

Acute deep brain stimulation changes in regional cerebral blood flow in obsessive-compulsive disorder

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OBJECTIVE Deep brain stimulation (DBS) is a reversible, nonlesion-based treatment for patients with intractable obsessive-compulsive disorder (OCD). The first studies on DBS for OCD stimulating the ventral capsule/ventral striatum (VC/VS) yielded encouraging results for this neuroanatomical site's therapeutic efficacy. This investigation was conducted to better understand which regions of the cortico-striatal-thalamic-cortical network were acutely affected by VC/VS DBS for OCD. Furthermore, the objective was to identify which brain regions demonstrated changes in perfusion, as stimulation was applied across a dorsoventral lead axis that corresponded to different anatomical locations in the VC/VS.

METHODS Six patients receiving VC/VS DBS for OCD underwent oxygen-15 positron emission tomography (¹⁵O-PET) scanning. Monopolar DBS was delivered at each of the 4 different electrodes on the stimulating lead in the VC/VS. The data were analyzed using SPM5. Paired t-tests were run in SPSS to identify significant changes in regional cerebral blood flow (rCBF) between stimulation conditions. Pearson's r correlations were run between these significant changes in rCBF and changes in OCD and depressive symptom severity.

RESULTS Perfusion in the dorsal anterior cingulate cortex (dACC) significantly increased when monopolar DBS was turned on at the most ventral DBS contact, and this increase in dACC activity was correlated with reductions in depressive symptom severity ($r(5) = -0.994$, $p = 0.001$). Perfusion in the thalamus, striatum, and globus pallidus significantly increased when DBS was turned on at the most dorsal contact.

CONCLUSIONS DBS of the VC/VS appears to modulate activity in the regions implicated in the pathophysiology of OCD. Different regions in the cortico-striatal-thalamic-cortical circuit showed increased perfusion based on whether the stimulation was more ventral or dorsal along the lead axis in the VC/VS. Evidence was found that DBS at the most ventral site was associated with clinical changes in depressive symptom severity, but not OCD symptom severity.

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KEY WORDS deep brain stimulation; positron emission tomography; obsessive-compulsive disorder; ventral capsule/ventral striatum; cortico-striatal-thalamic-cortical circuit; functional neurosurgery

OBSESSIVE-COMPULSIVE disorder (OCD) affects between 0.7% and 2.9% of adults in the United States.¹² It is characterized by persistent and distressing thoughts (obsessions) and ritualistic behaviors (compulsions), such as counting, checking, or hand washing, to overcome anxiety caused by the obsessions. Cur-

rent treatments such as cognitive-behavioral therapy and serotonin reuptake inhibitors can reduce the severity of OCD symptoms.¹⁰ However, patients often continue to experience some symptoms even after effective treatment, and an estimated 10% of patients become treatment resistant.²⁰

ABBREVIATIONS ACC = anterior cingulate cortex; dACC = dorsal anterior cingulate cortex; DBS = deep brain stimulation; FDG = fluorodeoxyglucose; FWHM = full width at half maximum; HAM-D = Hamilton Depression Rating Scale; MGH = Massachusetts General Hospital; MNI = Montreal Neurological Institute; OCD = obsessive-compulsive disorder; OFC = orbitofrontal cortex; rCBF = regional cerebral blood flow; ROI = region of interest; VC/VS = ventral capsule/ventral striatum; vmPFC = ventromedial prefrontal cortex; Y-BOCS = Yale-Brown Obsessive Compulsive Scale; ¹⁵O-PET = oxygen-15 positron emission tomography.

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While the pathophysiology of OCD remains completely understood, converging lines of evidence point to abnormalities in the cortico-striatal-thalamic-cortical circuit or the medial and orbital frontal-basal ganglia circuit. Stereotactic neurosurgical lesions in the anterior limb of the internal capsule, anterior cingulate, and/or subcaudate region—all of which interrupt this circuit—are effective for the treatment of refractory OCD.⁸ Results from neuroimaging studies also support the central role of the frontal-basal ganglia-thalamic circuit in the pathophysiology of OCD. Specific abnormalities have been identified in the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC), striatum, and medial thalamus. Structural neuroimaging studies of OCD have found subtle differences in the OFC striatal and thalamic volumes in subjects with OCD versus controls.^{4,11,19,21,22} Functional neuroimaging studies have documented hyperactivity at rest in this circuit when comparing OCD subjects to controls. Furthermore, this regional hyperactivity is accentuated during the provocation of OCD symptomatic states.¹⁸ Conversely, several studies have consistently found reductions in the activities in these same regions following successful treatment of OCD, regardless of the mode of treatment, including pharmacological, behavioral,¹ and neurosurgical therapies.¹⁴

In the past few years, deep brain stimulation (DBS) has emerged as a viable, reversible, nonlesion-based treatment option for those suffering from severe, intractable OCD. The first studies on DBS for OCD that used the ventral (internal) capsule/ventral striatum (VC/VS) as the target of stimulation yielded encouraging results for the therapeutic efficacy of this neuroanatomical site.¹⁵ Greenberg et al.⁷ found comparable outcomes using a more posterior target within the VC/VS site. At multiple sites worldwide, DBS for OCD has not achieved the near 100% response rate seen in DBS for movement disorders.⁶ OCD and movement disorders are admittedly significantly different conditions. However, it is possible that part of the reason for OCD's lower response rates to DBS is that the mechanism of action for DBS of the VC/VS is not well understood (even though we have learned much about improving electrode placement). Clinicians are thus limited in their ability to adjust the stimulation parameters in order to maximize symptom control. The current investigation was conducted to understand more precisely which regions of the cortico-striatal-thalamic-cortical neural network are acutely affected by DBS of VC/VS for OCD.

We tested the hypothesis that acute electrical stimulation at the VC/VS target would affect activity in the OFC, ACC, and functionally related areas, including the striatum, globus pallidus, and thalamus. A study by Rauch et al.¹⁷ used oxygen-15 positron emission tomography (¹⁵O-PET) to demonstrate how perfusion in the OFC, ACC, striatum, globus pallidus, and thalamus increased when DBS was turned on in comparison with when it was turned off. These results led to our a priori hypotheses based on both the purported anatomy of the VC/VS and the proposed mode of action of DBS at VC/VS as a therapy for OCD. The purpose of this study was to replicate and extend these findings by delineating regional brain modulation associated with acute DBS at the VC/VS target. Furthermore, DBS is delivered via stimulating leads that have 4 cylindrical

electrode contacts that are 3 mm in length and spaced 4 mm apart (Fig. 1). Each electrode contact therefore stimulates slightly different anatomical locations along the VC/VS. Rauch et al.¹⁷ investigated the perfusion effects of DBS only at the ventral contacts. Another aim of this study was to identify which brain regions demonstrated changes in perfusion as stimulation is applied across a dorsoventral lead axis, corresponding with different anatomical locations in the VC/VS.

Methods

Patient Sample

This study was approved by the institutional review board of Massachusetts General Hospital (MGH). The clinical trial of DBS for OCD, from which the subjects were drawn, was approved by the institutional review boards of the participating hospitals. This study was also registered with the ClinicalTrials.gov database (<http://clinicaltrials.gov>), and its registration number is NCT00640133.

After the present imaging study was advertised to all patients in the clinical trial, 6 individuals expressed interest in participating, provided informed consent, and were subsequently enrolled. The 6 subjects who received DBS for OCD and participated in this study had severe treatment-refractory OCD, which was defined as having failed multiple adequate trials of anti-obsessional medications and 1 or more adequate trial for behavioral therapy (exposure and response prevention). Treatment failure was determined by the multidisciplinary MGH Psychiatric Neurosurgical Committee. The mean age of the 6 participants was 41.5 ± 9.91 years (range 28–57 years), and 5 of 6 participants were right-handed (1 participant was ambidextrous). The diagnosis of OCD and comorbid Axis I disorders was ascertained by performing a structured clinical interview using the Structured Clinical Interview for DSM-IV Disorders³ prior to enrollment in the DBS clinical trial. The severity of OCD was assessed using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS),⁵ and the severity of depressive symptoms was assessed using the Hamilton Depression Rating Scale (HAM-D).⁹ At the time of the scan, the participants had been implanted with the DBS system for approximately 5 years \pm 11 months (\pm SD) (see Table 1 for the therapeutic DBS contacts). They had moderately severe OCD, as reflected by a mean Y-BOCS score of 19.67 ± 3.98 (range 13–23) of a possible score of 40. Depressive symptoms were also present, as reflected by a mean HAM-D score of 6.17 ± 4.88 (range 0–12). In addition to OCD, the comorbid psychiatric conditions included dysthymia. Patients were also taking psychotropic medications at the time of the study, including diazepam, venlafaxine, fluvoxamine, aripiprazole, and duloxetine.

Clinical Procedure

DBS was implemented similarly at all participating centers at Butler Hospital, Cleveland Clinic, and the University of Florida. All patients in this study underwent implantation at one of these 3 centers. All centers used identical stimulating leads (model 3391; Medtronic, Inc.). The leads were 1.27 mm in diameter with 4 cylindrical electrode contacts that were 3 mm in length and spaced 4

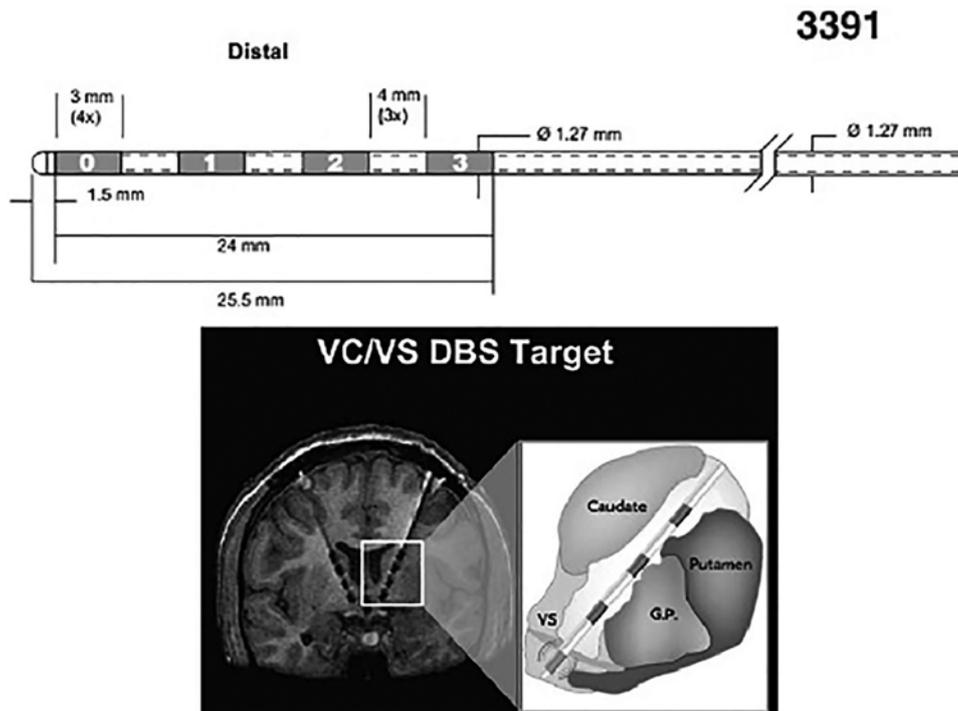


FIG. 1. Stimulating lead with 4 electrode contacts. **Upper:** DBS was delivered via stimulating leads that had 4 cylindrical electrode contacts that were 3 mm in length and spaced 4 mm apart. Each electrode contact was set independently as positive, negative, or off. DBS was turned on and off in the bipolar configuration between contacts 0 (+) and 1 (–), and the monopolar configuration for Contact 0, Contact 1, and Contact 3 in this study protocol. Image reprinted with the permission of Medtronic, Inc. © 2016. **Lower:** Each electrode contact stimulates slightly different anatomical locations along the VC/VS. G.P. = globus pallidus.

mm apart. Each electrode contact was set independently as positive, negative, or off. Contacts were numbered from 0 (most ventral) to 3 (most dorsal).⁶ The DBS leads were placed bilaterally into the VC/VS along the anterior limb of each internal capsule and extended into the VS. Stereotactic coordinates were determined based on the patient's individual structural neuroanatomy using high-resolution MRI and CT. Once the leads were implanted, intraoperative testing was performed to evaluate the effects of acute stimulation and avoid any untoward effects.¹⁶

The electrodes were then connected through a wire to a programmable internal pulse generator (i.e., a battery with a microprocessor that controls the stimulation), which was surgically implanted under the pectoral muscle. The connecting wires were tunneled subcutaneously while the patients were under general anesthesia. The wires traveled from the scalp, through the neck, and into the pectoral region. Internal pulse generator implantation was carried out either the same day of surgery or about 1 week later depending on the neurosurgeon's preference.

PET Protocol

Fluorodeoxyglucose (FDG) and oxygen-15 are 2 radiotracers used with PET. Both FDG-PET and ¹⁵O-PET are tightly coupled with neuronal activity. FDG-PET measures glucose metabolism. In the standard FDG-PET protocol, FDG is injected, uptake occurs for approximately 30 minutes, and then a PET scan is obtained. Therefore, FDG-PET provides a “snapshot” of metabolism during the 30-minute FDG-uptake period. ¹⁵O-PET measures cerebral blood flow or perfusion. Oxygen-15 can be inhaled,

and has a short (~ 2-minute) half-life. This enables the measurement of perfusion during multiple 1-minute runs every 10 minutes (since it takes 5 half-lives for oxygen-15 to decay). Therefore, this allows for multiple “snapshots” of cerebral blood flow during different conditions, such as DBS and DBS at Contact 0, Contact 1, or Contact 3. For this study, we used ¹⁵O-PET.

All patients traveled to MGH for the ¹⁵O-PET scan. Images were acquired using a 15-slice, whole-body tomographic scanner (model 4096; Scanditronix, General Electric) in stationary mode. The slice geometry consists of contiguous slices with a center-to-center distance of 6.5 mm (axial field 97.5 mm) and axial resolution of 6-mm full width at half maximum (FWHM). Image reconstruction was performed using computed attenuation correction and a Hanning-weighted reconstruction filter set to yield an 8-mm, in-plane, spatial resolution FWHM. Additional corrections were made in the reconstruction process to account for scattered radiation, random coincidences, and counting losses due to dead time in camera electronics.

Head alignment was made relative to the canthomeatal line using projected laser lines whose positions were known with respect to the slice positions of the scanner. An inflatable headholder was used to minimize head motion. Once the head was in place, an overlying face mask attached to a vacuum and a nasal cannula were positioned to deliver ¹⁵O-CO₂ (concentration 2960 MBq/L; flow rate 2 L/min).

The device was turned off for a minimum of 2 hours prior to the beginning of the scan session. Ten runs (representing duplicate runs of 5 conditions) were performed: 1)

TABLE 1. The active contacts used for chronic and therapeutic DBS in the 6 patients with OCD

Patient No.	Active Contacts on the Left	Active Contacts on the Right
1	Off	Contacts 0 (+) & 1 (-)
2	Contacts 3 (+) & 0 (-)	Contacts 3 (+), 0 (-), 1 (-)
3	IPG (+) & Contact 1 (-)	IPG (+) & Contact 1 (-)
4	Contacts 3 (+) & 1 (-)	Contacts 3 (+), 0 (-), 1 (-)
5	Contacts 1 (+) & 2 (-)	Contacts 1 (+) & 2 (-)
6	IPG (+), Contacts 0 (-) & 1 (-)	IPG (+), Contacts 0 (-) & 1 (-)

IPG = implantable pulse generator.

DBS off; 2) DBS on in the bipolar configuration between Contacts 0 (+) and 1 (-); 3) DBS on in the monopolar configuration at Contact 0; 4) DBS on in the monopolar configuration at Contact 1; and 5) DBS on in the monopolar configuration at Contact 3 (Fig. 1). The stimulation frequency was set to 135 Hz, 90- μ sec pulse width, and an amplitude of 4 V for all of these configurations. Subjects were instructed to keep their eyes closed during tracer uptake and PET acquisition. Acute stimulation was initiated at the designated parameters at 1 minute prior to each PET run and terminated at the end of each PET run (total on time 2 minutes). A 10-minute rest period was imposed between each successive PET run to allow for the decay of the 15 O radiation signals to the background levels. The 2 runs with DBS off were performed first and last. The 2 runs using each of the other conditions were performed consecutively to minimize the number of changes in the stimulation parameters. The order of the resulting blocks of the 2 runs for each condition was counterbalanced across subjects.

PET Data Analysis

The PET images were realigned for interscan head movement, spatially normalized to the coordinate system developed and distributed by the Montreal Neurological Institute (MNI) and implemented in the SPM5 software package (Wellcome Department of Cognitive Neurology), and smoothed and scaled using a 2D Gaussian filter (8-mm FWHM).

We then created contrast images for each subject under each condition (DBS off, DBS on for Contacts 0 [+] and 1 [-], DBS on for Contact 0, DBS on for Contact 1, and DBS on for Contact 3). These individual contrast images were brought forward into a group random effects, flexible, factorial model. Contrast images were created to investigate changes in regional cerebral blood flow (rCBF) when 1) DBS was turned on at Contacts 0 (+) and 1 (-) in comparison with DBS off, 2) DBS was turned on at Contact 0 in comparison with DBS off, 3) DBS was turned on at Contact 1 in comparison with DBS off, and 4) DBS was turned on at Contact 3 in comparison with DBS off.

We identified the peak voxels of activation in our a priori regions—the ventromedial prefrontal cortex (vmPFC), OFC, dorsal anterior cingulate cortex (dACC), striatum, globus pallidus, and thalamus—using anatomical masks from the Wake Forest University Pick Atlas¹³ and a significance level of $p < 0.05$.

Spherical regions of interest (ROIs; radius = 2 mm) were created around the peak voxels of activation in our a priori regions. MarsBaR, an ROI toolbox for SPM (<http://marsbar.sourceforge.net>),² was used to extract beta weight values from these ROIs in each subject for each condition of interest. All values were scaled to 100. Paired sample *t*-tests were run in SPSS using the beta weight values for the DBS off and on conditions in order to determine if there were significant changes in rCBF when DBS was turned on in comparison with when it was turned off. Pearson's *r* correlations were run between these significant changes in rCBF and changes in OCD and depressive symptom severity from baseline to the time of the PET scan. Therefore, a total of 24 correlations were run (4 significant acute DBS-related changes in brain activity \times 3 different conditions [activity when DBS was off, activity when DBS was on, and the percent signal change in activity between DBS off and DBS on] \times DBS-related changes in 2 clinical measures [Y-BOCS and HAM-D scores at the time of the scan – the scores before DBS implantation]). To correct for multiple comparisons, a Bonferroni correction was applied, such that the new significance threshold for these correlation analyses was $p < 0.002$ (i.e., $0.05/24$).

Results

As predicted, acute changes in rCBF were seen when DBS was turned on in comparison with when it was turned off. When DBS was turned on at the more ventral Contact 0, perfusion in dACC increased (Fig. 2; MNI coordinates 10, 32, and 18; paired $t(4) = -3.438$; $p = 0.026$).

When DBS was turned on at the more dorsal contact 3, rCBF significantly increased in the thalamus (MNI coordinates -2, -12, and 0; paired $t(5) = -2.679$; $p = 0.044$), striatum (MNI coordinates 24, 12, and 4; paired $t(5) = -3.684$; $p = 0.014$), and globus pallidus (MNI coordinates 16, 6, and 4; paired $t(5) = -4.070$; $p = 0.010$; Fig. 3).

Control analyses that were run on spherical ROIs in the hippocampus (MNI coordinates 30, -26, and -14) showed a decrease in the beta values (from DBS off to DBS on). This suggests that our significant findings did not reflect a global effect. We did not find statistically significant changes in rCBF with bipolar DBS between Contacts 0 (+) and 1 (-), or with monopolar DBS at Contact 1 (all *p* values > 0.05). We also did not find statistically significant changes in rCBF in the OFC or vmPFC.

Increased dACC activity due to DBS being turned on at Contact 0 was significantly correlated with decreases in depressive symptom severity (Fig. 4; Pearson's $r(5) = -0.994$; $p = 0.001$). In other words, the more of an increase in dACC activity, the more of a reduction in depressive symptom severity. There were no significant correlations between changes in obsessive-compulsive symptom severity scores and changes in rCBF in our a priori regions. There were also no significant correlations between the rCBF changes caused by DBS being turned on at Contact 3 and clinical changes.

Discussion

DBS of the VC/VS appears to modulate activity in the regions implicated in the pathophysiology of OCD. Mono-

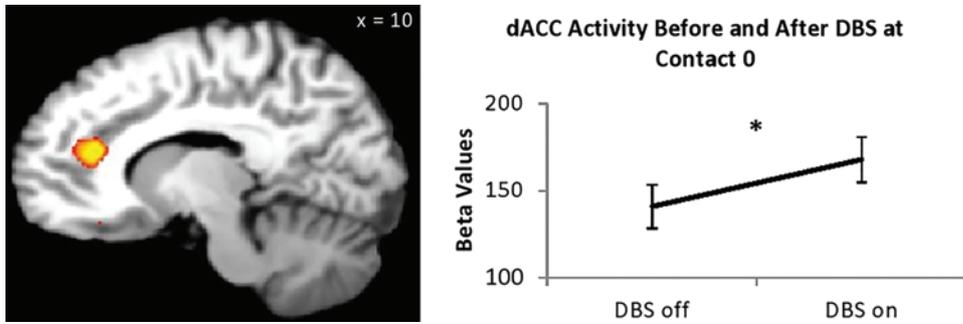


FIG. 2. Increased perfusion in the dorsal anterior cingulate cortex after DBS at Contact 0. Regional cerebral blood flow increased in the dACC after DBS was turned on at contact 0 (MNI coordinates 10, 32, and 18; paired $t(4) = -3.438$, $p = 0.026$).

polar DBS at Contact 0 of the DBS electrode is associated with increased activity in the dACC (Fig. 2), which was correlated with reductions in depressive symptom severity (Fig. 4). Monopolar DBS at Contact 3 was associated with increased thalamus, striatum, and globus pallidus perfusion (Fig. 3).

Our study partially replicates and extends the findings by Rauch et al.¹⁷ We also found that DBS of the VC/VS increases perfusion across multiple regions in the cortico-striatal-thalamic-cortical circuit. However, we extended this initial work (which only explored the effects of DBS at ventral contacts) by showing that perfusion specifically

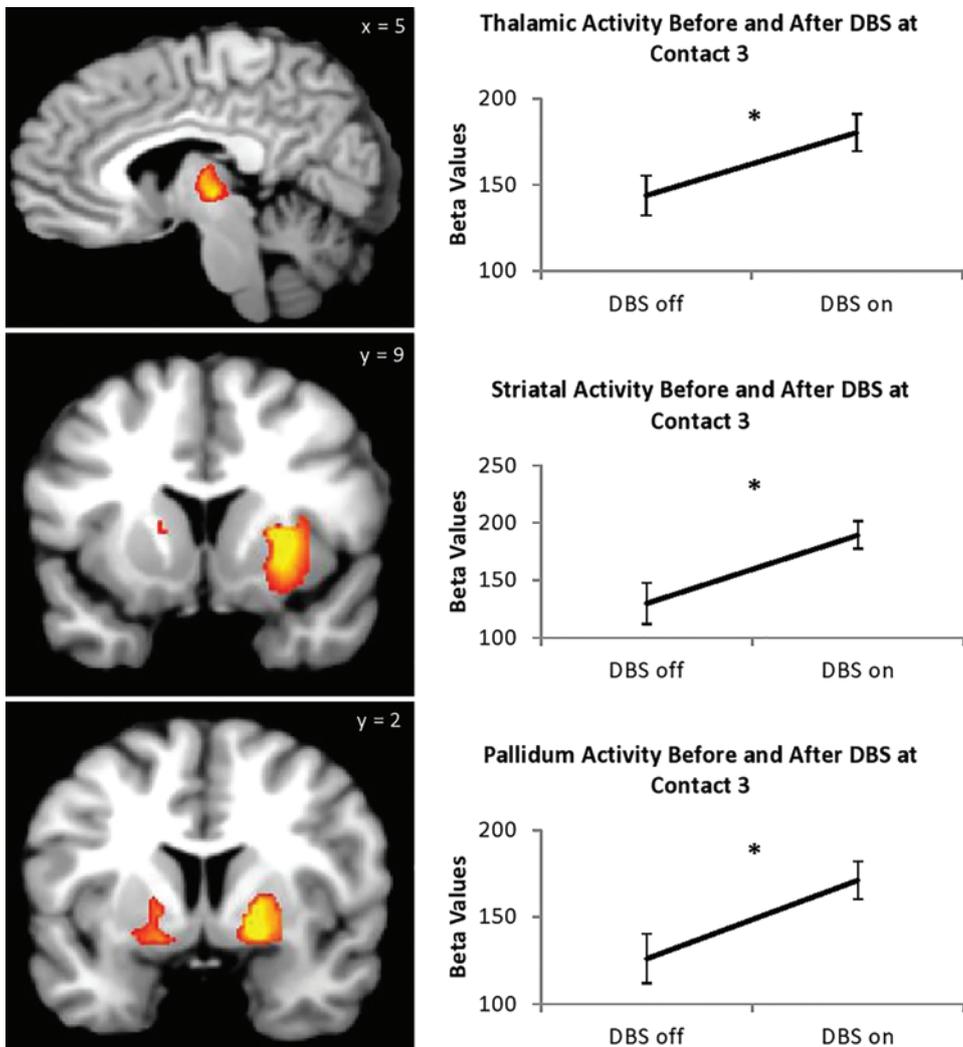


FIG. 3. Increased perfusion after DBS at Contact 3. Regional cerebral blood flow increased in the thalamus (MNI coordinates -2, -12, and 0; paired $t(5) = -2.679$; $p < 0.044$), striatum (MNI coordinates 24, 12, and 4; paired $t(5) = -3.684$; $p = 0.014$), and globus pallidus (MNI coordinates 16, 6, and 4; paired $t(5) = -4.070$; $p = 0.010$) after DBS was turned on at contact 3.

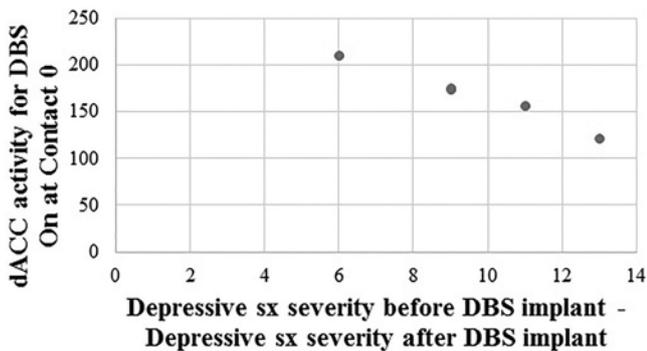


FIG. 4. Correlation between changes in depressive symptom severity and perfusion in the dACC after monopolar DBS at the most ventral contact. Increased dACC activity due to DBS being turned on at the most ventral contact (Contact 0) was significantly correlated with reductions in depressive symptom severity (Pearson's $r(5) = -0.994$; $p = 0.001$). Higher negative values indicate greater reductions in depressive symptom severity from baseline (before DBS implantation) to the time of the PET scan. sx = symptom.

in the dACC increased during monopolar DBS at the most ventral contact, whereas perfusion in the thalamus, striatum, and globus pallidus specifically increased when DBS was turned on at the most dorsal contact.

We did not replicate the finding of significantly increased perfusion in the frontal regions, such as the OFC and vmPFC, following DBS to the ventral contacts. rCBF in the vmPFC and OFC increased when DBS was bipolar between Contacts 0 (+) and 1 (-), rCBF increased in the vmPFC for monopolar DBS at Contact 0, and rCBF increased in the OFC for monopolar DBS at Contact 1. However, these findings were not statistically significant increases (all p values > 0.244). We further found that DBS at the dorsal contacts did not cause changes in frontal rCBF.

The initial treatment data suggest that stimulation at the 2 ventral contacts (Contacts 0 and 1) of the DBS electrode, which correspond to locations in the VS and VC, respectively, are associated with optimal behavioral responses. We found that DBS at ventral Contact 0 caused increased perfusion in the dACC, which was correlated with reductions in depressive symptom severity. We did not find significant correlations between changes in obsessive-compulsive symptom severity and significant DBS-related changes in our a priori regions. However, we did find that changes in obsessive symptom severity were positively correlated with increased (but not significant) perfusion in the thalamus (Pearson's $r(5) = 0.922$; $p < 0.05$) when bipolar DBS was turned on in the bipolar configuration between Contacts 0 (+) and 1 (-).

The present investigation was a cross-sectional study and not designed to assess chronic versus acute stimulation. However, anecdotally, patients have universally experienced the dramatic worsening of symptoms after the device has been turned off (e.g., battery depletions). This could suggest that stimulation has more acute rather than chronic effects. This study was also not designed to specifically investigate functional changes due to chronic stimulation at the patients' therapeutic settings (Table 1). Future imaging protocols that include the patients' active clinical settings would be valuable and important.

One limitation that should be noted is the small sample size. DBS studies with psychiatric patients are inherently small, and only a subset of individuals from the clinical trial on DBS at the VC/VS for OCD was interested in participating in this add-on imaging study. Therefore, these findings should be considered preliminary in nature.

Conclusions

We partially replicated previous findings that DBS of the VC/VS increases rCBF in the cortico-striatal-thalamic-cortical circuit. We further specified that different regions in the cortico-striatal-thalamic-cortical circuit showed increased perfusion based on whether the stimulation was more ventral or dorsal along the lead axis in the VC/VS. That is, DBS of the ventral contacts specifically increased perfusion in the dACC, whereas DBS of the dorsal contacts specifically increased perfusion in the thalamus, striatum, and globus pallidus. We found some initial evidence that DBS of the more ventral Contact 0 was associated with clinical changes in depressive symptom severity. Future work needs to be done to identify changes in brain activity that correspond more specifically to changes in obsessive-compulsive symptom severity.

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Disclosures

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Author Contributions

Conception and design: Dougherty, Cusin, Evans, Greenberg, Deckersbach. Acquisition of data: Dougherty, Chou, Cusin, Deckersbach. Analysis and interpretation of data: Dougherty, Chou, Corse, Arulpragasam, Widge, Evans, Greenberg, Deckersbach. Drafting the article: Dougherty, Chou, Greenberg. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Dougherty. Statistical analysis: Chou, Corse, Arulpragasam, Evans, Deckersbach. Administrative/technical/material support: Chou, Corse, Arulpragasam. Study supervision: Dougherty, Deckersbach.

Supplemental Information

Previous Presentations

Portions of this work were presented in poster form at the 70th annual scientific meeting of the Society of Biological Psychiatry, Toronto, Canada, on May 14, 2015.

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