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Inferior thalamic peduncle deep brain stimulation for treatment-refractory obsessive-compulsive disorder: A phase 1 pilot trial

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ABSTRACT

Background: Several different surgical procedures targeting the limbic circuit have been utilized for severe, treatment resistant obsessive-compulsive disorder; however, there has only been limited exploration of the inferior thalamic peduncle (ITP). The aim of this study was to determine the safety and initial efficacy of ITP deep brain stimulation (DBS) in patients with severe obsessive-compulsive disorder.
Methods: Patients with severe, treatment-refractory obsessive-compulsive disorder were enrolled into this open-label phase 1 DBS pilot study. Bilateral ITP DBS devices were implanted between November 2010 and December 2015. The primary outcome was safety. The initial efficacy was determined by Yale-Brown Obsessive-Compulsive scale (YBOCs) scores. Component Y-BOCs scores, Hamilton Depression Severity Scale, Quality of Life Assessment (SF-36), Oxford Happiness Questionnaire, Warwick-Edinburgh Mental Well-Being Scale, and Sheehan Disability Scale were also analyzed for a minimum of 2 years after surgery. Additionally, preoperative and three-month postoperative FDG-PET studies were performed on two patients.
Results: Five patients (2 males, 3 females; age range 25–48 years) received ITP DBS. All five patients were considered responders at one year (52% improvement in YBOCs scores compared to baseline (range 39–73%, $p < 0.01$) and last follow-up (54% improvement; range 38–85%; $p < 0.01$). At two years follow-up, there were three adverse events that occurred in two patients. One patient had his DBS system removed after one year due to the device becoming the object of his obsession. The other two adverse events were not related to the device. Post-operative FDG-PET imaging in two patients demonstrated decreased glucose uptake within the right caudate, right putamen, right supplementary motor area, and right cingulum and increased glucose uptake in bilateral motor areas, left temporal pole, and left orbitfrontal cortex.
Conclusions: ITP DBS has a favorable safety profile and is potentially an efficacious treatment for severe obsessive-compulsive disorder. Larger clinical trials are necessary to determine efficacy.

Introduction

Obsessive-compulsive disorder (OCD) is characterized by chronic, persistent intrusive thoughts or urges that result in anxiety and subsequent compulsions, such as repetitive behaviors or mental rituals. OCD affects approximately 2% of the population [1], and is associated with a high risk of morbidity and mortality. Recent evidence indicates 10–27% of OCD patients attempt suicide [2]. While medical management, including selective serotonin-reuptake inhibitors (SSRIs) and cognitive behavioral therapy (CBT), are successful at treating these symptoms [3], 40–60% of patients have refractory symptoms that impair quality of life and normal day-to-day function [4,5].

The underlying pathophysiology of OCD is not entirely understood; however, studies comparing OCD patients and control individuals suggest there is a disruption in the orbito-fronto-striato-thalamo-cortical circuit. Neuroimaging studies in OCD patients demonstrate increased activity in the frontal cortex and subcortical structures, including orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), caudate, and thalamus [6–9]. These differences in

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local brain activity are associated with difficulties in executive function, attention, and memory [10].

Several clinical trials have been aimed at modulating this abnormal circuitry. Repetitive transcranial magnetic stimulation (rTMS) has been used to disrupt various nodes in this circuit, such as the dorsolateral prefrontal cortex, OFC, and the supplementary motor area, with limited success [11]. Surgical interventions to alter this circuitry have also been pursued. The first of these interventions were stereotactic lesioning procedures, including capsulotomy and cingulotomy, which have had varied results [12,13]. Among patients who underwent anterior cingulotomy, 41% significantly improved with a mean YBOCs score improvement of 37% [12]. Anterior capsulotomy has also been explored for OCD with a response rate of 54% and improvement ranging from 51 to 57% [12,14].

Deep brain stimulation (DBS) provides adjustable and reversible therapy and has been shown to be safe and effective for treating movement disorders. New potential neuropsychiatric indications for DBS have emerged, including Tourette's syndrome, major depressive disorder, and treatment-refractory OCD [15]. DBS studies have targeted many subcortical structures for OCD, including the ventral capsule/ventral striatum (including anterior limb of the internal capsule, nucleus accumbens) [16–19], bed nucleus of the stria terminalis (BNST) [20], subthalamic nucleus (STN) [21], ACC [22], medial forebrain bundle (MFB) [23], and inferior thalamic peduncle (ITP) [24].

The VC/VS is important in the cortico-striatal-pallidal circuitry (including the NAc, ventral tegmental area and amygdala) and is important in reward, motivation, and decision-making based [25]. The BNST has also been targeted due to its role in reward, fear, and anxiety [26–28]. VC/VS DBS and BNST studies have resulted in clinically significant symptom reductions and functional improvements in up to 60% of patients undergoing DBS [16–18]. Smaller studies have suggested a 50% response rate for MFB DBS [23] and a 75% response rate for medial STN DBS [21]. More recently, the ACC has also been targeted due to its increased metabolic activity in OCD patients and involvement in conflict resolution [22].

The ITP is a white matter tract that transmits bidirectional information from the OFC to the thalamus. This thalamic-orbitofrontal circuitry, along with the ascending reticular activating system, is thought to be involved with the motor and cognitive components of selective attention [29,30]. The role of this circuitry in behavior and evidence of its dysfunction in disease provides the neuroanatomical rationale for DBS to modulate this circuitry in severely disabled and treatment resistant OCD patients. Jimenez et al. previously reported a six patient case series of ITP DBS for OCD that demonstrated a 51% improvement in YBOCs scores at one year in all of the patients [31]. Of note, ITP DBS has also had promising results for major depressive disorder [31,32]. Currently, there is no clear consensus among neurosurgeons and psychiatrists which treatment is best for OCD, and no consensus on which site is best for DBS. Based on these observations, we designed a phase 1 pilot trial to assess the safety and potential efficacy of chronic ITP DBS for severe, treatment-refractory OCD.

Methods

Study design and patient selection

This study was designed as a prospective, open-label pilot study to assess the safety and initial efficacy of ITP DBS. The study was approved by the Institutional Review Board (REB # C-09-06) and performed at the Toronto Western Hospital (November 2010 to April 2018).

Patients were identified through the Division of Psychiatry at Toronto Western Hospital and community referrals. Patients were considered for inclusion if they met DSM-IV-TR criteria for OCD [33], were age ≥18, medication refractory, and had disabling symptoms related to OCD. All patients were evaluated by a single psychiatrist that specializes in the care of OCD patients (PG) and subsequently enrolled within 6–8 weeks prior to surgery. Medically refractory patients were defined as those patients who had trialed at least four medications for OCD at therapeutically appropriate doses, had been treated medically for at least five years with stable medication doses for at least six months, and continued to have severe OCD symptoms (Yale-Brown Obsessive Compulsive scale (YBOCs) scores greater than 23).

Patients were excluded from the study if they had not completely fulfilled criteria as medication refractory, had YBOCs scores <20, had unstable depression symptoms, active suicidal ideation, or required further treatment for psychiatric comorbidities. Full inclusion and exclusion criteria can be found in Supplemental Table 1. Informed consent was obtained from all patients enrolled.

Surgical procedure and programming

On the day of surgery, a Leksell G stereotactic frame was fixed to the skull, and volumetric T1 MR imaging was obtained. Images were fused using Framelink planning software (Medtronic, Minneapolis, MN, USA). Standard stereotactic coordinates were determined from the anterior and posterior commissures. The ITP was targeted with the following parameters: 6.5 mm lateral to the midsagittal plane, 3.0 mm posterior to the posterior margin of the anterior commissure, 0.5 mm below the anterior commissure-posterior commissure (AC-PC) line (Fig. 1). Electrodes were implanted under local anesthesia with the patient fully awake. Bilateral burr holes were drilled 2 cm lateral to the sagittal suture and 1 cm anterior to the coronal suture. Electrodes (Medtronic model 3387, Medtronic, Minneapolis, MN, USA; or St. Jude model 6143ANS, St. Jude Medical, St. Paul, MN, USA) were inserted to depth and confirmed with fluoroscopy. Electrodes were tested up to 10 V to assess for acute changes in mood or anxiety, and adverse effects. Once testing was completed, the electrodes were fixed to the skull. An implantable internal pulse generator (Medtronic Activa PC or St. Jude LibraXP) was placed subcutaneously below the right clavicle under general anesthesia. Each patient underwent a structural MRI or CT on postoperative day 1 to confirm electrode location. Patients were discharged home with the stimulator turned off.

After 4–6 weeks, patients returned to the psychiatry clinic and subsequently programmed in a series of visits by a single psychiatrist (PG). Contacts closest to the ITP, based upon postoperative imaging, were initially stimulated at 3.5 V, 90μs pulse width, and 130 Hz. Successive adjustments were made to the stimulation parameters based on clinical improvement or adverse side effects, such as anxiety or depression.

Outcomes and patient evaluations

Primary outcomes of the study were safety and initial efficacy of ITP DBS at one-year after surgery. Safety was assessed by the treating neurosurgeon (AML) and psychiatrist (PG) who recorded adverse effects at predefined clinical encounters from surgery. Actions taken to address complications and responses/outcomes were documented. Initial efficacy of ITP DBS was determined by reduction in one-year postoperative YBOCs score. Patients were considered responders to treatment if they had a greater than 35%

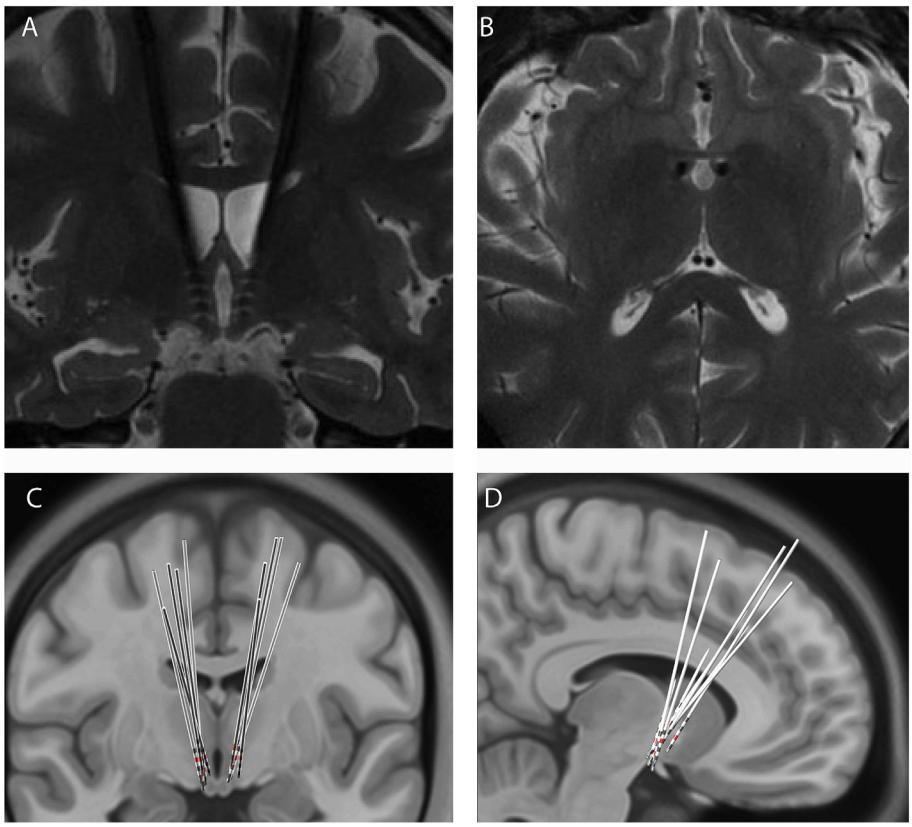

Fig. 1. DBS Electrode Placement. (A) Representative coronal and (B) axial MRI of electrodes terminating in bilateral ITP. (C) Coronal and (D) sagittal placements of all patient leads in MNI Space.

reduction in YBOCs score (determined by a single psychiatrist (PG) not blinded to treatment status).

Secondary outcomes of the study were improvements in psychiatric comorbidities and radiological assessments of brain metabolism. Depression was assessed by the Hamilton Depression Severity Scale (HAM-D). Additional outcome measures include the Quality of Life Assessment (SF-36), Oxford Happiness Questionnaire (OHQ), Warwick-Edinburgh Mental Well-Being Scale (WEMWBS), and Sheehan Disability Scale- Visual Analog Scale (VAS).

DBS electrode localization and volume of tissue activation estimation

DBS electrodes were localized with Lead DBS into MNI space [34]. Post-operative MRI scans were rigidly registered to corresponding pre-operative stereotactic MRI scans with SPM12. Subsequently, the immediate postoperative images were non-linearly normalized based on the pre-operative MRI using Advanced Normalization Tools [35], and the DBS lead contacts were manually localized in MNI space (ICBM 2009b NLIN asymmetric).

Based on patients' DBS settings at one-year follow-up, the volume of tissue activation (VTA) associated with each electrode was modeled with open-source software as implemented in Lead-DBS [36]. A volume conductor model of each electrode and the surrounding tissue was produced using the integrated Iso2Mesh toolbox. Based on this volume conductor model and given voltage values, the potential distribution of stimulation was estimated with the FieldTrip-SimBio finite element model (FEM) pipeline. The gradient of potential distribution was then calculated by derivation of the FEM solution and subsequently thresholded at 0.2 V/mm.

VTA volumes were lateralized (right-sided volumes were flipped to left) using Fslswapdim (FSL version 5.0) to facilitate cohort-level VTA analysis. Two types of volumes were created to describe the location and extent of VTAs at the cohort level: (1) a non-weighted average zone of stimulation derived from the voxel wise summation of binarized VTAs divided by the total number of VTAs and (2) a probabilistic weighted average zone of stimulation obtained by multiplying the non-weighted average zone by a clinically-weighted average zone (percentage change from baseline to 1 year follow-up). Two probabilistic weighted average zones of stimulation were produced: one based on YBOCs improvement at one year follow-up, the other based on HAMD improvement at one year follow-up.

PET/FDG image acquisition and analysis

Statistical analyses were performed using SPM8 (Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (version 9.2, Mathworks Inc., Natick, MA). Positron emission tomography (PET) of cerebral glucose metabolism ([^{18}F]-2-deoxy-2-fluoro-D-glucose) scans were reoriented and normalized into a standard three-dimensional space using the MNI ICBM 152 stereotactic template within SPM8. Baseline and three month post-operative scans were then smoothed using a 6 mm FWHM Gaussian kernel for two patients (Patient 3 and 5). Change in FDG uptake pre- and post-DBS was determined using a paired *t*-test for the two patients at baseline and 3 months postoperatively. For all analyses, results are reported at a significance level of $p < 0.05$ uncorrected. Brain locations are reported as x, y, z coordinates in MNI space with approximate Brodmann areas (BA), where appropriate, identified using MRIcron [37]. The analysis involved a paired

t-test, relative threshold masking at 0.8, overall grand mean scaling to 50 and proportional global normalization. The data is all uncorrected at 0.05 with a minimum cluster size of k = 40 [38].

Statistical analysis

Since this study was a five patient case series, statistical analysis was limited. Paired t-tests were performed comparing baseline scores to one-year data and last follow up data. One-way ANOVA tests were performed to compare all follow-up data.

Results

Demographics

Five patients were enrolled in the study and underwent bilateral ITP DBS. Patient demographics are detailed in Table 1. Three patients were women. Mean age of onset for OCD symptoms was 14 years (range 8–20), and mean disease duration prior to surgery was 15 years (range 5–38 years). Mean age at surgery was 32 years (range 25–48 years). At the time of surgery, none of the patients were employed; all but one patient was on social disability; and none were married or had children. Before surgery, three patients had attempted suicide, and two of these had multiple suicide attempts. All patients had been hospitalized for severe OCD symptoms prior to DBS implantation (mean 3.4, range 2–6 times).

Surgical results and device settings

Intraoperative macrostimulation did not result in any adverse side effects (up to 10 V). In two patients, macrostimulation led to decreased anxiety and increased optimism. Surgical implantation of bilateral ITP DBS electrodes and subclavicular internal pulse generators (IPGs) were successful in all patients. After surgery, devices were programmed with a mean voltage of 6.8 V (range 5.0–8.5 V), 90μs pulse width, and 130 Hz. Average length of time between IPG exchanges ranged from 8 to 36.5 months (Table 2).

Safety - adverse events

Serious adverse events occurred in two patients (Table 3). One patient had two separate hospitalizations. The first hospitalization occurred 16 months after surgery secondary to a cocaine overdose. The second hospitalization occurred 51 months after implantation and was due to serotonin syndrome from overdosing on prescription medication (clomipramine, clonazepam, and fluvoxamine). He was discharged to home with adjustments in his OCD medication (clomipramine held). This patient had a prior history of substance abuse, but had been abstinent for over 6 months prior to enrolling in the trial.

A second patient requested to have the device removed because it caused him severe distress, and had become a part of his obsession syndrome. He wanted to constantly feel stimulation. The device was removed without complication 21 months after implantation. After explantation, the patient was lost to follow-up. There were no mortalities or suicide attempts during the study (21–85 months after DBS, median 24 months).

Clinical outcomes

All five patients were considered responders at one-year after implantation. There was a significant reduction in YBOCs score at one-year (52% reduction (range 39–73%), $p < 0.01$) and at last follow-up (54% reduction (range 38–85%), $p < 0.01$; Fig. 2A and B). Similarly, there was a 51% (range 39–75%) reduction in the YBOCs obsessive score and 53% (range 38–71%) reduction in the YBOCs compulsive score after one year (Fig. 2A). Of note, the patient who had the device removed had a 51% reduction at time of explantation.

One year after surgery, there was no significant difference in HAM-D scores ($p = 0.13$), but there was a significant improvement in HAM-D scores at the two-year follow up ($p < 0.05$). At last follow-up, there was a trend towards improvement in HAM-D scores ($p = 0.07$). Notably, four patients had a reduction in HAM-D scores (Fig. 2C and D). The one patient who did not have a decrease in HAM-D scores had a low baseline score.

Table 1
Demographics.

Patient	Age at Time of Surgery (years)	Disease Duration (years)	Gender	Pre-Op Y-BOCS	Preop HAM-D	On Disability	Level of Education	Number of Pre-DBS suicide attempts	Pre-operative medications (daily)	Medications at 2 year follow up (daily)
1	25	17	F	34	14	Yes	High School	0	Paroxetine 60 mg Risperidone 0.5 mg Olanzapine 15 mg Lorazepam 1 mg	Paroxetine 60 mg Risperidone 1 mg Olanzapine 2.5 mg Lorazepam 1 mg
2	48	38	M	33	5	Yes	College	4	Fluvoxamine 200 mg Clomipramine 175 mg Olanzapine 10 mg Clonazepam 0.5 mg	Fluvoxamine 100 mg Clomipramine 125 mg
3	34	14	M	37	14	Yes	DNF High School	6	Clomipramine 50 mg Clozapine 500 mg	Clomipramine 50 mg Clozapine 500 mg
4	25	5	F	33	12	Yes	College	0	Escitalopram 10 mg Clomipramine 250 mg Aripiprazole 7 mg	Escitalopram 10 mg Clomipramine 250 mg Aripiprazole 7 mg
5	30	7	F	38	25	No	DNF College	1	Citalopram 60 mg Clomipramine 150 mg Aripiprazole 5 mg Quetiapine 75 mg Lorazepam 3 mg	Citalopram 60 mg Clomipramine 150 mg Aripiprazole 5 mg Quetiapine 50 mg Lorazepam 3 mg

*Patient 3 was taking clozapine for antidepressant augmentation after other atypical antipsychotics were unsuccessful. It did not worsen or improve the OCD symptoms.

Table 2
Stimulation parameters.

Patient	Device Manufacturer	Right Electrode configuration	Left Electrode configuration	Electrode Settings	Average Battery Replacement Interval
1	St. Jude	C+2-	C+10-	8.5 V, 130 Hz, 91μsec	No battery changes (removed after 15 months)
2	St. Jude	C+1-	C+9-	8.5 V, 130 Hz, 91μsec	21 months
3	Medtronic	C+2-	C+10-	5.3 V, 130 Hz, 90μsec	8 months
4	Medtronic	C+1-	C+9-	6.5 V, 130 Hz, 90μsec	36.5 months
5	Medtronic	C+1-	C+9-	5.0 V, 130 Hz, 90μsec	26 months

Table 3
Serious adverse events.

Patient	Serious Adverse Event	Length of Follow-Up
1	–	59 months
2	Substance Abuse (cocaine) Serotonin Syndrome	60 months
3	Removal of system due to DBS system becoming the object of obsession	21 months
4	–	85 months
5	–	24 months

One year after surgery, there was no improvement in the Quality of Life Assessment (QOLA SF-36; mental component, $p = 0.14$; physical component; $p = 0.54$; Fig. 2E) or Oxford Happiness Questionnaire (OHQ, $p = 0.12$; Fig. S1B). There was a trend towards an improvement in the Warwick-Edinburgh Mental Well-Being Scale (WEMWBS, $p = 0.06$; Fig. S1A). There was a significant improvement in two of the three subscore components of the Sheehan Disability Scale (social subscale, $p < 0.05$; family subscale, $p < 0.05$; work subscale: $p = 0.07$; Fig. 2F). In this cohort, two patients began work at 7 and 13 months after surgery, while an additional patient started volunteer work after 12 months. There were no significant changes in antidepressant or antipsychotic medications after implantation (Table 1).

Radiographic outcomes

Based upon the active contacts used and stimulation settings, the mean volume of tissue activation (VTA) was centered on the ITP (mean MNI coordinates (x,y,z): −6,-2,-6; Fig. 3A–C; Supplemental Table 2). The YBOCs zone of effectiveness was anterior and superior to the center of the VTA (mean MNI coordinates (x,y,z): −6,-1,-5; Fig. 3D–F), while the HAMD zone of effectiveness was further anterior, superior, and lateral to the center of the VTA (mean MNI coordinates (x,y,z): −7,1,-3; Fig. 3D–F).

PET analysis

After three months of ITP DBS, there was decreased glucose uptake within the right caudate, right putamen, right supplementary motor area, and right cingulum (Brodmann Area 8) relative to preoperative imaging ($p < 0.05$; Fig. 4A, Supplemental Table 3). There was increased glucose uptake after DBS in bilateral motor areas, left temporal pole, and left OFC ($p < 0.05$; Fig. 4B and C).

Discussion

In this DBS study, we targeted the ITP for treatment refractory OCD. This fiber bundle contains a cortico-striato-thalamo-cortical loop involving the OFC and ACC; two regions associated with increased metabolic activity in OCD (Fig. 4) [8,9]. Although two patients experienced a total of three serious adverse events, there were no deaths, suicide attempts, strokes, infections, seizures or device-related events during the study time period (range 21–81 months). YBOCs scores improved an average of 52% at one year postoperatively, and were sustained throughout the two-year (56%) and last follow up (54%).

ITP DBS and the cortico-striato-thalamo-cortical circuit

The precise mechanism of action of DBS for OCD is unknown; however, recent neuroimaging, genetic, pharmacological, and electrophysiological studies suggest that striatal circuits are involved in OCD and obsessive compulsive-spectrum disorders [39]. PET studies have demonstrated that OCD patients have increased metabolic activity in the OFC, ACC, caudate, and thalamus. This increased activity has been positively correlated with the severity of OCD symptoms [8,9]. CBT and SSRI treatment leads to decreased metabolism within the cortico-striato-thalamic circuit, in particularly the OFC [40,41]. Interestingly, increased OFC activity is also seen in patients with depression [42]. While it is possible that increased OFC activation could suggest co-morbid depression in OCD patients, the increase in OFC PET activation occurred in both a patient who had depression and another who did not. While speculative, one hypothesis is that the increased activity in the cortico-striato-thalamic circuit (including the OFC) may be more globally involved in mood disorders that affect general states like emotional valiance, negative affect, anxiety and sadness [42,43].

Our small sample of patients undergoing PET studies precludes making conclusions regarding the circuit effects of ITP DBS. However, our results are consistent with network engagement as we found decreased activation in the caudate, putamen, and cingulum after three months of chronic DBS, which is comparable to medical treatment [40,41]. Similarly, ALIC DBS has been associated with decreased metabolism in the cingulum and caudate nucleus [44]. However, contrary to CBT and SSRI treatment, we demonstrated increased left-sided OFC activity with ITP DBS (Fig. 4, Supplemental Table 3). DBS studies have previously found that acute electrical stimulation increases cortical and subcortical activation of distal nodes within the limbic circuit. For instance, ventral capsule/ventral striatum (VC/VS) stimulation in OCD patients results in increased cerebral perfusion within the dorsal ACC, thalamus, striatum, and globus pallidus [45,46]. One potential explanation for the seemingly contradictory metabolic findings in the OFC is that the DBS cohort were medically refractory cases. Differences in PET imaging and metabolic discrepancies between effective cognitive therapy, medical therapy, and acute and chronic electrical stimulation suggest different underlying mechanisms for symptomatic relief in OCD. In this trial, medication dosages were relatively stable throughout the trial, suggesting that continuing medications are necessary in severe OCD.

While there is growing evidence of limbic circuit dysfunction in OCD, the nuances of the circuit that contribute to distinct aspects of attention, reward, and action selection remain unknown. As such, multiple DBS targets have been studied to modulate these pathways. The ITP is a fiber bundle that connects the OFC and ascending reticular activating system (ARAS) with the thalamus (Fig. 5). The ARAS is important in determining the significance of sensory

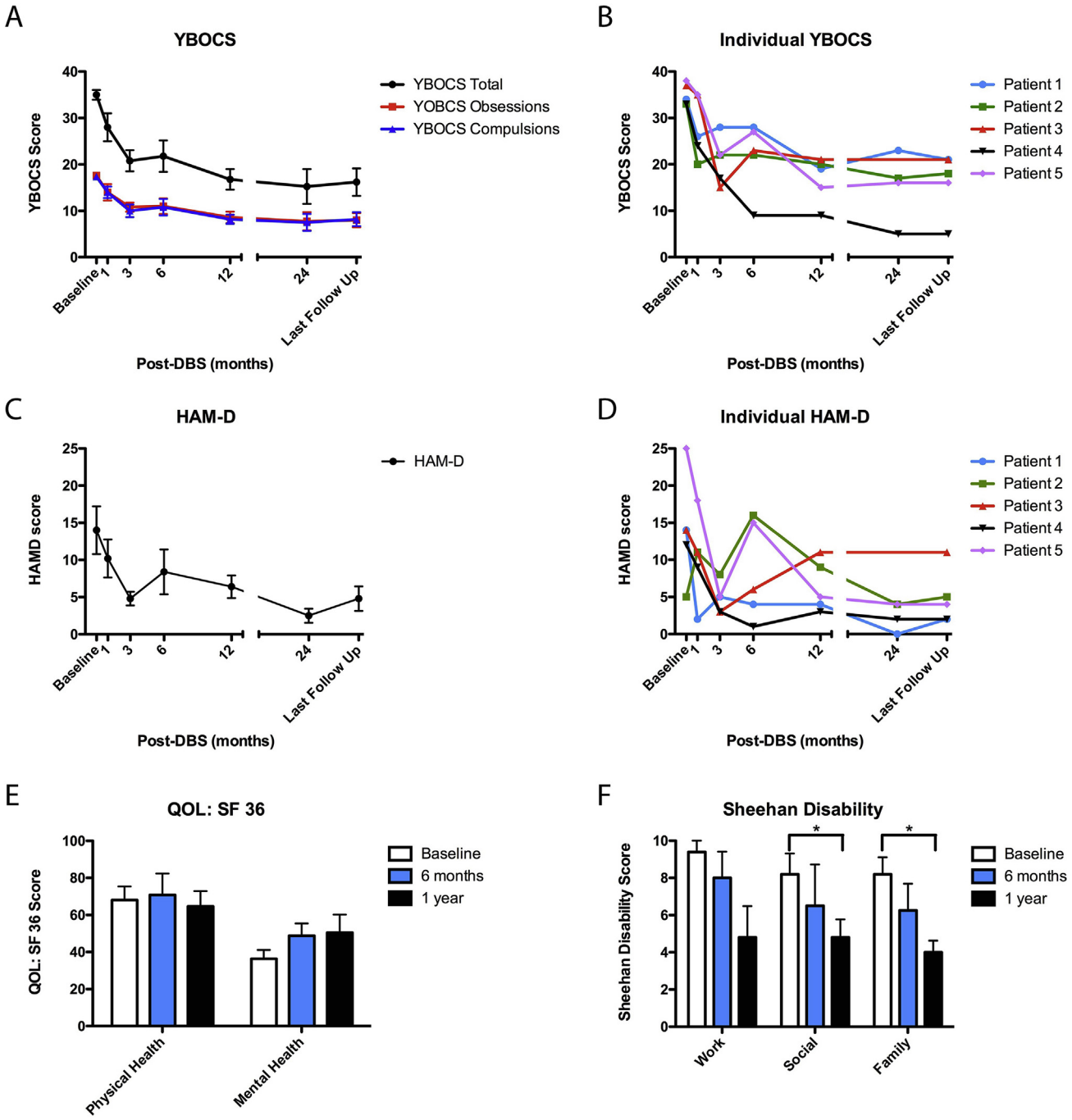

Fig. 2. Clinical Outcomes. (A) Average and (B) individual Y-BOCS scores demonstrated a significant reduction (52% (39–73%), $p < 0.01$) at 1-year and at last follow-up. The YBOCs obsessive score was reduced by 51% (39–75%) while the compulsive score was reduced by 53% (38–71%) at 1-year. (C) Average and (D) individual postoperative HAM-D scores showed no significant difference between baseline and 1-year scores ($p = 0.13$); however, there was a significant improvement at the two-year follow-up ($p < 0.05$). HAM-D scores were reduced in 4/5 patients, with a trend towards improvement at last follow-up ($p = 0.06$). (E) There was no difference in preoperative Quality of Life Assessment (SF-36) (QOL: SF36) scores. (F) Sheehan Disability scales demonstrated significant improvement in the social and family domains ($p < 0.05$), but not the work domain.

information, while the OFC-thalamic circuitry filters irrelevant information [47]. When this region is modulated, it can lead to a state of increased selective attention. Since the ITP is a key structure in this circuit, DBS may modulate multiple dimensions of abnormal subcortical thought processing, a hallmark of severe OCD. As evidence by the VTA analysis, other adjacent structures, such as the more anterior BNST, may also be activated during ITP stimulation (Fig. 3A–F). The calculated zone of effectiveness for YBOCs and HAM-D scores were anterior to the center of the VTA, further suggesting a potential role for ITP and BNST stimulation for OCD.

Limitations

This study was designed as an open label pilot study with a target enrollment of five patients. Given this study design and patient number, limited statistical analysis could be performed and

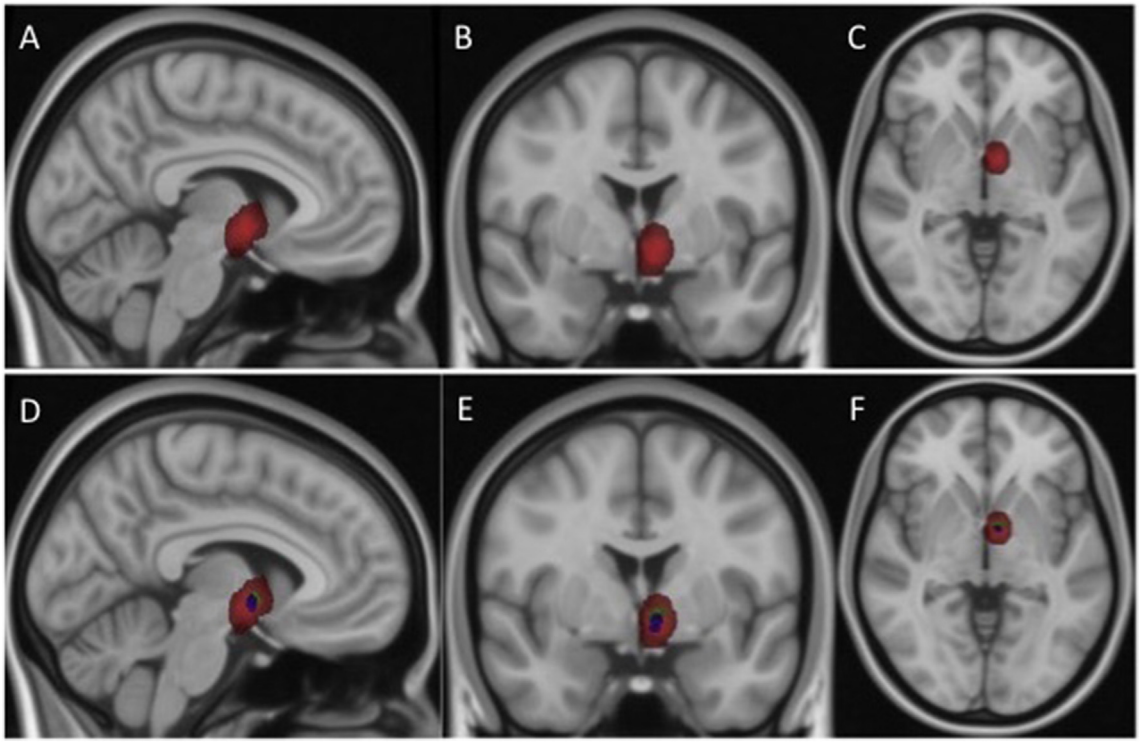

Fig. 3. Volume of Tissue Activation (VTA), Zone of Effectiveness, and. (A) Sagittal, (B) Coronal, and (C) axial volume of tissue activation regions and (D) sagittal, (E) coronal, and (F) axial zone of effectiveness regions for YBOCs (blue) and HAM-D (green) illustrated in MNI space. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

data extrapolation or generalization of treatment effects should be made with caution. This study did not include a randomized, blinded phase where some patients had their devices turned on while others had their device implanted without activation. Both patients and assessors were unblinded to treatment, which introduces inherent biases including placebo responses and observer biases. This study was not designed to compare ITP DBS with other surgical treatments for OCD.

The stimulation amplitude is relatively high compared to standard DBS treatment. The current activation function-based VTA models has been argued to overestimate the spatial extent of neuronal activation [48]. However, given the high voltages employed in this case series, it is likely that there was still considerable current spread to nearby structures in addition to the target, such as the BNST, which could potentially conflate the true effect of ITP stimulation versus stimulation of nearby structures.

Conclusions

Based on the results of this study, it is reasonable to conclude that ITP DBS has a safety profile that is similar to previously reported DBS treatments for OCD. Despite the small cohort, as all five patients were considered treatment responders, ITP DBS should be explored as a potential treatment for medically refractory OCD.

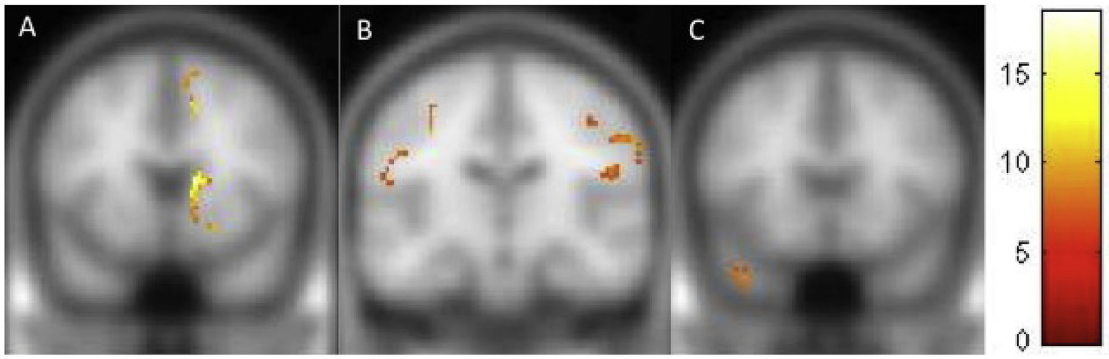

Fig. 4. PET scans after 3 months of deep brain stimulation compared to baseline. (A) After three months of ITP DBS, there was decreased glucose metabolism seen within the right caudate and putamen, the right SMA and the right cingulum ($p < 0.05$). (B,C) In contrast, Increased glucose metabolism was observed in the bilateral motor areas, left temporal pole, and left orbitofrontal cortex.

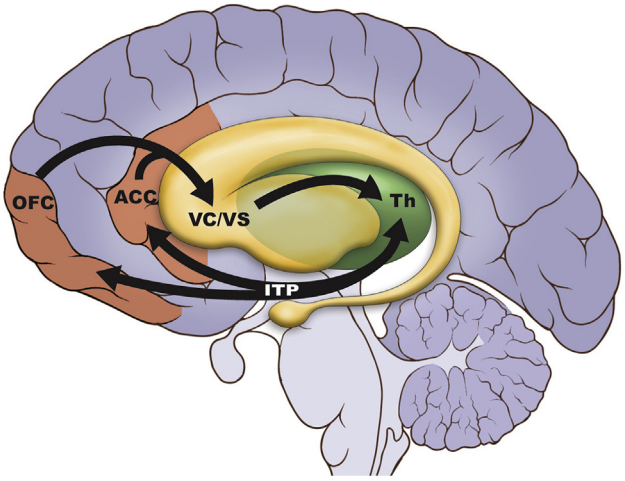

Fig. 5. ITP DBS Circuit. The cortico-striato-thalamo-cortical circuit implicated in the pathophysiology of OCD. Glutaminergic excitatory projections from the OFC and ACC synapse at the VC/VS. Through several direct and indirect pathways, the striatum projects inhibitory fibers to the mediodorsal nuclei of the thalamus. The thalamus projects bidirectional excitatory fibers back to the frontal cortical areas via the ITP. Disinhibition of the loop in OCD is thought to increase thalamocortical tone, and the ITP is therefore targeted in DBS surgery aimed at restorative inhibition of this pathway. OFC: orbito-frontal cortex; ACC: anterior cingulate cortex; Th: Thalamus; ITP: inferior thalamic peduncle; VC/VS: ventral capsule/ventral striatum.

Conflict of interest and disclosures

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2018.11.012.

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