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Title: Cerebral blood flow responses to dorsal and ventral STN DBS correlate with gait and balance responses in Parkinson disease

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Abstract

Objectives: The effects of subthalamic nucleus (STN) deep brain stimulation (DBS) on gait and balance vary and the underlying mechanisms remain unclear. DBS location may alter motor benefit due to anatomical heterogeneity in STN. The purposes of this study were to (1) compare effects of DBS of dorsal (D-STN) versus ventral (V-STN) regions on gait, balance and regional cerebral blood flow (rCBF) and (2) examine relationships between changes in rCBF and changes in gait and balance induced by D-STN or V-STN DBS. *Methods:* We used a validated atlas registration to locate and stimulate through electrode contacts in D-STN and V-STN regions of 37 people with Parkinson disease. In a within-subjects, double-blind and counterbalanced design controlled for DBS settings, we measured PET rCBF responses in *a priori* regions of interest and quantified gait and balance during DBS Off, unilateral D-STN DBS and unilateral V-STN DBS. *Results:* DBS of either site increased stride length without producing significant group-level changes in gait velocity, cadence or balance. Both sites increased rCBF in subcortical regions and produced variable changes in cortical and cerebellar regions. DBS-induced changes in gait velocity related to premotor cortex rCBF changes during V-STN DBS ($r = -0.40, p = 0.03$) and to rCBF changes in the cerebellum anterior lobe during D-STN DBS ($r = -0.43, p = 0.02$). *Conclusions:* DBS-induced changes in gait corresponded to rCBF responses in selected cortical and cerebellar regions. These relationships differed during D-STN versus V-STN DBS, suggesting DBS acts through distinct neuronal pathways dependent on DBS location.

Keywords: deep brain stimulation; gait; positron emission tomography; Parkinson disease; subthalamic nucleus

Introduction

Reductions in gait velocity and stride length characterize the postural instability and gait disturbances common in idiopathic Parkinson disease (PD) [Ferrandez and Blin 1991]. Deep brain stimulation of the subthalamic nucleus (STN DBS) improves gait and balance in some individuals with PD [Faist *et al.* 2001; Nilsson *et al.* 2009] yet its mechanisms of action remain unclear. Understanding the mechanisms underlying response variability may provide insights into the neural control of gait and balance and the functional anatomy of the STN.

One key factor contributing to response variability may be stimulation of different anatomic sites in the STN region. Investigations of STN circuitry in non-human primates reveal distinct regions with potentially disparate functions. The dorsolateral STN region connects to sensorimotor areas of the basal ganglia and to motor cortical areas while the ventral STN region connects to higher order cortical regions subserving cognitive functions [Parent and Hazrati 1995]; in vivo magnetic resonance imaging techniques may confirm this in humans [Lambert *et al.* 2012b]. Electrode contact location along the typical dorsolateral to ventromedial surgical implantation trajectory through the STN region may therefore influence the clinical effects of DBS. In support of this hypothesis, unilateral stimulation of the ventral STN region (V-STN DBS) impaired response inhibition performance in individuals with PD more than stimulation of the dorsal STN region (D-STN DBS) [Hershey *et al.* 2010]. On the other hand, the influence of contact location on gait and balance remains unclear: D-STN stimulation [Johnsen *et al.* 2010] or V-STN stimulation [Hilliard *et al.* 2011] may be optimal, or either location may be equally effective for improving gait and balance [McNeely *et al.* 2011].

Neuroimaging can identify pathways activated by DBS [Ballanger *et al.* 2009; Hershey *et al.* 2003; Perlmutter *et al.* 2002] and the responses in these pathways subsequently correlated with behavioral responses [Campbell *et al.* 2008; Karimi *et al.* 2008]. Stimulation of different STN regions

could activate distinct downstream cortical and cerebellar areas dependent upon different anatomic connections. Therefore, comparing regional cerebral blood flow (rCBF) responses during D-STN versus V-STN DBS and evaluating any relationships between rCBF and motor responses may provide further insights into the functional anatomy of the STN. These comparisons may help to determine which circuits subserve motor functions and to explain the variability of motor responses to STN DBS.

Thus the purposes of this study were to compare the effects of D-STN versus V-STN DBS on gait, balance and rCBF and then determine the relationships between motor performance and rCBF responses. To achieve these goals, we employed a validated process to locate [Videen *et al.* 2008] and selectively stimulate through electrode contacts in the D-STN and V-STN regions. In our within-subjects, double-blind and counterbalanced design controlled for stimulation variables (voltage, pulse width, frequency) we measured rCBF responses (PET imaging with ¹⁵O-labeled water), gait (GaitRITE Systems), and balance (Mini-BESTest) during each of three stimulation conditions: DBS Off, unilateral D-STN DBS, and unilateral V-STN DBS.

Methods

Participants

Thirty-seven participants with idiopathic PD and previous implantation of bilateral STN DBS electrodes (electrode model 3389, Medtronic Activa System; Medtronic Inc., Minneapolis, Minnesota, USA) were recruited to participate in a two-day protocol. All participants were diagnosed with PD based on established criteria [Hughes *et al.* 1992] and had undergone DBS surgery [Tabbal *et al.* 2007] at least three months prior to enrollment to allow adequate time for optimization of clinical stimulation settings, confirmation of response to DBS, and resolution of micro-subthalamotomy effects. Participants were selected based on our validated contact localization procedure [Videen *et al.* 2008] to ensure the

presence of electrode contacts within the D-STN and V-STN regions on the side of the brain contralateral to the more affected side of the body as determined by a Unified Parkinson Disease Rating Scale III (UPDRS-III) assessment in the off-medication and off-stimulation state. Additionally, participants were free of other neurological diseases, confounding medications, or injuries affecting gait or balance. All participants provided informed written consent and the study protocol was approved by the Human Research Protection Office (local internal review board) and the Radioactive Drug Research Committee of Washington University in St. Louis.

Experimental Design

Participants were evaluated on two separate days after overnight withdrawal (>8 hours) of antiparkinsonian medications. The first day included PET scans using ^{15}O -labeled water to measure qualitative rCBF while the participant was lying at rest with eyes closed and the second day included quantitative analyses of gait and balance. Evaluations on both days were completed in each of three stimulation conditions, performed in a double-blind manner with order counterbalanced across participants: off stimulation (OFF), unilateral D-STN DBS, and unilateral V-STN DBS. Unilateral stimulation was contralateral to the more affected side of the body as determined by a UPDRS-III assessment in the off-medication and off-stimulation state. All testing occurred at least 42 minutes after changes in stimulator settings to evaluate participants near the steady-state of most motor symptoms [Temperli *et al.* 2003;Sturman *et al.* 2008].

Contact Localization and Stimulator Settings

DBS electrode contacts were localized within the STN region using a previously validated method [Videen *et al.* 2008]. In brief, anatomic fiducials near the STN region were identified on pre-surgical MR scans and the DBS electrode tip and four contacts were located on post-surgical CT scans. After co-registering the MR and CT scan, the anatomic fiducials were used to transform both images into

Mai atlas space [Mai *et al.* 2004] where the STN was identified and visualized with respect to the contact locations.

To distinguish the effects of stimulation in the D-STN and V-STN regions, we used similar stimulation settings at both sites across all participants: monopolar electrode configuration, 185 Hz frequency, 2.5V amplitude, 60 μ s pulse width. These settings provide measurable motor benefits while minimizing current spread to adjacent anatomical regions [Butson and McIntyre 2005; Butson and McIntyre 2006], minimizing adverse side effects and reducing possible overlap in current spread from the two stimulation sites [Hershey *et al.* 2010]. Unilateral stimulation eliminated the confound of non-symmetric electrode placement within the STN region.

Neuroimaging

Up to four PET scans were acquired in each stimulation condition using [^{15}O]-water as described [Karimi *et al.* 2008]. Real-time monitoring, surface electrodes, and videotapes were used [Karimi *et al.* 2008] to exclude scans with substantial movement or muscle activity from future analysis and thus control for movement confounds [Hershey and Mink 2006].

Emission data from the 40-second interval beginning with initial [^{15}O]-water uptake in the brain were reconstructed [Karimi *et al.* 2008] and smoothed using a 3D Gaussian filter to a resolution of 12mm full width at half maximum in all three dimensions. Each smoothed emission image was co-registered to the initial emission image, resliced to create an image in Talairach space, and globally normalized to a standard mean PET counts of 1000 [Talairach and Tournoux 1988; Woods *et al.* 1992].

After removing scans during which participants displayed visible movement or sustained EMG activity above baseline, the remaining 1-4 emission scans for each stimulation condition were globally normalized then averaged to create a mean condition image for each participant in each stimulation

condition. At least one scan was required in each stimulation condition for inclusion of a participant in further analyses.

Regions of Interest

Qualitative cerebral blood flow responses to DBS were examined in seven *a priori* regions of interest (ROIs) (Table I) chosen based on known effects of STN DBS on cerebral blood flow [Hershey *et al.* 2003], basal ganglia circuitry and the neural control of gait. The three subcortical ROIs (STN region, internal segment of the globus pallidus [GPi] and thalamus) were used to confirm that the stimulation paradigm produced quantifiable changes in rCBF while the two cortical regions (premotor cortex and supplementary motor area [SMA]) and two cerebellar regions (cerebellum anterior lobe hemispheres [CB_{AH}] and vermis [CB_{AV}]) were used to evaluate relationships between changes in rCBF, gait and balance. The thalamus was defined by an anatomic mask; all other ROIs were defined by spheres placed based on coordinates previously identified as peaks of DBS-induced rCBF changes (STN, GPi, SMA, CB_{AH}, and CB_{AV} from Hershey *et al.* 2003; premotor cortex from Karimi *et al.* 2008) (Table I).

Based on our hypothesis that gait and balance changes would relate to bilateral cortical and cerebellar rCBF changes, we did not differentiate responses ipsilateral and contralateral to the side of stimulation but instead averaged rCBF changes across sides in the five bilateral ROIs. This approach is supported by previous evidence of bilateral rCBF effects of unilateral stimulation [Tanei *et al.* 2009; Arai *et al.* 2008], and we compared the ipsilateral and contralateral rCBF changes to confirm that bilateral averaging did not mask effects of unilateral stimulation.

Motor Function Evaluations

Evaluation of motor function during each stimulation condition included (1) administration of the UPDRS-III by a validated rater, (2) gait analysis using a 4.8m GAITRite walkway (CIR Systems, Sparta, NJ, USA) and (3) balance analysis using the Mini-Balance Evaluation Systems Test (Mini-BESTest).

Participants walked across the GAITRite walkway three times at their preferred pace; gait velocity, stride length and cadence were measured. The Mini-BESTest is a 14-item clinical test of dynamic balance that rates patients on common tasks such as standing on one leg and rising from a chair; scores were reported out of 32 possible points [Franchignoni *et al.* 2010].

Statistical Analyses

To assess the effects of the two unilateral stimulation conditions, pairwise comparisons for D-STN vs OFF and also V-STN DBS vs OFF were conducted for each rCBF, gait and balance variable. To determine whether the effects of stimulation differed by contact location, an additional pairwise comparison was conducted for each dependent variable, comparing changes induced by D-STN DBS (i.e., D-STN – OFF) to those induced V-STN DBS. In all cases, paired samples t-tests were used for gait and rCBF data, Wilcoxon Signed Rank Tests were used for the non-parametric UPDRS-III and Mini-BESTest scores, and a Bonferroni correction was applied to correct for evaluation of multiple (4) ROIs or multiple (2) motor measures. For all analyses, statistical significance was assessed as $p_{corrected} < 0.05$ and trend level was defined as $p < 0.05$ before correction.

To assess the relationships between stimulation-induced changes in rCBF and changes in gait and balance, the percent change in rCBF induced by D-STN or V-STN DBS relative to OFF (e.g., $100 * (D-STN - OFF) / OFF$) was correlated with the corresponding percent change in gait velocity and with the difference in Mini-BESTest relative to OFF (e.g., D-STN – OFF). We used Spearman's rho and raw score differences for the Mini-BESTest analyses to avoid exaggerating the effect size of small changes in balance measured by the 32 point ordinal scale. These planned correlations were assessed with a Bonferroni correction for evaluation of multiple (4) ROIs posited to relate to gait and balance to control for possible Type I errors. For any region in which stimulation-induced rCBF changes correlated at least

at trend level ($p_{uncorrected} < 0.05$) with stimulation-induced gait velocity changes, the rCBF relationships with changes in cadence and stride length were also evaluated.

Results

Seven of the 37 participants were excluded from analyses due to visible tremor or excessive EMG activity during all PET scans in one or more stimulation condition. Demographic and clinical features of the 30 participants analyzed are listed in Table II. The seven participants excluded due to movement had similar characteristics [mean (SD): age 59.9(6.3), disease duration 12.1(6.5), months since DBS surgery 20.4(20.3), off-state UPDRS-III score 33.1(13.1)]. During preliminary evaluations of the standardized stimulation settings, eight participants experienced untoward effects including contralateral paresthesias and jaw, arm and leg dystonias. These effects occurred most often during testing of the V-STN contact and were resolved with reduction of voltages of both the D-STN and V-STN contacts to 2.3V (2 participants), 2.2V (1 participant), 2.1V (1 participant), and 1.8V (4 participants) for the duration of the study. Figure 1 shows the D-STN and V-STN DBS contact locations and estimated spheres of current spread for these 30 participants. All but four individuals had at least one contact between the stimulated dorsal and ventral contacts and the anatomic separation between dorsal and ventral contact coordinates was statistically significant in the three principle directions (paired t -tests, all $t(29) > 13.9$, all $p < 0.001$).

Validation of stimulation paradigm

We confirmed that unilateral stimulation at the selected contacts and settings affected motor performance and rCBF in subcortical regions near the stimulation site. Indeed, UPDRS-III scores improved with both D-STN DBS (Wilcoxon signed rank test, $Z = -4.01$, $p < 0.001$) and V-STN DBS ($Z = -4.27$, $p < 0.001$) compared to OFF (Figure 2A) and blood flow in several subcortical ROIs showed significant changes with stimulation: V-STN DBS increased rCBF relative to OFF in the STN region (paired

t -test, $t(29) = 3.86$, $p = 0.001$), GPi ($t(29) = 3.75$, $p = 0.001$), and thalamus ($t(29) = 2.38$, $p = 0.024$); D-STN DBS increased rCBF relative to OFF in the STN region ($t(29) = 2.40$, $p = 0.023$), GPi ($t(29) = 2.91$, $p = 0.007$) but not in the thalamus ($t(29) = 1.90$, $p = 0.068$) (Figure 2B).

To confirm that the decision to average bilateral rCBF responses did not mask unilateral effects, we compared rCBF responses ipsilateral and contralateral to the stimulation site in each of the bilaterally defined ROIs. The lateralized responses were not consistently different in the bilaterally defined ROIs (paired t -tests, all $p > 0.09$ except for the thalamus rCBF response to D-STN DBS in which case the ipsilateral response was larger [$p = 0.01$] than the contralateral response).

Effect of stimulation relative to OFF

Motor Effects. After Bonferroni correction for evaluation of multiple (2) motor behaviors, the Mini-BESTest did not show significant improvements with either V-STN (Wilcoxon signed rank test, $Z = -2.22$, $p_{corrected} = 0.052$) or D-STN DBS ($Z = -1.82$, $p_{corrected} = 0.138$) (Figure 2A). Notably, the small differences in median Mini-BESTest score between conditions were due to a large variability in response across participants (Table III) with changes ranging from -5 to +7 during D-STN DBS and from -5 to +9 during V-STN DBS. Similarly, after correction there were no significant improvements in gait velocity with either D-STN DBS (paired t -test, $t(29) = 2.32$, $p_{corrected} = 0.054$) or V-STN DBS ($t(29) = 1.25$, $p_{corrected} = 0.44$). Since STN DBS is reported to preferentially affect stride length over cadence we secondarily evaluated the effects of stimulation on these two variables. Stimulation of either STN region increased stride length (D-STN DBS: $t(29) = 3.31$, $p = 0.002$; V-STN DBS: $t(29) = 2.37$, $p = 0.025$) but neither stimulation condition produced a significant effect on cadence (D-STN DBS: $t(29) = -0.014$, $p = 0.99$; V-STN DBS: $t(29) = -1.01$, $p = 0.32$) (Figure 2A). To determine whether the effects of DBS on gait were more marked in individuals with worse OFF-state performance, we ranked patients by OFF-state gait velocity and evaluated those patients below the median. Among this subset ($n=15$), both D-STN (paired

t -test, $t(14) = 4.64$, $p_{corrected} < 0.002$) and V-STN DBS ($t(14) = 2.30$, $p_{corrected} = 0.08$) influenced gait velocity more strongly than they did for the entire group.

Regional Cerebral Blood Flow Effects. None of the cortical or cerebellar ROIs had rCBF response levels significantly different from OFF after correction for multiple (4) ROIs although V-STN DBS tended to decrease CB_{AH} rCBF relative to OFF (paired t -test, $t(29) = -2.47$, $p_{uncorrected} = 0.02$). Overall, rCBF in deep brain structures increased with stimulation whereas rCBF in the cortical and cerebellar regions showed more variability in the response direction (Figure 2B).

Comparison of the effects of dorsal and ventral STN DBS

The DBS-induced changes in UPDRS-III, Mini-BESTest, gait velocity, stride length and cadence performance did not vary based on stimulation location (Wilcoxon signed rank tests for scores, all $Z < -0.34$, $p_{uncorrected} > 0.74$; paired t -test for gait, all $t(29) < 1.4$, $p_{uncorrected} > 0.18$) (Figure 2A). After Bonferroni correction, none of the ROIs investigated had significantly different rCBF responses with D-STN compared to V-STN DBS. However V-STN DBS tended to increase rCBF responses in the premotor cortex ($t = -2.20$, $p_{uncorrected} = 0.036$) region more than D-STN DBS did relative to OFF (Figure 2B).

Correlation analyses of rCBF with gait and balance

Blood flow changes in the premotor cortex induced by V-STN DBS negatively correlated with the V-STN DBS-induced changes in gait velocity ($r = -0.40$, $p_{uncorrected} = 0.03$) (Figure 3A). This relationship with changes in gait velocity was driven primarily by a negative correlation with changes in cadence ($r = -0.42$, $p_{uncorrected} = 0.02$) (Figure 3B) but not with changes in stride length ($r = -0.30$, $p_{uncorrected} = 0.11$). Blood flow changes in CB_{AH} induced by D-STN DBS negatively correlated with the D-STN DBS-induced changes in gait velocity ($r = -0.43$, $p_{uncorrected} = 0.02$) (Figure 3C). This relationship was driven by a negative correlation with cadence ($r = -0.40$, $p = 0.03$) (Figure 3D) but not significantly by stride length ($r = -0.32$, $p = 0.08$). The correlations between DBS-induced changes in rCBF and DBS-induced changes in

gait velocity did not retain statistical significance after Bonferroni correction for evaluation of multiple (4) ROIs (adjusted alpha level = 0.013), and no other relationships were found between rCBF responses in the *a priori* ROIs and changes in gait or Mini-BESTest scores (Table IV).

To determine whether the observed relationships between DBS-induced blood flow responses and gait velocity responses persisted when controlled for age, time since DBS surgery or PD duration, we evaluated partial correlations controlled for each factor. The influence of each factor was evaluated separately due to the limitations of sample size ($n=30$). The D-STN DBS-induced relationship between CB_{AH} rCBF changes and gait velocity changes and the V-STN DBS-induced relationship between premotor rCBF changes and gait velocity changes both retained trend level significance ($p_{uncorrected} < 0.05$) when controlled for age (D-STN: $r = -0.44$, $p_{uncorrected} = 0.02$; V-STN: $r = -0.40$, $p_{uncorrected} = 0.03$) or PD duration (D-STN: $r = -0.39$, $p_{uncorrected} = 0.04$; V-STN: $r = -0.37$, $p_{uncorrected} = 0.046$). The D-STN DBS-induced relationship lost this statistical significance when controlled for time since surgery ($r = -0.35$, $p_{uncorrected} = 0.06$) but the V-STN DBS-induced relationship persisted ($r = -0.42$, $p_{uncorrected} = 0.03$).

Discussion

D-STN and V-STN do not differentially affect gait or balance, and are only minimally different in their effects on selected regions of blood flow. However, the influence of STN DBS on gait may be mediated by different circuits depending on the site of STN region stimulation. Specifically, V-STN DBS induced changes in gait velocity correlated with changes in rCBF in the premotor cortex whereas D-STN DBS induced changes in gait velocity correlated with changes in rCBF in CB_{AH} . In both cases, stimulation-induced decreases in rCBF were associated with improvements in gait velocity.

In agreement with several previous studies [Faist *et al.* 2001; Johnsen *et al.* 2009], we found that STN stimulation improved gait velocity primarily by increasing stride length while its influence on

cadence was variable. In our study, these gait responses were similar during D-STN and V-STN DBS, supporting previous findings that location of active electrode contact in the STN region did not influence gait responses [McNeely *et al.* 2011]. Others report that D-STN and V-STN DBS have different effects on gait [Johnsen *et al.* 2011]. Our study differs from those reporting differential effects of D-STN and V-STN DBS in that: our comparisons were done within-subjects and a time delay between stimulation settings allowed participants to approach a steady-state before evaluation; uniform stimulation variables, selected to minimize overlap between the volumes of tissue activated by each stimulation site, were used for all participants; the localization process did not employ anatomical tracing of the STN on pre-operative MRI or contact localization on post-operative MRI. By eliminating several confounding variables, these features thus improved our chances of isolating the effects of stimulation and recognizing a difference between the effects of D-STN and V-STN DBS on gait and balance if such a difference exists.

The relatively large between-subjects variability of gait responses to DBS enhanced our ability to detect a correlation between changes in gait velocity and DBS-induced changes in cortical and cerebellar blood flow. Controlling for age, disease duration, and time since DBS surgery did not explain these relationships. The relationships between gait velocity changes and rCBF changes in cortical and cerebellar regions support the notion that DBS mediates motor effects through basal ganglia-thalamo-cortical and cerebello-thalamo-cortical circuits [McIntyre and Hahn 2010; Doya 2000] but do not exclude the possibility that the DBS-induced relationships are mediated by pathways other than the parallel loops described by traditional models. For example, recent studies using viral tracers demonstrate an anatomic substrate for two-way communication between the basal ganglia and the cerebellar cortex [Bostan *et al.* 2010]. Similarly, a recent resting state functional connectivity study demonstrates strong functional but not necessarily direct anatomical connectivity between striatum and an extended brainstem region that includes thalamus, midbrain, pons and cerebellum [Hacker *et al.* 2012].

Alternatively, other pathways could mediate the observed DBS-induced rCBF and motor changes rather than or in addition to the traditional model of cortically-linked basal ganglia and cerebellar loops.

Neither D-STN nor V-STN DBS at the selected settings produced a consistent directional effect on rCBF in the cortical or cerebellar regions examined. However, patients whose rCBF decreased in the CB_{AH} during D-STN DBS or in the premotor cortex during V-STN DBS tended to demonstrate the greatest stimulation-induced improvements in gait velocity. While the rCBF changes in cortical and cerebellar regions likely reflect activity changes of distant input neurons through some of the networks discussed above, these changes also could be driven by changes in local interneuronal activity [Hershey and Mink 2006]. Therefore, the association of decreases in rCBF with gait improvements may suggest that larger reductions in interneuronal activity relate to improvements in gait function.

Our findings of distinct relationships between rCBF and gait responses to D-STN versus V-STN DBS suggest that while producing similar changes in motor function, the neuronal pathways by which DBS exerts these influences may vary with stimulation location. These findings are consistent with non-human primate data showing motor cortex projections to the dorsal STN region and premotor cortex projections to the ventromedial STN [Parent and Hazrati1995]. Notably, implanted electrode trajectory results in contact positions that differ not only in the dorsal-ventral dimension under investigation, but also in the anterior-posterior dimension; controlled sampling across all dimensions of the STN would be necessary for more detailed functional mapping. A recent study using diffusion-weighted imaging to evaluate STN connectivity in 12 healthy adults demonstrated in-vivo the presence of three sub-regions within the human STN distinguished by cortical and subcortical connections [Lambert *et al.* 2012a]. Although the specific delineations of the STN sub-regions in these studies are not directly comparable, the non-human primate anatomy, combined with the evidence of in-vivo segregation in humans,

supports our finding that V-STN but not D-STN DBS induced a strong relationship between changes in premotor cortex rCBF and changes in gait.

In this study, motor changes during D-STN DBS did not correlate with changes in SMA or premotor cortex rCBF, but rather these changes correlated to rCBF changes in CB_{AH}. As our analyses were limited to *a priori* regions of interest, we cannot exclude involvement of other brain regions or circuits. Whole-brain analyses of rCBF changes may be useful for identifying additional regions involved but will require more participants given the reduced magnitude of stimulation voltage that we chose to help distinguish effects of D-STN and V-STN DBS. Anatomic connections between STN and CB_{AH} that may occur via pedunculo-pontine nucleus [Bostan and Strick 2010] may mediate the relationship between gait changes and CB_{AH} rCBF changes during D-STN DBS. Alternatively, this relationship may reflect stimulation of cerebellothalamic fibers passing by the STN [Gallay *et al.* 2008] or functional brain networks involved in motor control, altered in Parkinson disease, and potentially affected by deep brain stimulation [Hacker *et al.* 2012; Wu *et al.* 2009; Poston and Eidelberg 2011; McIntyre and Hahn 2010]. One resting-state functional connectivity study demonstrated topographically organized functional coupling between the cerebellum and specific cortical areas including the premotor, somatomotor, and association cortices [Buckner *et al.* 2011]. The CB_{AH} region we investigated may be functionally coupled with a specific cortical region in a basal ganglia-thalamo-cortical circuit influenced preferentially during D-STN DBS compared to V-STN DBS. Such functional coupling could explain the observed stimulation-location dependency of the relationship between DBS-induced changes in CB_{AH} rCBF and gait changes. Future resting-state fMRI studies may test this hypothesis by investigating resting-state networks from CB_{AH} and premotor cortex.

Our finding of rCBF-gait relationships dependent on stimulation location also provides insight into the neural control of gait. Stimulation of different STN regions and consequent activation of distinct

circuits produces similar changes in gait but may do so by disparate mechanisms. As gait involves integration and coordination of input from multiple sensory systems including the visual, vestibular, and somatosensory systems, DBS could influence gait by altering any of these systems. Indeed, several studies have noted the influence of DBS on behaviors such as eye movements [Fawcett *et al.* 2010; Lohnes and Earhart 2012] and posture regulation [Guehl *et al.* 2006]. The relevant functional organization of STN remains unknown, but DBS-induced gait changes may be mediated by modification of motor and cognitive behaviors that could be differentially influenced by stimulation location. Thus, the optimal DBS target for improving gait may be less regionally specific than for cognitive functions such as response inhibition [Hershey *et al.* 2010]. An alternative interpretation is that the relationship between cerebellar responses and gait changes represents compensation for dysfunction in the basal ganglia system. Finally, during stimulation at clinically-optimized settings (which typically have voltages higher than our study settings) DBS may spread farther and have greater effects on nearby fiber tracts including the zona incerta, Fields of Forel, and internal capsule [Kuncel and Grill 2004].

An important caveat of this study is that stimulation was provided unilaterally at settings distinct from those optimized for clinical effectiveness. The results of this study were not intended to directly suggest changes in practical patient management but rather, the selected settings permitted us to differentially stimulate the dorsal versus ventral STN regions while avoiding the potential confound of non-symmetric lead placement and overlapping current spheres. Our decision to evaluate axial motor symptoms during unilateral stimulation is supported by previous studies demonstrating axial effects from unilateral stimulation [Germano *et al.* 2004; Kelly *et al.* 2010] and similar effects on gait but with a smaller magnitude compared to bilateral stimulation [Bastian *et al.* 2003]. Indeed the effects on gait in this study were more modest than those reported in response to clinically optimized DBS [Bastian *et al.* 2003]. The influence of unilateral STN DBS on rCBF is not as well established, but accumulating evidence indicates that unilateral DBS produces bilateral rCBF responses [Tanei *et al.* 2009; Arai *et al.* 2008].

Bilateral connections of basal ganglia nuclei shown by anatomic studies [Marani *et al.* 2008;Parent and Hazrati1995] likely account for the observed contralateral effects. Functional connectivity studies [Palmer *et al.* 2010] and electrophysiological recordings from contralateral STN during unilateral STN DBS in rats [Shi *et al.* 2006] and humans [Liu *et al.* 2002;Walker *et al.* 2011] further support this notion.

We demonstrated that DBS-induced bilateral rCBF changes in selected cortical and cerebellar regions correlate with changes in motor behaviors and that these relationships are dependent on stimulation location. We observed no consistent difference between DBS-induced rCBF changes ipsilateral and contralateral to stimulation thereby adding to the growing body of evidence of bilateral connections of basal ganglia nuclei. Additional studies examining the effects of unilateral versus bilateral stimulation on cerebral activity and further evaluating functional organization of the STN are warranted.

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Figure Captions

Figure 1. Distribution of dorsal (green) and ventral (purple) contacts in the STN region (red outline) for the sample (N=30). A 2mm radius sphere is centered on each study contact. Contacts on left side of the brain are flipped across x-axis for display. Color gradient denotes number of contacts within 2mm of each voxel.

Figure 2. Average change (\pm SEM) in motor function (A) and regional cerebral blood flow (rCBF) (B) during stimulation of dorsal (D-STN) and ventral (V-STN) subthalamic nucleus regions measured relative to no stimulation (OFF). UPDRS-III and Mini-BESTest evaluations are shown as score changes; gait and rCBF measures are shown as percent changes. N=30 except for Mini-BESTest as two individuals did not complete this evaluation. STN, subthalamic nucleus; GPi, internal segment of the globus pallidus; CB_{AH}, hemispheres of the anterior lobe of the cerebellum; CB_{AV}, vermis of the anterior lobe of the cerebellum; SMA, supplementary motor area. * Measure during STN DBS is significantly different from OFF after Bonferroni corrections described in text. Note: Removal of statistical outliers beyond 3 standard deviations from the mean does not eliminate statistical significance of any comparisons.

Figure 3. DBS induced changes in gait related to changes in regional cerebral blood flow (rCBF). Stimulation of the ventral STN region (V-STN) induced changes in premotor cortex rCBF negatively correlated with gait velocity (A), specifically cadence (B). Stimulation of the dorsal STN region (D-STN) induced changes in rCBF in the hemispheres of the anterior lobe of the cerebellum (CB_{AH}) negatively correlated with changes in forward walking velocity (C) and more specifically, cadence (D). Statistical outliers beyond three standard deviations from the mean are marked with asterisks. Removal of these data eliminates the correlation in Figure D ($r = -0.09$, $p = 0.66$) but does not significantly change relationships in A, B, or C.

Figure 1

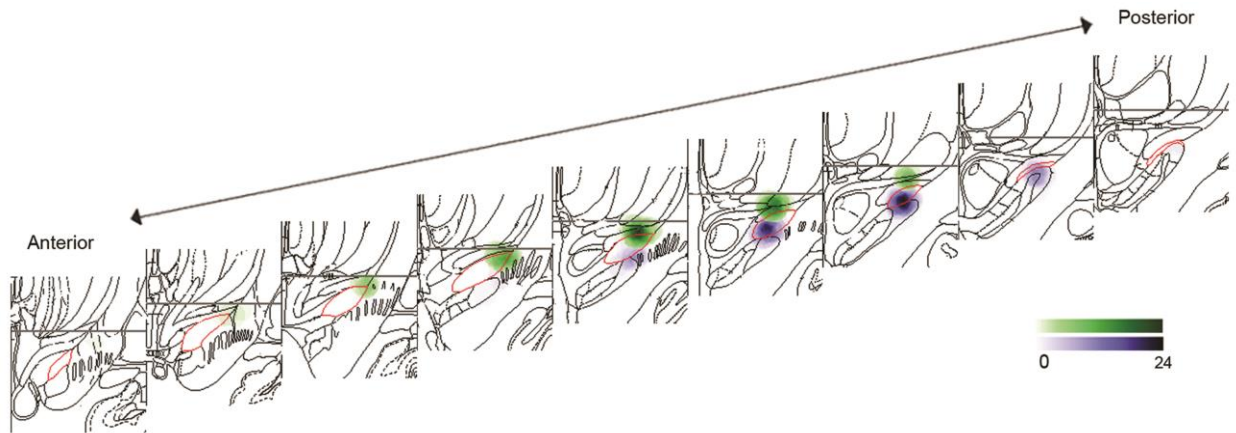


Figure 2

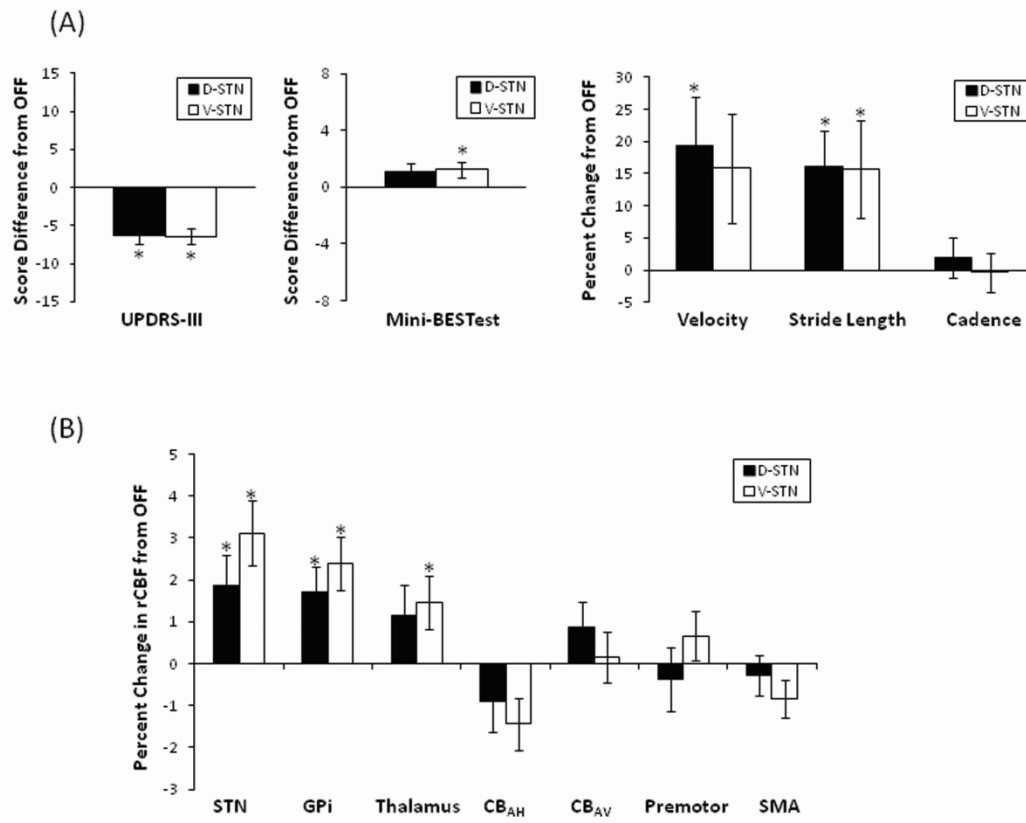


Figure 3

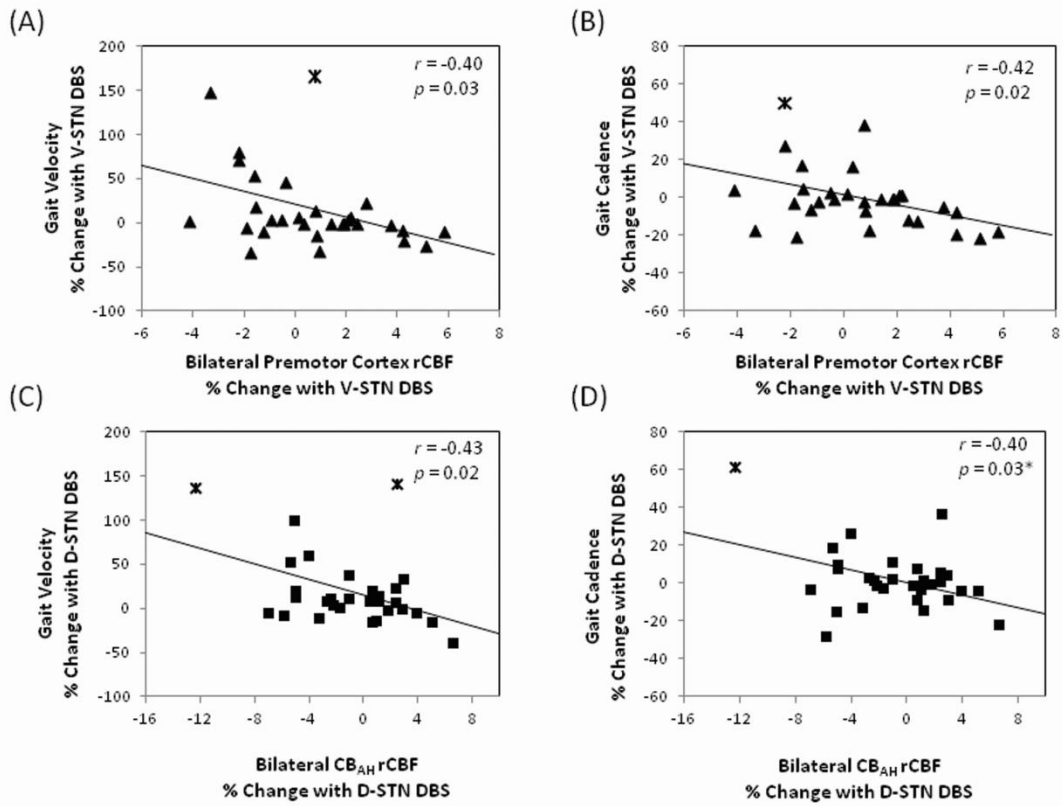


Table I Radius and Talairach Coordinates of Spherical Regions of Interest

	radius (mm)	x	y	z
Premotor cortex	5	-43 (L), +45 (R)	3	42
Supplementary motor area (SMA)	6	0	-16	50
Cerebellum – anterior lobe, hemispheres (CB _{AH})	5	±14	-38	-16
Cerebellum – anterior lobe, vermis (CB _{AV})	5	0	-60	-8
Subthalamic nucleus (STN)	5	±11	-14	-4
Internal segment of globus pallidus (GPi)	5	±16	-6	-1
Thalamus	(bilateral thalami defined by an anatomic mask)			

Table II Participant Demographics and Stimulation Characteristics

	Mean (SD)
Demographics	
Gender	19 male, 11 female
Age (years)	64.0 (7.7)
Disease duration (years)	14.3 (5.6)
Time since DBS surgery (months)	22.4 (20.8)
UPDRS-III score (off medication, off DBS)	35.5 (10.5)
Clinically optimized stimulator settings	
Voltage (V)	2.8 (0.7)
Pulse width (μ s)	62.1 (7.7)
Frequency (Hz)	185 (0.0)
Study stimulation characteristics	
Side of stimulation	14 left, 16 right
Subjects with clinical contact as study contact	9 dorsal, 8 ventral
Voltage (V)	2.4 (0.2)
Pulse Width (μ s)	60 (0.0)
Frequency (Hz)	185 (0.0)
Dorsal x (absolute value)	12.7 (1.0)
Dorsal y	-17.6 (1.5)
Dorsal z	-1.6 (0.7)
Ventral x (absolute value)	11.8 (1.0)
Ventral y	-19.5 (1.3)
Ventral z	-5.3 (0.8)

Note. Clinically optimized settings are reported for the clinical contact on same side of brain as study stimulation. Average x, y and z position of the study contacts are reported in Mai atlas coordinates.

Table III Variability of Motor Responses to Dorsal and Ventral STN DBS

	D-STN DBS vs OFF		V-STN DBS vs OFF	
	Mean Percent Change	Number (Percent) of Patients Improved	Mean percent Change	Number (Percent) of Patients Improved
UPDRS-III ^a	-6.5	25 (83%)	-6.5	24 (80%)
Mini-BESTest ^a	0.5	14 (50%)	1	16 (57%)
Gait velocity	19	19 (63%)	16	15 (50%)
Gait stride length	16	22 (73%)	16	17 (57%)
Gait cadence	2	15 (50%)	0	11 (37%)

Note. Improvements are defined as negative changes in UPDRS score and by positive changes in all other variables.

^aMedian change in score is reported instead of mean percent change

Table IV Correlation coefficients (uncorrected significance level) of all investigated correlations between DBS-induced motor responses and rCBF responses in *a priori* regions of interest.

	Premotor	SMA	CB _{AH}	CB _{AV}
Correlations between D-STN DBS-induced motor and rCBF responses				
Gait velocity	$r = -0.27$ ($p = 0.15$)	$r = 0.15$ ($p = 0.45$)	$r = -0.43$ ($p = 0.02$)	$r = 0.28$ ($p = 0.88$)
Mini-BESTest	$r_s = -0.23$ ($p = 0.23$)	$r_s = 0.21$ ($p = 0.28$)	$r_s = 0.11$ ($p = 0.56$)	$r_s = 0.11$ ($p = 0.56$)
Correlations between V-STN DBS-induced motor and rCBF responses				
Gait velocity	$r = -0.40$ ($p = 0.03$)	$r = -0.03$ ($p = 0.89$)	$r = 0.10$ ($p = 0.60$)	$r = 0.05$ ($p = 0.81$)
Mini-BESTest	$r_s = -0.15$ ($p = 0.43$)	$r_s = 0.12$ ($p = 0.55$)	$r_s = 0.12$ ($p = 0.55$)	$r_s = 0.20$ ($p = 0.32$)

Note. Correlations with $p < 0.05$ are in bold; no correlations are significant after Bonferroni correction for evaluation of multiple (4) *a priori* regions of interest (adjusted alpha level of 0.013).