# Mapping Movement, Mood, Motivation, and Mentation in the Subthalamic Nucleus

Running Title: Dorsal vs. ventral effects of STN DBS

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## Abstract

The motor and non-motor response to deep brain stimulation of the subthalamic nucleus (STN DBS) varies significantly among people with Parkinson disease (PD). One common hypothesis about what underlies this variability is that the precise anatomical location of STN DBS may determine the degree or type of response. Our previous study tested that hypothesis by treating location as a three-dimensional (3D) variable, based on the acute effect of unilateral DBS at the clinically optimized DBS settings and active contact of each participant. Here, in a new data set, we investigated whether the 3D location of stimulation in ventral and dorsal STN significantly affected motor and non-motor responses, with standardized DBS parameters. In 74 individuals with PD and STN DBS, 44-84 years old, contacts were selected, blind to clinical response, near the dorsal and ventral border of the STN contralateral to the more affected side of the body. Participants were tested after PD medications were withdrawn for > 8 hours in each of 3 conditions (ventral STN DBS, dorsal STN DBS and DBS off) for acute effects on mood, working memory, response inhibition and motor function. Voltage, frequency, and pulse width were standardized across DBS conditions and individuals, and participants and raters were blind to condition. In a categorical analysis, both dorsal and ventral STN DBS improved mean motor function and had no cognitive effects, with dorsal STN DBS inducing greater improvement in rigidity than ventral STN DBS; there were some mood effects with ventral STN DBS inducing greater improvement in anxiety and mood than dorsal STN DBS. In the 3D analysis, contact location was significant for bradykinesia and resting tremor, with greatest improvement occurring with dorsal STN and zona incerta DBS. These results provide new, direct functional evidence for the anatomically-derived model of STN using the novel 3D analysis, in which motor function is most represented in dorsal STN. However, our data suggest that any functional segregation between motor and non-motor areas of the STN is limited, since locations that induce improvements in motor and mood function overlapped substantially.

## Introduction

Parkinson disease (PD) is the second most common neurodegenerative disease, and varies in its presentation, with symptoms including motor impairment (*e.g.* bradykinesia, rigidity or tremor), disturbed sleep, depressive symptoms, and cognitive complications.[1,2] Deep brain stimulation of the subthalamic nucleus (STN DBS) can improve many of the motor symptoms,[3] but changes in mood, motivation and cognition also occur and may be either beneficial or detrimental to the patient. [4] In fact, clinical results vary substantially among patients. Some evidence suggests that the location of stimulation within or around the STN may contribute to the motor, mood, and cognitive effects of STN-DBS, given its relatively segregated anatomical connections to motor, somatosensory, and limbic neural circuits. [5] However, the methods used to test this hypothesis in the past have had limitations including not examining the entire relevant volume of the brain[6,7,8], not determining the statistical significance of relationships between behavior and DBS site[9,10,11,12], or not correcting for Type 1 errors due to the multiple comparisons inherent in 3D statistical maps with many data points (i.e. voxels)[13]. Some studies examined the effects of DBS on neuronal response with reference to the volume of tissue predicted to be activated based on electrical field models.[14] Our previously published method combines the anatomical location of the stimulated electrode with clinical data to produce statistical images that demonstrate DBS locations associated with improvement and worsening of each measured symptom. Statistical significance is determined from these images using a permutation approach. [15] This method avoids the above-mentioned issues and identifies whether location relates to clinical response in a statistically rigorous manner controlled for multiple comparisons.[16]

Using this method, we previously examined the acute effects of unilateral STN DBS in PD, using each person's clinically optimized stimulation parameters. Mood, cognition and motor function were assessed with DBS OFF and ON at least 8 hours after the most recent PD-related medications. The 3D analyses suggested that location of stimulation was significantly associated with mood, cognition, and some motor outcomes. [15] Most motor measures improved with DBS everywhere in the STN, while a few motor, cognitive, and mood measures differed depending on the location of stimulation. An important weakness of this study was that stimulation parameters (e.g. voltage) differed across individuals, which could differentially impact behavior. Additionally, the contact and stimulation parameters used were determined through the clinical

programming process. Thus, the results cannot distinguish whether all participants would have had similar motor benefit with DBS anywhere in the STN, or whether the ideal DBS location simply varied by participant. Therefore, in this new study, all PD participants had separate, blinded, unilateral stimulation conditions at both dorsal *and* ventral STN locations, chosen by brain imaging blind to clinical results. All stimulation parameters were maintained across condition and participant. We hypothesized that our findings would be qualitatively similar to those in our previous report, but that effects might be more striking due to the consistent stimulation parameters and the wider range of contact locations used.

# Materials and methods

## Participants

Seventy-four PD patients were recruited through the Movement Disorders Center at Washington University St. Louis School of Medicine (WUSM). Inclusion criteria included bilateral STN DBS therapy for clinically definite PD, as previously defined[17] based on established criteria.[18,19] Patients waited at least 3 months after DBS implantation to participate in the study. Exclusion criteria included neurological conditions such as: history of stroke; history of serious head injury (any neurologic sequelae, open skull fracture or hospitalization); history of definite encephalitis or oculogyric crises; drug-induced parkinsonism; sustained remission from PD; strictly unilateral features after 3 years; supranuclear gaze palsy; cerebellar signs (ataxia of gait or limbs, central nystagmus, scanning dysarthria or truncal ataxia); early severe autonomic involvement; early severe dementia (within first year of onset) with disturbances of memory, language, and praxis; extensor plantar reflex; Mini Mental Status score < 24 [17]; any defect on brain imaging (such as infarcts, brain tumor, hydrocephalus or congenital defects like lissencephaly but not cavum septum pellucidum); or MPTP exposure, for which patients were screened prior to DBS surgery. The study was approved by the Human Research Protection Office at WUSM and was carried out in accordance with the principles expressed in the Declaration of Helsinki. All participants provided written, informed consent. The demographics of the participants of the study are shown in **Table 1.**

## STN DBS Electrode Contact Selection

The side of the brain contralateral to the more affected side of the body was stimulated. The more affected side of the body was defined by the side of the body that had higher UPDRS scores in the off medication, off stimulation state (Hershey *et al*, 2010). The DBS electrode contacts for each individual were placed in atlas space using a validated method[20,21] to identify the contact locations with respect to the STN. Dorsal and ventral STN DBS contacts were chosen for each participant based on examination of their position in atlas space. Specifically, a contact within 2mm of the ventral STN border was chosen as the ventral contact, and a contact within 2mm of the dorsal STN border was chosen as the dorsal contact, ideally with one unused contact in between (Hershey *et al,* 2010).

## Stimulation Protocol

Participants stopped PD medications at midnight before the morning of the study. The UPDRS ratings and mood and cognitive tasks were completed during separate dorsal, ventral, and OFF STN DBS sessions over the course of one day. The order of the dorsal, ventral, and OFF sessions was randomized and blinded to the participants and raters. The voltage, frequency, and pulse width were 2.5V, 185 Hz, and 60 μs, respectively, for most participants. However, 14 participants experienced side effects from 2.5V and voltage was reduced to 1.6-2.3V.

## Measurements

Motor symptoms were rated with the Unified Parkinson Disease Rating Scale (UPDRS), part III-motor, administered by a trained clinician blind to stimulation condition. UPDRS subscale scores for bradykinesia, rigidity, tremor at rest, and total were summed contralateral to the stimulated side of the brain.

Cognition was evaluated via the spatial delayed response (SDR) and the Go/No-Go (GNG) tasks. The SDR task assesses short-term and working memory for spatial information, and was performed as described previously; the variable of interest was the distance between recalled and actual cue locations, or error (Campbell et al., 2008; Hershey et al., 2004)[22,23] . The GNG task assessed the ability to select and inhibit a pre-potent motor response appropriately under conditions of high pre-potent response strength (Braver *et al.*, 2001), and was performed as described previously (Hershey et al., 2010). The discriminability index, Pr, was the outcome

measure, defined as the proportion of hits minus the proportion of false alarms. Only data from participants who reached a criterion of Pr > 0.5 in the OFF DBS condition was included in the analyses.

Current affective state was assessed using visual analog scales (VAS) and transformed to valence and arousal scores as described previously. [15,16,24] Separate scores for anxiety and apathy were also measured using VAS. Higher scores on valence, anxiety and apathy represented better state.

## Primary Statistical Analyses

**Outliers.** In the data sets for all measures in both statistical analyses – univariate and 3D – outliers were calculated as data values above or below 3 standard deviations from the mean. The data sets and statistical outcomes shown are based on the data sets with these outliers removed.

**Univariate statistics.** To determine whether STN DBS conditions induced changes in motor, cognitive, and mood measures, we calculated difference scores by subtracting OFF condition scores from dorsal and ventral DBS condition scores to obtain "dorsal DBS difference scores" and "ventral DBS difference scores", respectively. Dorsal and ventral DBS scores were compared using paired *t*-tests, for total contralateral UPDRS, tremor at rest, rigidity, bradykinesia, SDR Accuracy, Go-No-Go Pr, valence, arousal, apathy, and anxiety.

**Statistical mapping of DBS effects to STN anatomy.** Our mapping method is described in detail in Eisenstein et al. [15] Briefly, four statistical maps were generated for each measure. 1) An *N*-image shows the number of stimulated contacts that contributed dorsal or ventral DBS difference scores to each voxel of the map, *i.e.* within 1.3 mm. Voxels with $N < 6$ were not included in further steps. 2) A weighted mean image, containing the weighted mean difference scores across participants, with nearer contacts weighted higher. 3) A *t* image depicting weighted *t* values derived from single-sample *t* tests comparing the mean difference scores (dorsal – OFF or ventral – OFF) at each voxel to zero. 4) A *p* image containing *p* values for the *t* test at each voxel.

**Type I error correction for multiple comparisons and sample bias.** To test whether the anatomical location of the active DBS contact significantly contributed to clinical effects we used a permutation test as previously described. [15] Briefly, for each measure, a summary score reflecting the extent and amplitude of significant voxels in the *p* image was generated, and

compared to 1000 summary scores generated similarly but from randomly chosen pairings of the active contact locations and difference scores. We considered a $p$-value $\leq 0.05$ (*i.e.*, a summary score that would place it in the top 50 of the 1000 random data permutations) to indicate that DBS location significantly contributed to a measure's difference scores.

# Results

## Distribution of Contacts

The stimulated contacts from 74 participants, each with a dorsal and ventral score, are shown in **Figure 1**. All contacts were located within 2 mm of the STN.

## Univariate Results

Effects of dorsal or ventral STN DBS on mood, cognitive and motor measures (irrespective of 3D active contact location) are described in **Table 2**. Ventral or dorsal DBS significantly improved contralateral UPDRS3 items summed across all of the appendicular items scored and ratings for rigidity, tremor at rest, bradykinesia, and anxiety. Ventral DBS (only) significantly improved apathy and affective valence. Unilateral STN DBS did not significantly affect the mean scores for the Go/No-Go and SDR cognition tests. Dorsal scores differed significantly from ventral scores for anxiety, valence, and rigidity, with anxiety and valence improving more with ventral DBS, and rigidity improving more with dorsal DBS.

## STN DBS effects depend on DBS site

For the analysis based on 3D location of DBS, statistical significance for each measure is shown in **Table 3.** DBS location significantly contributed to the effects of STN DBS on bradykinesia and on tremor at rest. Statistical maps for these two effects are shown in **Figure 2**.

# Discussion

The results support the conclusion that 3D electrode contact location contributes to the motor effects of STN DBS. The peak $p$ values for DBS-induced improvements in motor function were located more dorsally in the STN. This confirms our findings in a different sample, using a different experimental design,[15] which showed greater motor improvement in dorsolateral STN, particularly for tremor at rest. Similarly, previous studies also suggested greater improvement in motor function in dorsal STN and the zona incerta (ZI). [25, 26, 27] -This fits with organization of the

STN with the dorsolateral portion of the STN an integral part of the basal ganglia feedback loop for motor function. Additionally, these studies have implicated the zona incerta in motor and limbic systems, therefore the increased improvement near this region is also anatomically plausible.

In the current study, electrode contact site, as a 3D variable, did not significantly impact the effect of STN DBS on cognitive and mood function in PD. The lack of effect on mood may be only a Type II error: $p$ was 0.10 for the affective valence permutation analysis, and ventral STN stimulation improved valence more than dorsal STN stimulation in the univariate analysis. A previous study[28] correlating changes in mood from STN DBS with initial psychiatric diagnosis showed increased mood improvement in those with pre-existing anxiety/mood disorders or higher symptom severity. Our current study did not show these significant improvements in most mood symptoms; however no correlation between initial mood disorder level and improvement was tested. The nonsignificant association of contact location and cognitive function is more surprising, given the present sample size and our previous findings that DBS effects on cognitive measures were location dependent. However, there are several differences between the current study and the previous study. First, the previous study's ON sessions tested participants with their individually optimized DBS settings, including choice of active contact. In other words, in that study the contact selection was not chosen blind to clinical response. Furthermore, since in that study the contacts and settings were optimized clinically, cognitive or affective responses may have contributed to the selection of contact or pulse settings that were more likely to improve mood or thinking than the anatomically chosen DBS contacts and standardized pulse settings in the present study. The current study also used lower voltage for all participants in contrast to the higher voltages in our past study, which may limit potential changes in cognitive function.

Strengths of this study include its relatively large sample size, acute stimulation paradigm, assessment blind to the location stimulated, and innovative statistical approach. Limitations include the fact that DBS electrode implantation targets the dorsal posterolateral STN, which necessarily limits the number of contacts that fall in the anterior or medial-ventral STN. The limited number of data points reflects this bias, and thereby reduces power, in parts of the ventromedial and anterior STN. Second, participants or examiners may have detected when STN

was turned on. However, as the focus of the study was the correlation of effect with DBS site, and neither the participants nor the examiners knew the precise locations of the contacts, the study was still blinded for the key variable under investigation, *i.e.*, the location of the active contact. Third, the interval (42 minutes) between DBS OFF and ON settings was chosen based on previous experience with motor signs, but there may be longer-term effects—on mood and cognitive function in particular—that this investigation may have missed. However, the time limit on the OFF session was also chosen with ethical and practical considerations in mind that preclude extending the time to study more delayed effects. Lastly, statistically significant changes in the visual analog scales used to measure the mood measures of valence, apathy, anxiety and arousal may not imply syndromal or clinically significant changes.

Our previous study[15] in a different PD sample did not support complete functional segregation within the STN of mood, motor, and cognitive function. This new sample provides some functional evidence for a dorsal–ventral, motor–non-motor gradient of benefit. Rigidity, resting tremor, and bradykinesia improved significantly more with dorsal stimulation (Table 2), and the 3D analysis found significant location effects for bradykinesia and tremor at rest (Table 3), with the evidence for improvement stronger in dorsolateral STN or ZI for both measures (Figure 2, upper panel, *p* image, and lower panel, weighted mean image). By contrast, anxiety and affective valence improved significantly more with ventral than dorsal stimulation (Table 2), and in the 3D analysis, affective valence tended to improve most with ventral STN stimulation (Figure 2, weighted mean image; $p$=0.10). On the other hand, stimulation of either ventral or dorsal STN improved motor function, anxiety and apathy, and cognitive effects did not differ with stimulation site. Therefore the direct, functional evidence supports only a mild dorsal–ventral gradient for motor and non-motor effects of STN DBS, rather than a strict dorsal–ventral functional segregation.

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## Author contributions

design of the study: SAE, MCC, JSP, TH, KJB

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data analysis: AG, SAE, NTT, JMK

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revising the manuscript: AG, SAE, NTT, MCC, MU, JSP, TH, KJB

All authors approved the final manuscript and have no conflicts of interest to report.

## Tables and Figures

**Table 1.** Demographics and clinical characteristics of 74 Parkinson disease research participants.

| | **Mean (S.D., range)** |
|---|---|
| Age (years) | 62 (9.1, 43-80) |
| Education (years) [^] | 15.1 (2.7, 10-20) |
| Disease duration (years) | 12.4 (5.1, 0.51-26.5) |
| Time since STN DBS surgery (months) | 18.2 (16.1, 3-77) |
| | |
| | **Distribution** |
| Sex | 50 male, 24 female |
| Race [*] | 65 Caucasian, 4 Native American/Alaskan Native, 1 African American, 1 Asian, 2 Unknown/Other |
| More affected side, by UPDRS III subscore | 41 right, 33 left |
| Dominant hand [*] | 65 right, 7 left, 1 ambidextrous |
| Current PD medication [a, b] | 74 CD-LD, 12 CD-LD ER, 33 DA agonist [c], 7 MAO inhibitor, 32 COMT Inhibitor, 25 benzodiazepines, 40 amantadine, 7 antidepressants [d], 21 other meds |

CD-LD = carbidopa-levodopa; CD-LD ER = carbidopa-levodopa extended release; DA = dopamine; MAO = monoamine oxidase; COMT = catechol-O-methyl transferase. [^], 4 participants missing data; [*], 1 participant missing data; [a], prior to abstinence on the day of study; [b], participant may fall in more than one medication category; [c], no participant was taking extended release formulations of DA agonists; [d] antidepressants; amitriptyline, buproprion, duloxetine, nortriptyline, trazodone

**Table 2.** Outcome measures, by STN DBS conditions and DBS site (dorsal *vs.* ventral STN).

| | **Mean difference (S.D.)** | **d.f.** | **Sig. (2-tailed)** |
|---|---|---|---|
| **Mood and motivation**[a] | | | |
| Anxiety: Dorsal vs. OFF | 6.2 (15.9) | 69 | **0.002** |
| Anxiety: Ventral vs. OFF | 9.5 (16.9) | 69 | **<0.001** |
| Anxiety: Dorsal vs. Ventral | −3.3 (12.8) | 69 | **0.04** |
| | | | |
| Arousal: Dorsal vs. OFF | 0.002 (0.2) | 69 | 0.9 |
| Arousal: Ventral vs. OFF | −0.03 (0.2) | 69 | 0.1 |
| Arousal: Dorsal vs. Ventral | 0.03 (0.1) | 69 | 0.07 |
| | | | |
| Valence: Dorsal vs. OFF | 0.04 (0.3) | 69 | 0.3 |
| Valence: Ventral vs. OFF | 0.2 (0.3) | 69 | **<0.001** |
| Valence: Dorsal vs. Ventral | −0.16 (0.3) | 69 | **0.003** |
| | | | |
| Apathy: Dorsal vs. OFF | 7.1 (20.6) | 69 | **0.01** |
| Apathy: Ventral vs. OFF | 6.3 (23.5) | 69 | **0.03** |
| Apathy: Dorsal vs. Ventral | 0.8 (17.8) | 69 | 0.7 |
| | | | |
| **Cognition**[b] | | | |
| GNG: Pr Dorsal vs. GNG Pr OFF | 0.01 (0.2) | 66 | 0.5 |
| GNG: Pr Ventral vs. GNG Pr OFF | 0.03 (0.2) | 66 | 0.1 |
| GNG: Pr Dorsal vs. GNG Pr Ventral | −0.02 (0.1) | 66 | 0.2 |
| | | | |
| SDR: Accur Dorsal vs. OFF | 0.1 (3.7) | 65 | 0.8 |
| SDR: Accur Ventral vs. OFF | 0.2 (4.5) | 65 | 0.7 |
| SDR: Accur Dorsal vs. Ventral | −0.1 (3.8) | 65 | 0.9 |
| | | | |
| **Movement**[c] | | | |
| Bradykinesia: Dorsal vs. OFF | −0.5 (0.6) | 70 | **<0.001** |

| | | | |
|---|---|---|---|
| Bradykinesia: Ventral vs. OFF | −0.5 (0.6) | 70 | **<0.001** |
| Bradykinesia: Dorsal vs. Ventral | −0.01 (0.6) | 70 | 0.8 |
| | | | |
| Rigidity: Dorsal vs. OFF | −1.1 (1.1) | 70 | **<0.001** |
| Rigidity: Ventral vs. OFF | −0.8 (1.2) | 70 | **<0.001** |
| Rigidity: Dorsal vs. Ventral | −0.3 (0.9) | 70 | **0.01** |
| | | | |
| Tremor at Rest: Dorsal vs. OFF | −1.2 (1.6) | 70 | **<0.001** |
| Tremor at Rest: Ventral vs. OFF | −1.2 (1.7) | 70 | **<0.001** |
| Tremor at Rest: Dorsal vs. Ventral | −0.01 (1.1) | 70 | 0.9145 |
| | | | |
| UPDRS: Total Dorsal vs. OFF | −4.2 (3.6) | 70 | **<0.001** |
| UPDRS: Total Ventral vs. OFF | −4.2 (3.5) | 70 | **<0.001** |
| UPDRS: Total Dorsal vs. Ventral | 0.02 (2.6) | 70 | 0.9469 |

[a], Four VAS participants were statistical outliers and were omitted. [b], One GNG and 2 SDR participants were outliers and were omitted, and 6 other GNG and 7 other SDR participants were omitted due to missing/incomplete data. [c], Three UPDRS participants were outliers and were omitted.

**Figure 1.** Distribution of contacts included in the analyses shown green (dorsal) and purple (ventral) spheres, with paired contacts of each participant indicated by yellow connecting rods, and blue transparent regions indicating the subthalamic nucleus (STN).

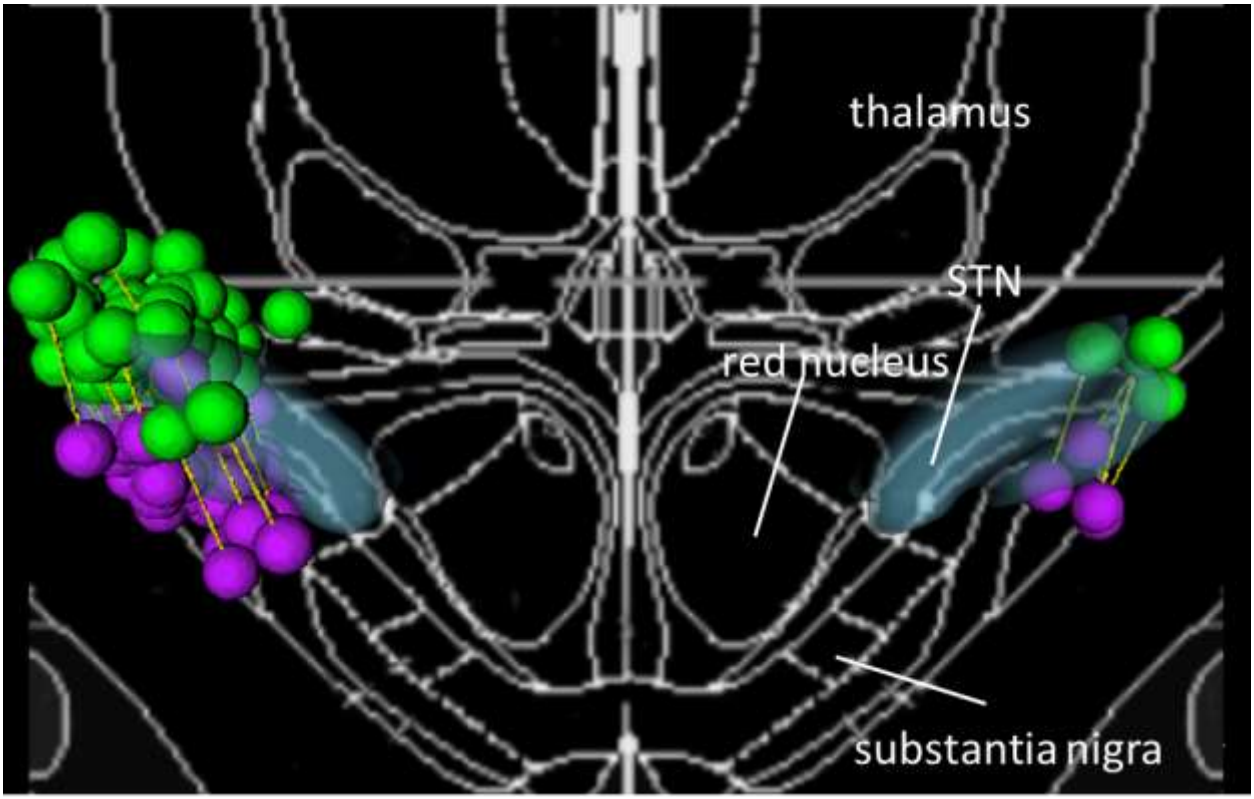
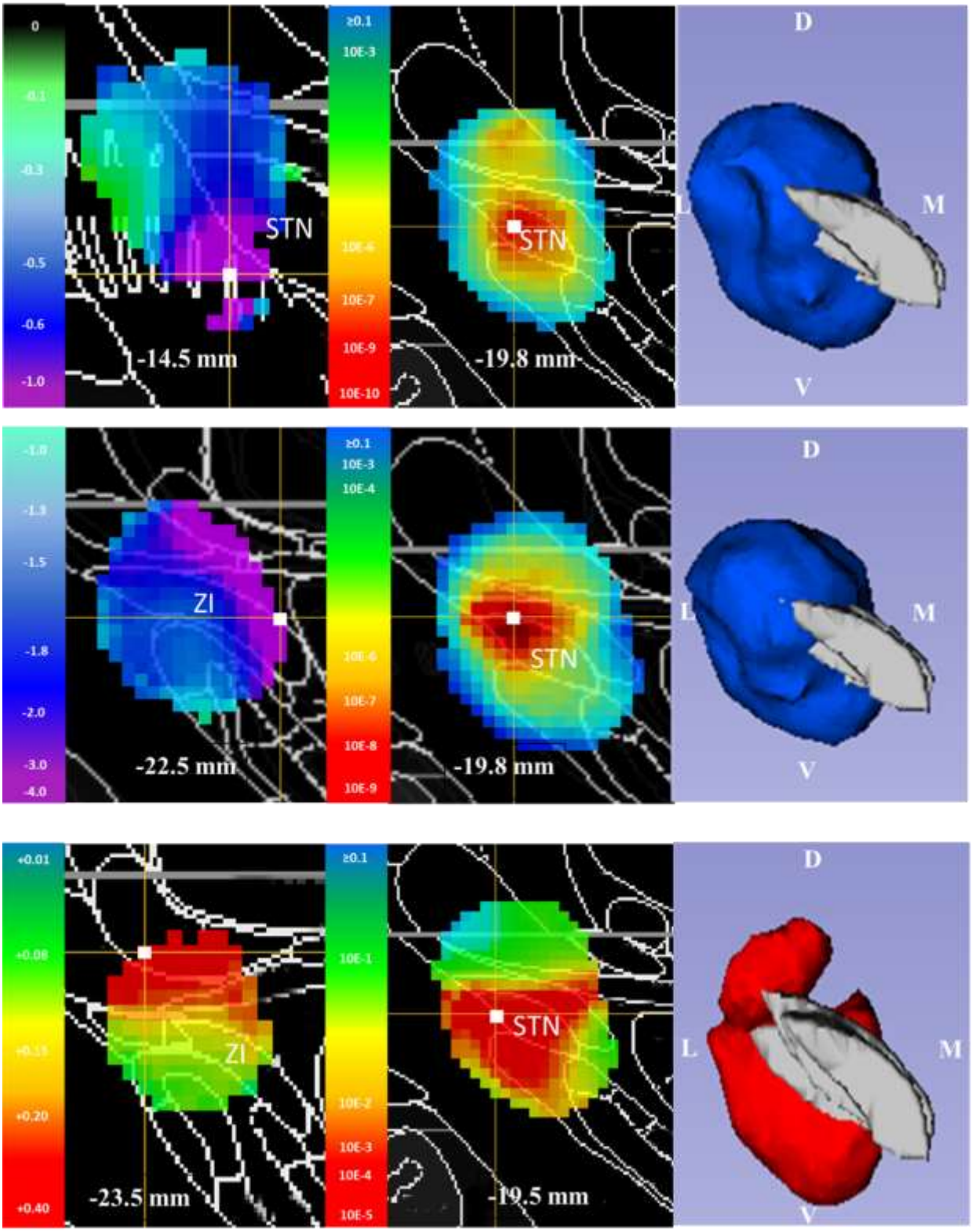


**Table 3.** Statistical summary of 3D analyses [^]

| | *p* (permu-tation) | Peak in *p* image | Peak *p* Location (x, y, z) | Peak *p* Location | Peak Weighted Mean Value | Peak Weighted Mean Location (x, y, z) | Peak Weighted Mean Location |
|---|---|---|---|---|---|---|---|
| **Movement**[a] | | | | | | | |
| Bradykinesia | 0.01 | <0.001 | (12.9, -19.8, -4.1) | Dorsal STN | -1.1 | (11.5, -14.5, -5) | cp |
| Rigidity | 0.3 | | | | | | |
| Tremor at rest | 0.02 | <0.001 | (13.4, -19.8, -2.9) | Dorsal STN/ZI | -4.3 | (8.5, -22.5, -4.5) | ZI |
| UPDRS Total | 0.08 | <0.001 | (12, -21, -3.5) | ZI | -9.5 | (8.5, -22.5, -6) | ZI |
| **Mood and motivation**[b] | | | | | | | |
| Anxiety | 0.2 | | | | | | |
| Arousal | 0.2 | | | | | | |
| Valence | 0.1 | <0.001 | (14, -19.5, -4) | Dorsal STN/cp | 0. 42 | (13, -23.5, -2.5) | VPM |
| | | 0.01 | (9.5,-16,-2.5) | STN | -0.51 | (13, -13.5, 1.0) | H2 |
| Apathy | 0.2 | | | | | | |
| **Cognition**[c] | | | | | | | |
| GNG Pr | 0.9 | | | | | | |
| SDR % Accuracy | 0.6 | | | | | | |

^, Peak *p* and weighted mean values and locations are only listed for the measures found to be significant in the permutation analysis. [a], Seventy-one participants contributed to the analyses for the motor measures. [b], Seventy participants contributed to the analyses for the mood measures. [c], Sixty-seven and 66 participants contributed to the analyses for the cognitive measures of GNG and SDR, respectively. STN, subthalamic nucleus; cp, cerebral peduncle; ZI, zona incerta; VPM, ventral posterior medial thalamic nucleus; H2, lenticular fasciculus (field H2); GNG, Go-NoGo; SDR, spatial delayed response. There were both positive and negative difference scores for valence, so peak coordinates and weighted mean values are given for both positive and negative values.

**Figure 2 (see next page).** Weighted mean image, *p* image, and 3D *p* image for measures with significant effect of contact location in the 3D analyses. Upper panel: bradykinesia. Middle panel: tremor at rest. Lower panel: valence. For the weighted mean images, the cooler shades indicate where, on average, the difference scores (ventral−OFF and dorsal−OFF) are more negative (improvement relative to OFF for motor measures; worsening relative to OFF for valence) while the warmer shades indicate locations where the difference scores are more positive (worsening relative to OFF for motor measures; improvement relative to OFF for valence). For the 2D *p*-image, warmer shades indicate more significant *p* values, while the cooler shades indicate less significant *p* values. White squares indicate peak coordinates. In the 3D image, the blue/red volume indicates values <0.05 in the *p* image. STN, subthalamic nucleus; ZI, zona incerta


0
-0.1
-0.3
-0.5
-0.6
-1.0
STN
-14.5 mm
≥0.1
10E-3
10E-6
10E-7
10E-9
10E-10
STN
-19.8 mm
D
L
M
V
-1.0
-1.3
-1.5
-1.8
-2.0
-3.0
-4.0
ZI
-22.5 mm
≥0.1
10E-3
10E-4
10E-6
10E-7
10E-8
10E-9
STN
-19.8 mm
D
L
M
V
+0.01
+0.08
+0.15
+0.20
+0.40
ZI
-23.5 mm
≥0.1
10E-1
10E-2
10E-3
10E-4
10E-5
STN
-19.5 mm
D
L
M
V

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