Alonso et al. 2015; Lapidus et al. 2014). DBS involves the use of electrodes to send adjustable electrical pulses to specific locations in the brain. It can be done through an open-loop or closed-loop electrical system with voltage and pulse variations selected per symptom and subtype of disorder (Koning et al. 2013). DBS to the subthalamic nucleus (STN) is used mostly for Parkinson's but had initially displayed improved symptoms of OCD in those treated for movement disorders. Moving forward in OCD research, stimulation to the orbitofrontal cortex, ventral caudate, ventral striatum, and ventral capsule have been a priority focus to reduce OC symptoms in severe patients (Cleary et al. 2015; Lapidus et al. 2014).

Success, adjustability, and reversibility in DBS trials for OCD has deemed the treatment to be efficacious, safe, and a worthwhile addition to the standard of care in OCD treatment (Gabriëls et al 2003; Goodman and Insel 2009). In 2010, Medtronic's DBS device became approved by the Food and Drug Administration for the utilization in intractable OCD. Some DBS systems provide constant neuromodulation while other trial designs alternate between active and inactive stimulation for specific periods of time (Holtzheimer and Mayberg 2011). These DBS procedural methods change frequently due to the uncertainty of the best combination

of frequency, pulse width, voltage, and contact (Cleary et al. 2015). Depending where the stimulation is directed, patients have reported reductions in OCD severity between 41-54% with up to 60% of patients experience symptom reduction (Alonso et al. 2015). Moving DBS electrode targets closer to the NAc was observed to provide better outcomes, even with lower voltages and pulse widths (Cleary et al. 2015). This stimulation target within the ventral capsule/ventral striatum (VC/VS) has been associated with significantly improved OC symptoms as well as an improved impact on verbal episodic memory since the ventral striatum is linked to the memory formation within the hippocampus and the ventral striatal reward system/corticostriatal pathophysiological model (Kubu et al. 2013; Dougherty et al. 2002; Lapidus et al. 2014; Cleary et al. 2015). As of late, VC/VS stimulation has not been associated with neuropsychological decline, a statement to be further explored in this paper.

Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS) is a low risk neuromodulation technique for OCD. TMS uses an electromagnetic coil to deliver short bursts of magnetic energy to the dorsolateral prefrontal cortex (Lapidus et al. 2014). The magnetic field delivered over the scalp leads to small electrical currents, which stimulate or disrupt the neurons in that region (McLaughlin and Greenberg 2012). TMS was at first seen to provide a decrease in compulsive urges after repeated stimulation (rTMS), however once controlling patients for depression, there was not a significant difference in obsessive-compulsive symptoms in the DLPFC region (McLaughlin and Greenberg 2012). TMS has also been tested in the supplementary motor area (SMA) and shows promise for an effective target region (Lapidus et al. 2014). TMS originally was cleared by the FDA in the treatment of depression in 2008; in the past year, a TMS device

for the treatment of OCD has been cleared (FDA.gov). Most patients undergoing TMS treatment are concurrently being treated with pharmacotherapy (Cocchi et al. 2018). Due to the limited studies available on TMS, there lacks a standardization in its administration to patients. Further exploration of this treatment necessitates weighing the efficacy of TMS as a monotherapy or in combination with medication as well as evaluating its administration for patients "not suitable" for initial pharmacotherapy or behavioral therapy approaches (Cocchi et al. 2018).

Electroconvulsive Therapy

Electroconvulsive Therapy (ECT) has been used a method to treat depression for many years, with mixed reviews in its treatment of OCD. Using electrodes placed on the scalp to deliver low-energy electrical pulses, ECT targets the area of the brain affecting the mood (butler.org, Lapidus et al. 2014). ECT research has conflicting results on its efficacy of treating OCD due to insufficient data in published reports, small patient samples, questionable study designs, or inconsistent interpretations of limited data (Lapidus et al. 2014; Fineberg et al. 2015). Some reports displayed symptom improvement only when using ECT on patients with psychiatric comorbidities such as Tourette's and depression; conversely, other trials have found improvement in OC symptoms with patients independent of depressive disorders (Lapidus et al. 2014). Due to the uncertainties associated, applying ECT as a treatment solely for OCD is inadvisable (Mclaughlin and Greenberg 2012; Lapidus et al. 2014; Fineberg et al. 2015).

Vagus Nerve Stimulation

Vagus Nerve Stimulation (VNS) uses an implanted stimulator to send electrical impulses to the vagus nerve with the intention to inhibit focal cortical activities (McLaughlin and

Greenberg 2012; Kar and Sarkar 2016). The vagus nerve is known to send information to regions in the brain that are thought to be involved in the pathway that deals with somatic and cognitive symptoms and processing seen in anxiety disorders (Kar and Sarkar 2016; George et al. 2008). By inhibiting the activity, one VNS study for OCD found a significant reduction in patient symptom severity scores (McLaughlin and Greenberg 2012). In a small study evaluating seven patients undergoing VNS, 43% showed a positive response. Of the seven patients, five remained in the study through the design's full two years due to the benefits from this treatment (George et al. 2008). Small, positive results such as those found from the George et al study warrants increased research in VNS for treatment of OCD. However, as it does not show a greater benefit over DBS, the treatment is currently only FDA approved for epilepsy and depression (McLaughlin and Greenberg 2012).

Neuropsychology

Through neuropsychological (NP) testing, the safety and efficacy of established procedures such as anterior capsulotomy, anterior cingulotomy, subcaudate tractotomy, limbic leucotomy, and deep brain stimulation continues to be evaluated. NP assessments provide data on the effects of cognition which allows for further innovation through applied changes in each treatment, especially those as permanent as the ablative procedures. NP evaluations may provide information to inform predictors for good outcome in patients.

Although the permanence of an anterior capsulotomy can be intimidating for some, NP assessment shows little to none negative effects on cognition. There has been little reported observation of worsening of cognition or neuropsychology overtime through capsulotomy. Some

studies have reported an impaired executive functioning or decrease in working memory, yet later reported restorative effects over time (Nyman et al. 2001; Ruck et al. 2008).

In regard to the impaired executive functioning, Nyman et al determined that the less satisfactory NP effects could be assumed to stem from the associated trauma from the surgical procedure rather than the treatment's process. According to their discussion, recovery from surgical trauma within the first postoperative year would not allow sufficient time for symptomatic improvement to be seen in NP performance. Reading into Ruck et al's study, the participants had previously undergone more than one procedure or high doses of radiation. This affects their reported results of impaired working memory and executive functioning as there is an increased risk in adverse NP with patients who have experienced multiple capsulotomies or treatments with high radiation. Additionally, these studies stated a lack of correlation between a positive clinical outcome and affected NP results (Nyman et al. 2001; Ruck et al. 2008).

While there is a history of impairments in attention, executive control, and other cognitive dysfunction after cingulotomy (Ochsner et al. 2001 and Cohen et al. 1999 from Jung et al. 2006), more recently there have been no significant postoperative dysfunctions compared to baseline assessments (Jung et al. 2006; Kim et al. 2003). Instead there has been a reported improvement in total and perseverative errors on the Wisconsin Card Sorting Test (McLaughlin and Greenberg 2012; Kim et al. 2003). This improvement is believed to be linked to the alteration to the anterior cingulate as it is implicated in thought/decision impairment in patients with severe OCD (Kim et al. 2003; Fukui et al. 2015).

There is limited information recorded of changes in cognitive effects from subcaudate tractotomy and limbic leucotomy procedures as studies are either outdated or extremely limited. There seems to be no record of neuropsychological changes in subcaudate tractotomy patients

(Lopes et al. 2004). In one study of limbic leucotomy, overall intelligence was not adversely affected and was reported to improve 6 weeks post-surgery; this sample, however, contained 53% of participants with 'obsessional neurosis' and while others had various psychiatric disorders (Kelly et al. 1973; McLaughlin and Greenberg 2012). Comparatively, patients undergoing limbic leucotomy for either major depressive disorder or OCD have been noted to experience "infrequent and transient" memory impairment (Montoya et al. 2002).

As with any neuromodulation procedure, there are similar cautions towards possible negative impacts in cognition from DBS to the VC/VS (Kubu et al. 2013). From the limited data available, there has been no observed significant decline or impact on patient cognition, intelligence, attention, executive functioning, and memory (Koning et al. 2013). Significant improvements (WMS Logical Memory Recall from Greenberg et al. 2006) and deficits (a slight increase in perseverative errors on WCST from Gabriels et al. 2003) within groups being treated with DBS were believed to not be strong enough to suggest pervasive neuropsychological change in any individual (Greenberg et al. 2006; Gabriels et al. 2003). In cases where significant memory and visuospatial improvement was presented, there was no statistical correlation between the improvement in OC symptoms and these statistically significant reported cognitive improvements (Greenberg et al. 2013).

The purpose of the study represented through this paper is to evaluate patient NP assessments to determine any changes in cognitive behavior and function. There has been an increase in research evaluating cognitive effects in patients after neuromodulatory and ablative treatment. Such research is important to consider when determining the cost-benefit of high risk procedures. Due to the limited data available, this study and its observations would stand to reinforce or bring to question the safety and efficacy of DBS for treatment of refractory OCD.

MATERIALS AND METHODS

Participants

Twenty-seven patients underwent VC/VS DBS treatment for refractory OCD as part of a multi-site NIH-funded clinical trial. Of the 27-total participants, 19 (8F, 11M) had full pre- and post-operative neuropsychological data. The sites included in this study are Butler Hospital (n=3), Cleveland Clinic (n=3), University of Florida (n=4), George Washington University (n=2), Kaiser Permanente (n=1), Massachusetts General Hospital (n=3), Mount Sinai (n=2), and Mayo Clinic (n=1).

At baseline, mean age was 42.93 years (SD = 12.63), with a range of 25 to 64 years. Mean YBOCS score was 33 (SD = 2.39), with a range of 29 to 39. The predominant ethnicity was Caucasian, with 1 participant identifying as Asian. Mean education of the sample was 14.68 years (SD = 2.52). See Table 1 for more demographic information.

Inclusion/Exclusion Criteria

Participants were included in this study if they had a symptom severity score of at least 28 out of 40, determined from the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). Participants needed a five-year or more persistence of severe symptoms despite participation in three prior pharmacotherapy trials alone or in combination with cognitive/behavior therapy. They had to be in good general health, able to fully understand and comply with instructions, and able to provide consent. Additionally, a family member or significant other with the referring psychiatrist was necessary for communication with the research team and ongoing care in case of worsening clinical status.

Participants were excluded from this study if they were under 18 years old or above 75 years old; had a cognitive impairment that would affect the participant's ability to give informed consent or provide self-reported data reliably; evidence of a current or past psychotic disorder, bipolar mood disorder, significant neurological disorder (other than a tic disorder), severe personality disorder, body dysmorphic disorder, or dementia; clinically significant abnormal MRI results; current or remittent substance abuse or dependence; inability to control suicidal ideations (determined from the Columbia-Suicide Severity Rating Scale); were pregnant or were of childbearing age not using effective contraception; had any labeled DBS contraindication (as determined by the FDA); or under the investigator's judgement had the inability to adhere to operational and administrative study requirements.

There were 27 patients that fit the criteria for the study described. Ultimately 19 were evaluated and their results are displayed below. Sample size decreased from 27 to 19 due to patient termination before one-year follow-up results were acquired.

Recruitment and Consent

This study had IRB approval at each study site. All patients underwent initial phone screenings (clinical records were subsequently gathered); if they met the study criteria, patients attended site visits for a more comprehensive screening. Consent forms were signed at the initial site visit and candidates were assessed for expectations of improvement post DBS treatment. Patients were cautioned against unrealistic expectations, such as immediate symptom recovery, to mitigate potential disappointment which could adversely affect their psychosocial functioning, quality of life, and response to treatment (Abelson et al. 2005). Once being approved by an external Independent Review Committee comprised of experts in OCD diagnosis and treatment,

patients were scheduled for surgery. During the time between the approval and surgery, patients signed the full consent form, completed the Informed Consent Evaluation Feedback Tool during a session with each site's Consent Monitor (ensuring patients were aware of the study's purpose, risks, and benefits), and underwent a battery of baseline assessments described below.

Table 1: Patient demographics and Baseline Y-BOCS scores

Demographics per patient include ethnicity, age, gender, education years, years between baseline and follow-up testing, and baseline Y-BOCS scores.

Pt #	Ethnicity	Age (yr)	Age (mo)	M/F	Edu Yrs	Yrs Btwn	BL YBOCS
B1	Caucasian	48, 9 mo	585	F	12	1.3	32
B2	Caucasian	59, 6 mo.	714	M	19	1.5	30
B3	Caucasian	47, 10 mo.	574	M	16	1.1	32
C1	Caucasian	38, 11 mo.	467	M	14	1.3	33
C2	Caucasian	36, 1 mo.	433	M	12	1.1	33
C3	Asian	29, 4 mo.	352	F	12	1.7	29
F1	Caucasian	50, 1 mo.	601	M	12	1.1	33
F2	Caucasian	41, 4 mo.	496	M	14	1.3	34
F3	Caucasian	59, 10 mo.	718	F	16	1.7	34
F4	Caucasian	55, 11 mo.	671	F	20	1.6	36
G1	Caucasian	29, 2 mo.	350	M	12	1.1	39
G2	Caucasian	34, 3 mo.	411	M	16	1.2	36
K1	Caucasian	31. 2 mo.	374	M	16	1.4	36
M1	Caucasian	57, 11 mo.	695	M	16	1.1	32
M2	Caucasian	25, 7 mo.	307	F	12	1.1	35
M3	Caucasian	64, 3 mo.	771	F	18	1.3	32
S1	Caucasian	27, 1 mo.	325	F	14	1.0	35
S2	Caucasian	31, 5 mo.	377	F	15	1.4	31
Y2	Caucasian	47, 2 mo.	566	M	13	1.7	33
Mean		42.93	515.11		14.68	1.306	33.42
Min	1 Asian	25.00	307.00	8F	12.00	0.950	29.00
Max	18 Caucasian	64.25	771.00	11M	20.00	1.700	39.00
SD		12.63	151.61		2.52	0.23	2.39

Treatment Procedure

During this experiment, concurrent therapies were allowed to proceed. The device leads and neurostimulators were implanted on the same day using a stereotactic surgical procedure. The brain leads and neurostimulator and connecting wire implantation were placed under general anesthesia. Using stereotactic imaging from appointments leading up to the surgery, coordinates were individually determined and the tetrapolar brain leads were inserted along the anterior limb of each internal capsule in a bilateral placement into the ventral striatum. The specific location targeted was approximately Target B, 2.5mm anterior to the posterior border of the anterior commissure, 2.5mm below the AC/PC plane, with model 3387 Medtronic DBS lead (each having 4 independently programmable contacts spanning approximately 10.5mm) inserted following the trajectory of the ALIC in the coronal plane. The extension wire from the scalp connected the leads to the two subcutaneous neurostimulator in the chest. The original implantation was with the Activa PC device and was later switched to an Activa RC rechargeable device when the PC batteries reached end of life. To monitor for surgical complications, participants had one overnight stay. Patients were discharged with the DBS device turned off to allow for bodily adjustment to the initial insertion. The DBS device was subsequently turned off every 3-4 weeks per DBS routine to allow for some resolution of insertional edema.

The treatment protocol was monopolar DBS, giving the most "anatomically selective stimulation," since current flows away from the negative electrode and does not return. The location, amplitude, and pulse width of the stimulation, in that order, has the greatest effect on mood and anxiety response. The amplitude was intended to not pass 8mA, as effects tend to plateau at this number. The pulse width range stayed within 90-120 microseconds. Parameters

were adjusted accordingly per individual patient's monopolar survey response at day 1, and left with the device turned off. Ultimately each participant's parameters varied due to personalization of treatment; if indicated, bipolar electrode surveys were used during optimization.

After initial optimization on the first day, the second day's bilateral testing used the best combination of amplitude and pulse width that yielded the most acute responses. Patients left the clinic with the best tested settings. Over the next four days further optimization occurred in terms of adjusting amplitude (in 2Ma increments), pulse width (in 30 microsecond increments), and the number of contacts activated. By the end of the week, patients scheduled a one-month appointment and left on the best parameters set over the term of the week.

Patients were randomly assigned to an Active or Sham Treatment group. The Active treatment group received open DBS treatment from the first appointment onwards. The Sham treatment group began open treatment after 3 months. After the 3 month mark, all patients in the study were on open DBS and had appointments every 3 months to measure OC symptom severity and the benefit of the stimulation. The appointments continued over the phone every 3 months until the year mark. The appointments then were moved to every 6 months, also over the phone. Further information on the trial's procedures can be found in Project number 1U01MH076179-01A1, under contact PI Benjamin Greenberg.

Baseline and Follow-Up Neuropsychological Assessments

All patients in this study underwent baseline and multiple follow-up assessments to evaluate their symptom severity. The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) looks at core features to identify a patient's obsessions and compulsions. The Y-BOCS then has

patients scale their symptoms to fully determine the overall impact of their OC symptoms on daily life. Patients are often required to have a Y-BOCS score of over 25 to be approved for a cingulotomy procedure (Dougherty et al. 2002). For this study, patients were required to have a minimum Y-BOCS of 28.

Measures

Baseline and follow-up neuropsychological (NP) exams were carried out to evaluate possible changes in cognition after DBS. The average amount of time between baseline and follow-up NP assessments was 1.3 years, with the range being 1.70 to 0.95 years (SD = 0.23).

Intelligence

Wechsler Abbreviated Scale of Intelligence (WASI Manual; Harcourt Assessment, Inc)

The WASI is an intelligence test that was performed to determine identification capabilities and overall intelligence. The four subtests composing of the full-scale intelligence quotient (IQ) effectively estimate an examinee's verbal, nonverbal, and general cognitive functioning (WASI Manual; Harcourt Assessment, Inc).

Memory

Wechsler Memory Scale (WMS-III)

The WMS is a comprehensive exam focused on immediate, delayed, and working memory by testing recall and recognition abilities through auditory and visual modalities. It is used to determine the level and pattern of memory functioning to identify possible cerebral dysfunction (WMS-III; Harcourt Assessment, Inc). Subtests evaluated were Digit Span, Letter-

Numbering Sequence, Spatial Span, Logical Memory I, Logical Memory II, Faces I, and Faces II.

Brief Visuospatial Memory Test-Revisited (BVMT-R)

The BVMT-R test assesses memory through the visual modality of 6 figures. The test is meant to assess memory ability and diminish practice effects in patients who undergo the test multiple times (BVMT-R; Psychological Assessment Resources, Inc). BVMT Form 1 was used in both the baseline and one-year follow-up assessments.

California Verbal Learning Test (CVLT)

The CVLT measures episodic verbal learning and memory in an attempt to measure memory deficits with lowered performance on certain tasks. Episodic memory is tested verbally through patient encoding, recall, and recognition ability over a series of trials (Delis et al. 2000; Elwood 1995).

Executive Functions

Wisconsin Card Sorting Test (WCST)

The WCST examines EF and cognitive flexibility by analyzing perseverative pattern and problem solving (Greenberg et al. 2013). It examines the ability of patients to acclimate to a changed pattern from one category to the next (Ruck et al. 2008; Jung et al. 2006), a skill affected by frontal lobe deficits (Greenberg et al. 2013).

Iowa Gambling Test (IGT)

The IGT measures risky decision making and the participant's ability to weigh cost/benefit for future outcomes (Burdick et al. 2014). Patients' decision-making between immediate prospects and future consequences are closely evaluated through the test's tasks.

Delis-Kaplan Executive Function System (DKEFS)

It has been observed that after damages to the PFC, there is a developed insensitivity to evaluate future consequences and risk aversion (Fukui et al. 2015). The DKEFS test assesses not only thought flexibility and impulse control, but also problem solving, planning, abstract thinking and concept formation (Homack, Lee, Riccio 2005). By keeping a record of EF before and after DBS through these tests, one can see if the treatment positively affects a patient's EF as previously observed (Fukui et al. 2005; Bechara et al. 1994). DKEFS subtests performed were Letter Fluency, Category Fluency, Trail Making, and Color-Word Interference.

Visuospatial Functions

Grooved Pegboard test (GPB)

The GPB measures manual dexterity, motor function, and visual-motor coordination to evaluate brain performance.

Judgement of Line Orientation (JLO)

The JLO tests visuospatial skills, in which the striatum plays a role, by having the examinee match the angle and orientation of lines in a figure (Greenberg et al. 2013).

Rey Complex Figure Test (RCFT)

The RCFT tests visuospatial abilities along with memory, planning, and executive functions by having participants duplicate a complex figure in a direct copy, an immediate freehand recognition, and from memory in a delayed recall.

Verbal Functions

Boston Naming Test (BNT)

The BNT sees verbal cognitive abilities and is utilized for determining "confrontational picture-naming abilities in patients" with possible brain deficits (Neils-Strunjas 1998).

Wide Range Achievement Test 4 (WRAT 4)

The WRAT4 is a simple assessment of reading skills to quickly evaluate the participant's effective learning, communication, and thinking (WRAT4; Psychological Assessment Resources, Inc).

Statistical Methods

All data collected from the NP evaluations was placed into SPSS Statistics (Version 24), an analytics software used to calculate means, ranges, standard deviations, and perform paired-sample and 2-tailed t-tests with the significance level at 5%. The data was not corrected for multiple comparisons.

All scores inputted into SPSS for analysis were standard scores with the exception of the raw scores used for the discriminatory results in the BVMT and raw scores for JLO. Standard scores were calculated from each test's professional scoring manual or computer program: WASI Manual, WMS-III Administration and Scoring Manual, WCST Computer Version 4: Research

Edition, BVMT Professional Manual, CVLT-II Second Edition, IGT Professional Manual, RCFT Professional Manual, DKEFS Professional Manual, WRAT 4 Professional Manual. GPB and BNT standard scores were taken from the Revised Comprehensive Norms for an Expanded Halstead-Reitan Battery Version 4.01.022 computer program.

RESULTS

Baseline and follow-up Y-BOCS results and analyses can be found in Tables 1 and 2 in addition to Figure 3. Results from the different categories of NP evaluations between baseline and follow-up are presented in Figures 1-13 as means for the whole group**.** If specific subtests were not administered to a participant, they were not included in that analysis.

Obsessive-Compulsive Symptoms

In the group of 19 participants, Y-BOCS decreased 40%, from a mean baseline of 33 (SD=2.39) to a follow-up mean of 20 (SD=8.79) (Figure 3). A two-tailed significance test displayed that there was a statistically significant difference in the means (p=0.000, t=7.056). It is important to note the significant improvement in OCD symptoms especially when analyzing the changes in cognitive function further described below.

According to the literature, full clinical response is measured by a 35% or higher Y-BOCS decrease and partial response, a 25-34% Y-BOCS decrease. Fifty-three percent of the participants were considered full responders to the DBS treatment at the time point closest to the 12-month neuropsychological assessment. In this study, 11% were partial responders. Thirty-seven percent had a less than 25% decrease in Y-BOCS demonstrating low efficacy of DBS for these patients (Table 2).

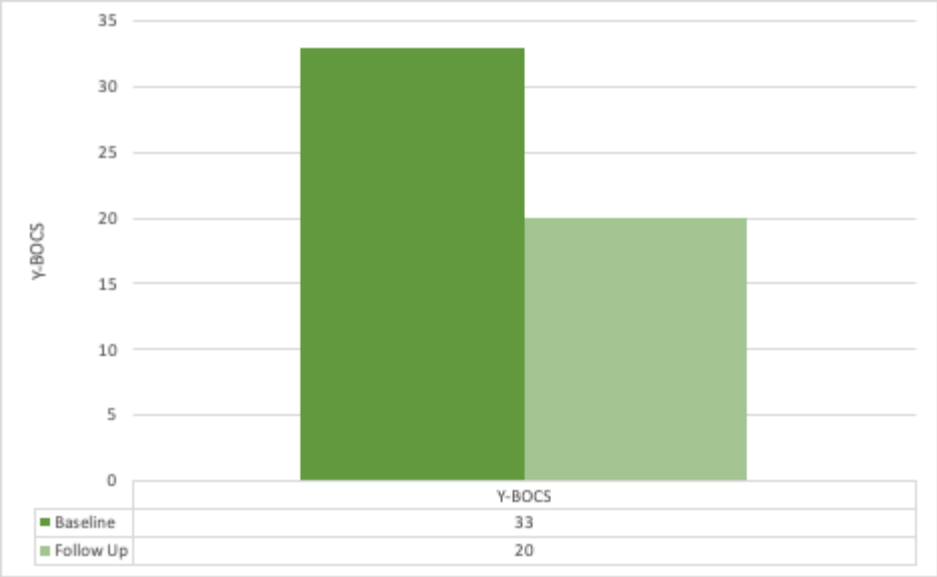
Table 2: Follow-Up Y-BOCS Scores and Percentage Improvement. Below each participants' follow-up Y-BOCS result and the percentage of change from baseline to follow-up

color-coded. Green is for full response, orange for partial response, and scores highlighted in red represent those who had no significant response to treatment.

Pt #	FU YBCOCS	% Change
B1	17	-47%
B2	23	-23%
B3	22	-31%
C1	16	-52%
C2	28	-15%
C3	22	-24%
F1	15	-55%
F2	17	-50%
F3	9	-74%
F4	33	-8%
G1	35	-10%
G2	12	-67%
K1	19	-47%
M1	0	-100%
M2	30	-14%
M3	22	-31%
S1	31	-11%
S2	17	-45%
Y2	14	-58%

Mean	20.11	-40%
Min	0.00	-8%
Max	35.00	-100%
SD	8.79	-34%

Figure 2: Y-BOCS Mean Changes Baseline to Follow-Up. Group mean Y-BOCS improved 40% from 33 to 20.



Neuropsychology

Baseline Neuropsychology Performance

This group of participants began this study with average baseline scores. The average range in scaled scores is between 8 and 10; T-score average values fall between 40 and 60; IQ average is 100. Participant WASI Intelligence IQ ranged from 100.37 to 105.32. WMS values fluctuated between 8.53 and 10.53. BVMT values remained on the lower side of average between 42.72 and 50.28. CVLT baseline values were analyzed on a z-score range; when comparing each result's standard deviation to find an average, participant results also remained average. Participants also exhibited average to slightly better than average executive functioning when analyzing their DKEFS baseline results with the range being between 8.06 and 12. The mean of T-score values for the BNT was 42.63 displaying average verbal skill. GPB dominant t-scores had a mean of 33.37 and the non-dominant mean was 34.72 displaying slightly less than average ability in this visuospatial task.

Follow-up Neuropsychology Performance

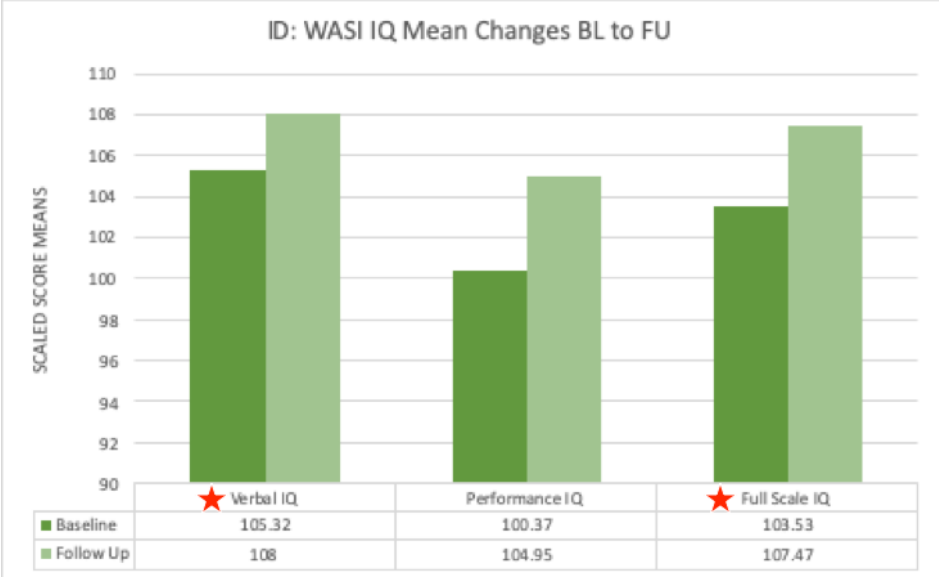
As an overall, the NP results from baseline to follow-up showed few significant changes in cognitive function. Looking at individual participant results per test and subtest display slight improvements or a slight decline of scores by a few not statistically significant points; there were no significant declines nor improvements in the WCST, IGT, DKEFS, GPB, JLO, RCFT, and BNT tests. Despite closely monitoring Executive Functioning (DKEFS, WCST, IGT, RCFT) for its historically reported potential in cognitive change, our results showed nothing of significance.

Intelligence

WASI

Figure 4 shows two IQ results presenting as statistically significant (when tested at p=0.05). Full-Scale IQ (FSIQ) (baseline=103.53, follow-up=107.47, t=-2.362) and Verbal IQ (VIQ) (baseline=105.32, follow-up=108, t=-2.275) in the WASI test had significant improvements at p=0.03 and p=0.035, respectively while the Performance IQ (PIQ) change was not significant. The significance referred to in the results and data was determined in a paired-sample t-test. The significance level was set at 5% (0.05). When checking for a correlation between these improvements to the decrease in Y-BOCS scores, Verbal IQ had a trend level of significant correlation at p = 0.052. This displays a possible interconnection between the improvement of Verbal IQ and the improvement of OC Symptoms from DBS.

Figure 3: Intelligence Mean Changes Baseline to Follow-Up (WASI IQ). Stars in Verbal IQ and Full Scale IQ indicate significant changes from 105.32 to 108 in VIQ and 103.53 to 107.47 in FSIQ.



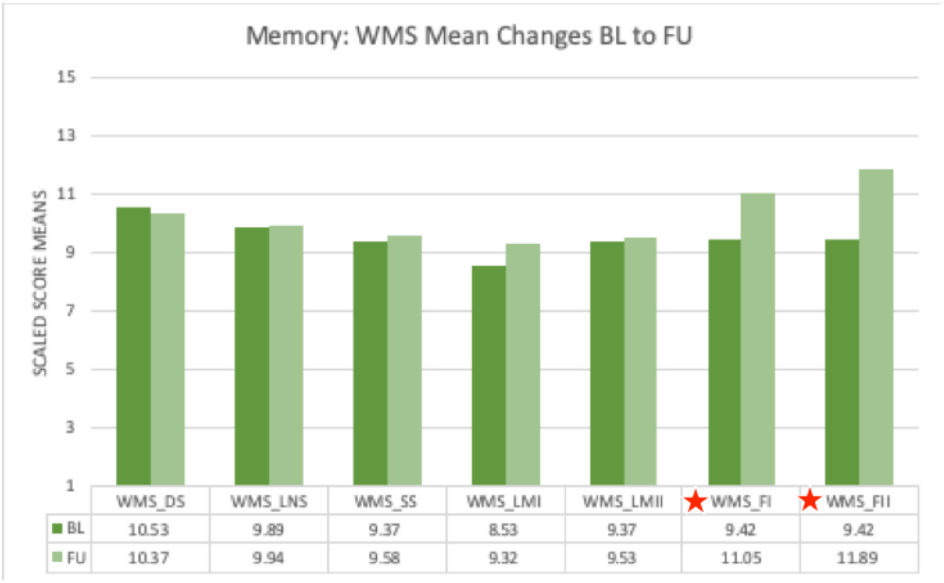
Memory

WMS

As displayed in Figure 5, statistically significant improvements are found in WMS Faces I (baseline=9.42, follow-up=11.05, p=0.025, t=-2.444) and WMS Faces II (baseline=9.42, follow-up=11.89, p=0.025, t=-2.855). These tests measure performance based on a visual presentation of stimuli to be remembered by the examinee (WMS-III; Harcourt Assessment, Inc). Together they test Visual Immediate, Visual Delayed, and General Memory.

When comparing the significant changes observed in WMS's Faces I and Faces II to the decrease in Y-BOCS score, only one has a statistical correlation. Faces II has a statistically significant correlation to the improvement in Y-BOCS score for the patient sample at p=0.03, implying there is a relationship between the improvement in Faces II/Memory Function and OC symptoms from DBS.

Figure 4: Memory Mean Changes Baseline to Follow-Up (WMS). Stars next to Faces I and Faces II indicate significant changes from 9.42 to 11.05 in Faces I and 9.42 to 11.89 in Faces II. A slight decrease from baseline to follow-up can be seen in the Digit Span results. Slight improvements are found in Letter-Number Sequencing, Spatial Span, Logical Memory I, and Logical Memory II.



BVMT

There were no statistically significant changes found in the BVMT.

CVLT

In Figure 7 significant improvement can be found in CVLT Total Learning Slope (CVLT_TLS). The TLS is used in the measurement of verbal memory; it is the increase in recall across the consecutive learning trials (Wright et al. 2009). SPSS calculation showed there was a p=0.02 significant increase in Total Learning Slope in the CVLT memory assessment (baseline=-0.263, follow-up=0.395, t=-2.563). When correlating the significant change observed in CVLT's

TLS to the improvement in OC symptoms measured in Y-BOCS scores, there was no significant statistical correlation.

Figure 5: Memory Mean Changes Baseline to Follow-Up (BVMT/CVLT). No significant changes are observed. Slight decreases in scores can be found in BVMT Direct Recall, Total Recall, and Learning comparing baseline to follow-up. Additionally, Figure 6 displays slight increase in the BVMT Discrimination score.

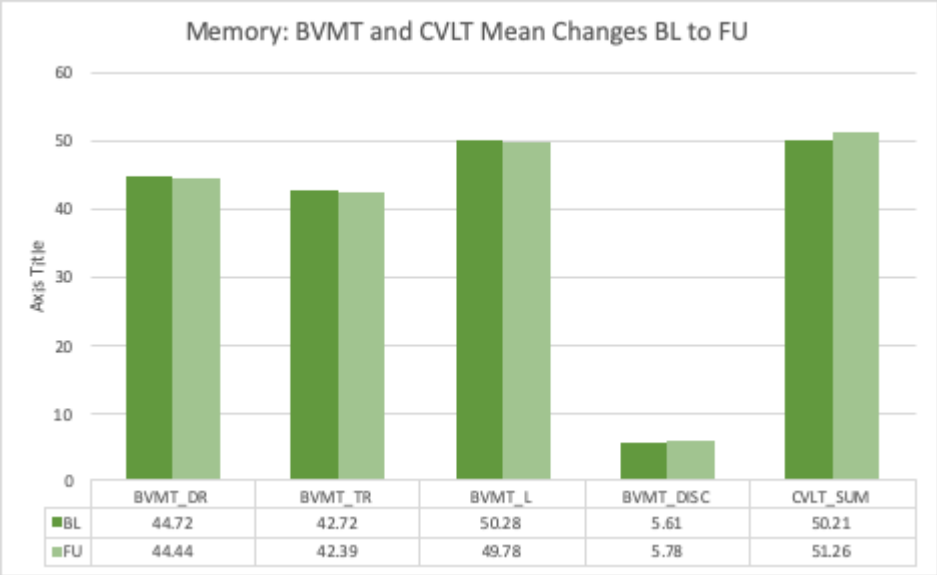
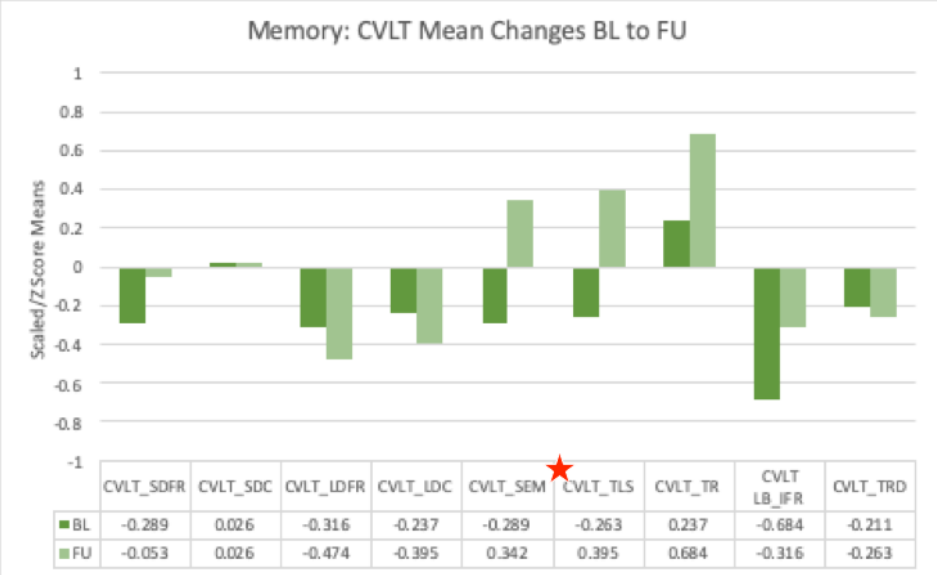


Figure 6: Memory Mean Changes Baseline to Follow-Up (CVLT). A star signifies a significant change in CVLT Total Learning Slope (CVLT_TLS) from -0.289 to 0.395. Within the group, no significant changes can be found in CVLT Short Delay Recall, Semantic Clustering, Total Learning Slope, List B Immediate Free Recall, Short Delayed Recall, Long Delayed Cued Recall, Total Repetitions, Total Recognition Discriminability, and Summation of T1-T5 scores.



Executive Functions

WCST

There were no statistically significant changes in the WCST (Figures 8 and 9).

Figure 7: Executive Functioning Mean Changes Baseline to Follow-Up (WCST/IGT). There are no significant changes.

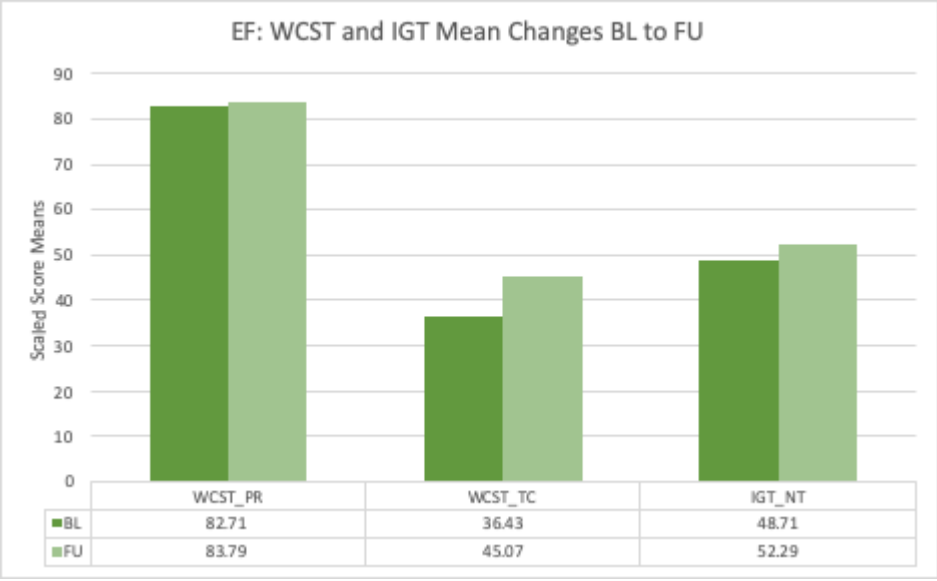
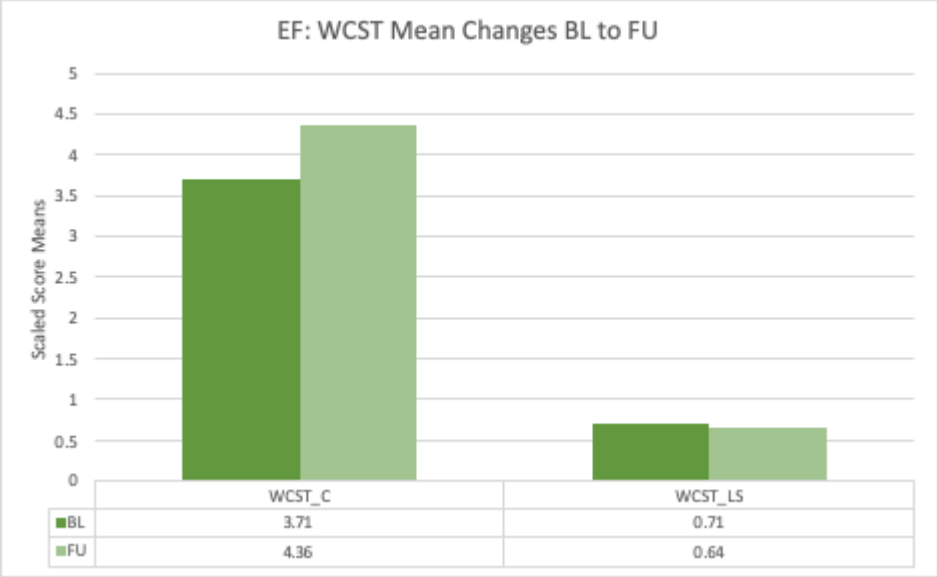


Figure 8: Executive Functioning Mean Changes Baseline to Follow-Up (WCST). There are no significant changes.



IGT

There are no statistically significant changes in IGT.

DKEFS

Scores were split through the four subtests as shown in Figure 10. These changes are not statistically significant.

Figure 9: Executive Functioning Mean Changes Baseline to Follow-Up (DKEFS Letter Fluency Subtest). There are no significant changes. Mean scores of the group show betterment in Category 1 Total Correct, Category Fluency Total Correct, Category Switching Total Correct Responses, and Category Switching: Switching Accuracy and a decline in Set Los Errors and Repetition Errors.

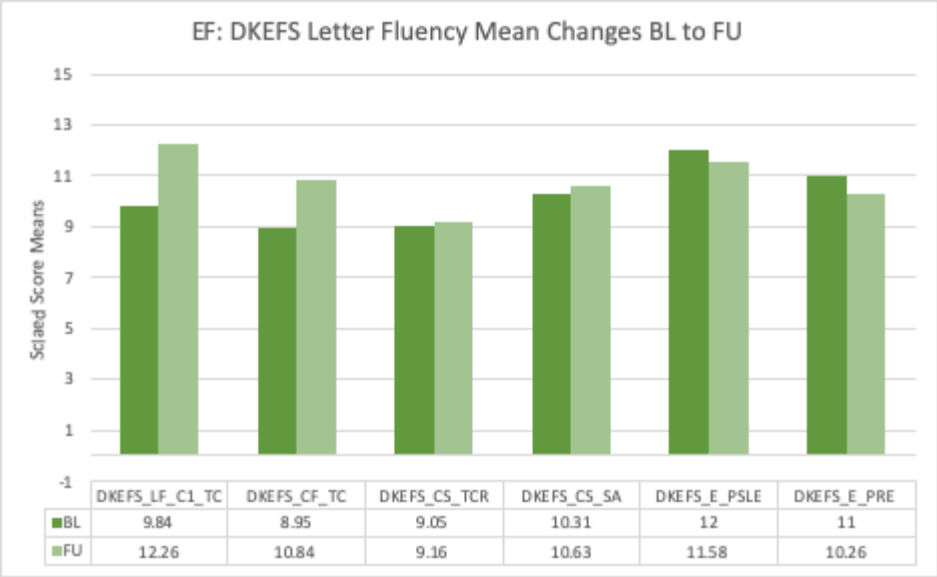


Figure 10: Executive Functioning Mean Changes Baseline to Follow-Up (DKEFS Trail Making Subtest). There are no significant changes.

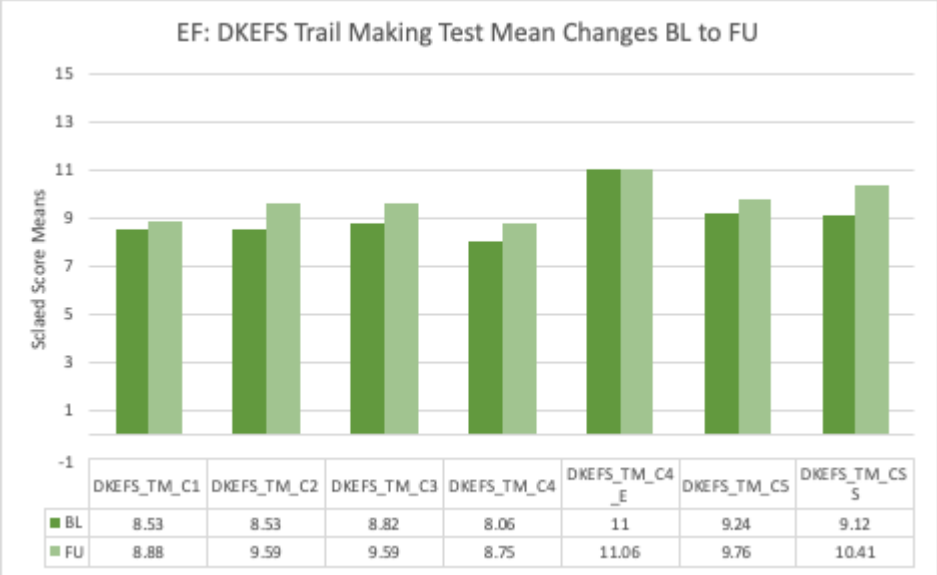
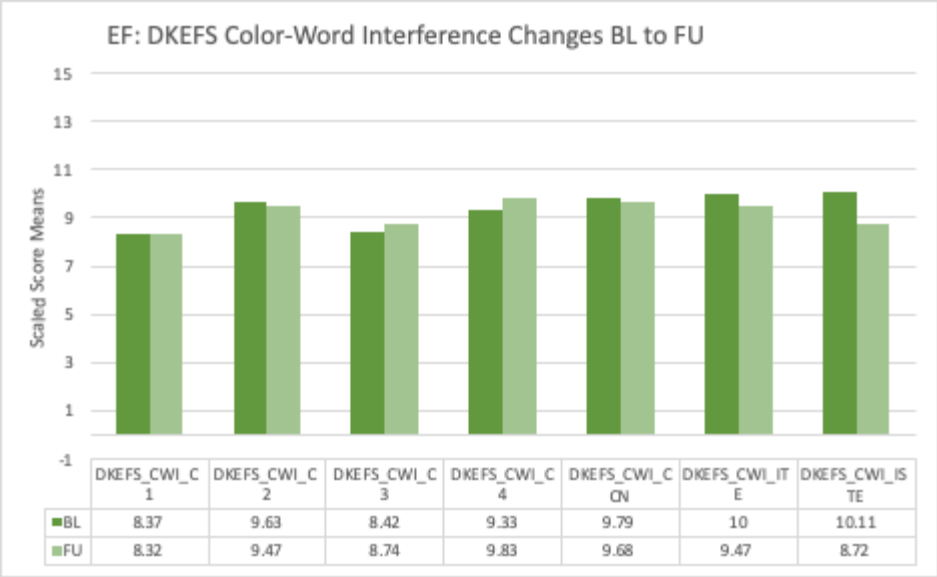


Figure 11: Executive Functioning Mean Changes Baseline to Follow-Up (DKEFS Color-Word Interference Subtest). There are no significant changes. Overall scores improve in the DKEFS Color-Word Interference Test except for the results of Category 4.

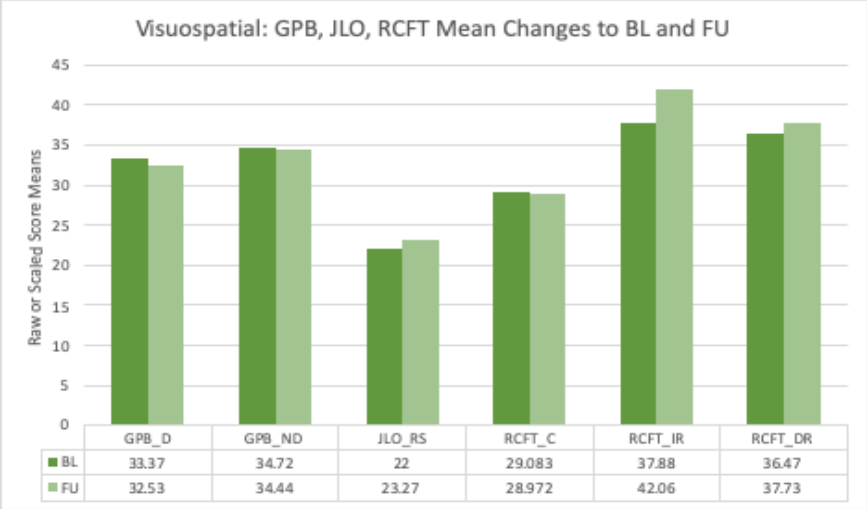


Visuospatial Functions

GPB, JLO, and RCFT

There were no statistically significant changes in visuospatial functions.

Figure 12: Visuospatial Mean Changes Baseline to Follow-Up (GPB/JLO/RCFT). There are no significant changes. Slight visuospatial improvement is seen in the decrease in time in the GPB test BL to FU, the JLO scores, and RCFT Immediate and Delayed Recall scores. The RCFT Copy scores slightly decline by less than a point.

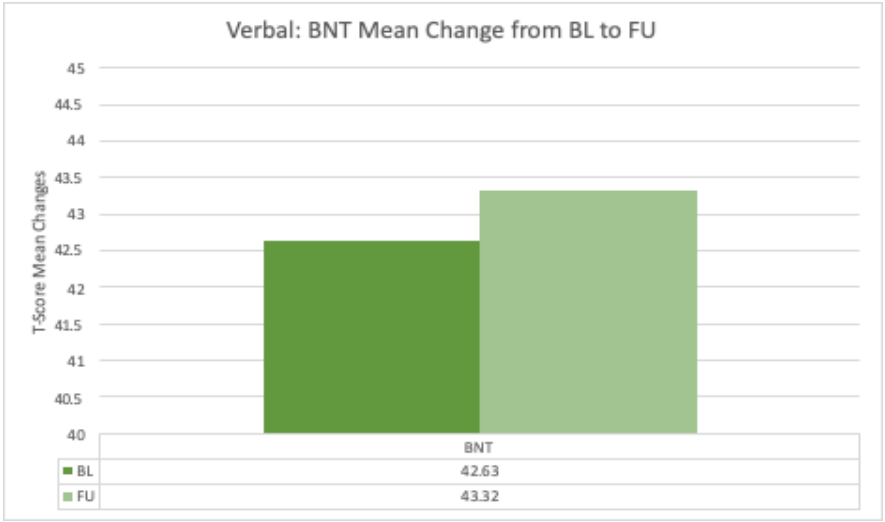


Verbal Functions

BNT

There were no statistically significant improvements in verbal functions.

Figure 13: Verbal Mean Changes Baseline to follow-up (BNT). Although the BNT increases by a little less than a full point from baseline to follow-up, there is not a significant change.



DISCUSSION

This study specifically examined cognitive behavior and possible changes from DBS to the ventral capsule/ventral striatum through neuropsychological examinations. From the data, it can be seen that there were no deleterious effects on cognition domains tested. These domains include intelligence, memory, executive functioning, visuospatial abilities, and verbal abilities. It is interesting to note that there were no significant changes in Executive Functioning since EF is most closely associated with the neurocircuitry of the brain region being stimulated and would be most assumed to alter. More noticeable than the overall lack of deficit change is the significant improvements in certain intelligence and memory functions.

In the sample's cognitive domain of Intelligence, the Verbal IQ (VIQ) and Full Scale IQ (FSIQ) displayed significant improvements. FSIQ is comprised of Verbal and Performance IQ (PIQ). PIQ subtests involving performance and time tests would have been most assumed to improve over verbal tests involving vocabulary and word similarities. The fact that VIQ was shown to change rather than the PIQ is a surprising find as prior surgery studies found the most change in PIQ due to symptom improvement from the treatment. The reduction of symptoms would have left the patient better able to take tests and display improvements in performance ability.

In the domain of Memory, Faces I and Faces II were shown to significantly improve. Faces I and II evaluated memory by measuring the patient's ability to recall and retain visual stimulation. This result is not as surprising since neuroimaging data demonstrates that DBS in the VC/VS is associated with changes in the left hippocampus due in part to the ventral striatal reward system in hippocampal-dependent memory formation (Kubu et al. 2013). An additional

memory improvement was found in the CVLT's Total Learning Slope results. The Total Learning Slope is calculated by measuring the increase in participant recall over consecutive trials in the test. A significant improvement in this measure of verbal memory demonstrates an increased memory ability. This reinforces the idea of DBS being involved in memory improvement from stimulation when targeting the VC/VS.

When examining the neuropsychological outcomes from stimulation in the ventral capsule/ventral striatum, the results display treatment safety. The lack of significant declines in cognitive functioning and instead the presence of significant improvements demonstrates an absence of neuropsychological hazards from DBS in the VC/VS.

This study displayed a 52.63% full response rate. A full response from treatment is measured as a 35% or more decrease in Y-BOCS score. This response result is comparable, if not better, to the results from Jung 2006's and Dougherty et al's 2002 cingulotomy Y-BOCS results. The improvement of Y-BOCS alone displays a clinically meaningful outcome for patients experiencing OCD to this severity; having over half of the sample experience a full response reinforces the benefits of this treatment.

These results come from a patient sample that was significantly impaired by OCD. Half of the significant neuropsychological improvements displayed a significant correlation to the improvement of OC symptoms. These results seem reliable as they either supplement prior research discussing improvements in memory from DBS or show slightly different, yet positive outcomes in intelligence improvement. Moreover, the high response rate to the treatment shows DBS to the ventral capsule/ventral striatum as an efficient treatment for OCD. The observable significant changes in intelligence and memory in concurrence with the improvement of OC

symptoms and severity imply that DBS for the treatment of refractory OCD can improve a patient's real-world functioning and therefore quality of life.

Limitations

This was a large-scale controlled study. The sample size, while originally at 27, decreased to an even smaller 19 participants with examinable data. This is due to patient termination from either deciding to no longer participate in the study or from the inability to travel for the multiple follow-up assessments between implantation and 1 year (when assessments are switched to the telephone). Among the 19 participants with usable baseline and follow-up NP files, there was little diversity. The overbearing homogeneity of this patient sample could lend itself to skewed data across ethnic groups. The patient sample gender was at 58% male to 42% female. The proximity to an equal gender representation is positive, though the abundance of male patients could also bias the data towards Caucasian males. The lack of diversity within the sample group does not affect this study's presented results. However, the implication that every patient regardless of background would have the same baseline and follow-up data is something worthwhile of further examination.

An additional limitation is the lack of adjustment in scores for practice effects. It has been known that repeatedly taking certain neuropsychological assessments contribute to score improvement (McCaffrey, Ortega, Haase 1993). This has been shown specifically for the WASI, WMS, DKEFS Trail Making test, GPB, and figural memory assessments (e.g. BVMT) (McCaffrey, Ortega, Haase 1993). Although these scores were not adjusted for possible practice effects, it should be mentioned that some of these exams have been improved to specifically lower practice effects since McCaffrey, Ortega, Haase's 1993 publication. Additionally, an effort

was made to practice effects by utilizing supplementary examinations for the cognitive domains of intelligence, memory, executive functioning, and visuospatial functioning. It is noteworthy to observe that the assessments notorious for displaying practice effects did not have statistically significant improvements.

CONCLUSION

Deep Brain Stimulation in the ventral capsule/ventral striatum has been repeatedly researched for DBS for refractory obsessive-compulsive disorder. Its placement near the frontal lobe leaves it subject to scrutiny. It is a concern that by not only implanting electrodes, but also exposing sections of the brain to electrical stimulation, that region of the brain could be adversely affected. This area of the brain is linked to not only cognition but also memory, impulse control, and attention. To further adversely affect skills currently negatively impacted by OCD would be unethical and ill-informed. Although this paper does not provide neuroimaging data, it does provide neuropsychological evaluation to reinforce the safety of DBS in the VC/VS for OCD.

This study of 19 participants provided data displaying the absence of a significant decline in cognition. There was instead a slight statistically significant improvement in certain memory and intelligence functions. Despite the limitations inherently provided with the study procedure, sample size, and sample demographics, chronic DBS to the VC/VS for OCD does not result in an impaired neuropsychology.

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