



Thalamic and ventricular volumes predict motor response to deep brain stimulation for Parkinson's disease



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ARTICLE INFO

Keywords:

Parkinson's disease

Deep brain stimulation

Magnetic resonance imaging

ABSTRACT

Background: Brain atrophy frequently occurs with Parkinson's disease (PD) and relates to increased motor symptoms of PD. The predictive value of neuroimaging-based measures of global and regional brain volume on motor outcomes in deep brain stimulation (DBS) remains unclear but potentially could improve patient selection and targeting.

Objectives: To determine the predictive value of preoperative volumetric MRI measures of cortical and subcortical brain volume on motor outcomes of subthalamic nucleus (STN) DBS in PD.

Methods: Preoperative T1 3D MP-RAGE structural brain MRI images were analyzed for each participant to determine subcortical, ventricular, and cortical volume and thickness. Change in Unified Parkinson's Disease Rating Scale (UPDRS) scores for subsection 3, representing motor outcomes, was computed preoperatively and postoperatively following DBS programming in 86 participants. A multiple linear regression analysis was performed to investigate the relationship between volumetric data and the effect of DBS on UPDRS 3 scores.

Results: Larger ventricular and smaller thalamic volumes predicted significantly less improvement of UPDRS 3 scores after STN DBS.

Conclusions: Our findings demonstrate in PD that regional brain volumes, in particular thalamic and ventricular volumes, predict motor outcomes after DBS. Differences in regional brain volumes may alter electrode targeting, reflect a specific disease trait such as postoperative progression of subclinical dementia, or directly interfere with the action of DBS.

1. Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) improves motor deficits in people with advanced Parkinson's disease (PD), although the degree of benefit varies across individuals [1,2]. DBS surgery requires preoperative imaging for electrode targeting, and prior studies have established that regional brain atrophy accounts for some variability in DBS outcomes. In patients undergoing DBS, smaller mesencephalic surfaces predict decreased ADL improvement, thickness in the paracentral region predicts motor outcomes, and hippocampal atrophy corresponds with postoperative conversion to dementia [3–5]. However, no study to date has demonstrated a relationship between motor outcomes and global measures of brain atrophy which may be obtained from routine structural MRI, and little data exists regarding the predictive value of other cortical and subcortical regions. As DBS

effectiveness varies and the procedure is not without risk, an additional tool to assess potential benefits from DBS may be useful in patient selection and improve clinical outcomes.

Brain atrophy occurs independent of DBS in PD and affects various cortical and subcortical structures, including lateral ventricles, sensorimotor, parietal and perisylvian cortex, hippocampus, and caudate [6–8]. While atrophy most strongly links to cognitive impairment in PD, the degree and pattern of brain atrophy also correlate with motor features of PD. In particular, sensorimotor cortex is among the regions most prone to atrophy in PD, and regional atrophy of sensorimotor cortex predicts increased motor symptoms of PD [7]. These areas are highly functionally connected to the common DBS targets of STN and internal globus pallidus, suggesting that atrophy affects regions that are modulated by STN DBS [9]. Additionally, STN not only anatomically connects to basal ganglia and thalamic regions but also anatomically

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<https://doi.org/10.1016/j.parkreldis.2018.11.026>

Received 15 August 2018; Received in revised form 27 November 2018; Accepted 27 November 2018

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connects to sensorimotor cortex [10,11]. As atrophy in PD affects regions with a high degree of anatomic and functional connectivity to the STN, the effect of STN DBS may be altered by changes in these regions.

We tested the predictive value of regional and global brain volumes measured by preoperative MRI on motor outcomes of STN DBS for PD. We hypothesized that reduced volumes of regions related to motor function like basal ganglia and thalamus and global brain volume would predict reduced motor benefit from DBS. We measured regional volumes and measures of global atrophy including ventricular and cortical volumes as well as global cortical thickness in preoperative MR images to determine which measure best predicts motor response to DBS.

2. Methods

2.1. Participants

Participants were retrospectively selected from a consecutive series of PD patients that underwent DBS surgery at the Movement Disorders Center in Washington University School of Medicine and agreed to participate in preoperative DBS research imaging, separate from clinical imaging, and outcomes. A protocol was approved by the Washington University Institutional Review Board, and written consent was obtained from all participants. Basic criteria for study inclusion were: diagnosis of idiopathic PD by UK Brain Bank criteria [12], placement of bilateral STN DBS between 2006 and 2015, presence of a preoperative high-definition structural MRI (acquisition details described below), and available preoperative and postoperative OFF-medication (practically-defined) Unified Parkinson's Disease Rating Scale Part 3 (UPDRS 3) data between 12 months prior to and 15 months after DBS implantation. Surgical exclusionary criteria included dementia (a score of ≤ 130 on the Mattis Dementia Rating scale), poor response to levodopa, and structural brain abnormalities that would increase surgical risk. 117 participants who fit inclusion criteria were identified by automated query of the Medical Automated Record System. MR images were inspected and 3 participants with missing or corrupted images and 6 participants with excessive motion artifact were excluded. Additionally, 22 participants were excluded due to insufficient clinical data to assess inclusion criteria, leaving a total of 86 participants.

2.2. Clinical evaluation

All participants were evaluated at the Movement Disorders Center at Washington University School of Medicine. UPDRS 3 was measured during the presurgical inpatient ON/OFF evaluation and during postoperative DBS programming clinical visits. UPDRS 3 interrater reliability was validated for all UPDRS 3 raters on an annual basis by completing video-based testing of rating UPDRS 3. Preoperative scores were collected within 12 months prior to DBS and postoperative ON-stimulation scores were collected between initial DBS programming (median 21 days postoperative, range 6–57 days) and 15 months after DBS placement. All UPDRS 3 scores were in the practically-defined medication-OFF state, after at least 8 h without medication for PD. The ON-stimulation ratings were performed after DBS settings were finalized at the end of each programming visit. We averaged preoperative and postoperative scores separately within each subject, and then calculated the change between preoperative OFF-medication and postoperative OFF-medication and ON-stimulation scores to determine the effect of DBS. Average scores within the entire postoperative period were used to mitigate random fluctuations and to represent the real-world performance of each subject after receiving DBS. Participants were classified as tremor dominant (TD), postural instability gait disorder dominant (PIGD) or mixed PD subtypes according to criteria described previously [13].

2.3. MRI technique and processing

High-resolution structural MRI data was acquired preoperatively within 4 months of DBS using a Siemens 3T MAGNETOM Trio scanner. Scans included a T1-weighted sagittal MPRAGE, TR = 2400 ms, TI = 1000 ms, TE = 3.14 ms, FA = 8°, 0.9 mm³ voxels) and a T2-weighted fast spin echo (TR = 3200 ms, TE = 469 ms, 1.0 mm³ voxels). Images were inspected for significant motion and susceptibility artifacts and images with artifacts interfering with cortical measurements were excluded. Cortical reconstruction and volume segmentation were performed with Freesurfer v5.3 (<http://surfer.nmr.mgh.harvard.edu/>). The technical details of these procedures are described in prior publications [14–16]. Image analysis included skull stripping, parcellation, measurement of cortical volume, cortical thickness, and ventricular volume (including lateral and third ventricles). Images and parcellation maps were inspected for errors and areas of mislabeling were corrected by reviewer blinded to clinical outcomes. All volumes were normalized to total intracranial volume. Parcellation was performed using the Desikan atlas [16]. Specific regions of interest previously reported to atrophy in PD included lateral parietal (LP), sensorimotor (SM), perisylvian (PS), and hippocampal (HC) regions [7,17]. LP was defined as superior parietal, inferior parietal and supramarginal regions, SM was defined as precentral, postcentral and paracentral regions, PS was defined as superior temporal and transverse temporal regions, and HC was defined as hippocampal or parahippocampal regions in the Desikan atlas. Subcortical regions also including thalamus, caudate, putamen and pallidum were delineated in Freesurfer as previously validated [18].

2.4. Neurosurgical procedure

All patients had bilateral STN DBS in accordance with standard clinical procedures at Washington University [19]. Patients were prescreened for medical and neuroanatomical comorbidities which would preclude safe electrode implantation and completed standard neuropsychological testing to exclude patients with dementia. Electrodes were stereotactically implanted into bilateral subthalamic nuclei. Accurate electrode placement was verified by intraoperative electrophysiological recordings, clinical responses to stimulation, and postoperative CT scans.

2.5. Statistical analysis

Statistical analysis was performed in SPSS Statistics (IBM Corp, 2017). Multiple linear regression analysis was performed to control for clinical variables of age, years since PD onset, level of education, levodopa equivalent dose (LED) as calculated by standard criteria [20], and baseline UPDRS score. Analyses were performed to determine relationships between change in UPDRS score and regional and global cortical volumes, subcortical and ventricular volumes, and cortical thickness, as defined above. Checks on assumptions for multiple linear regression included inspection for linearity of data, normality of residuals, absence of autocorrelation and multicollinearity, homoscedasticity, and absence of outliers using Cook's distance. For multiple linear regression results, multiple comparisons corrections were done with the Benjamini-Hochberg False Discovery Rate (FDR) method using a threshold of 0.05. Original p-values are reported with significance after FDR correction noted. For findings that were significant after multiple linear regression, scatterplots were generated and Pearson correlations were performed. A single apparent outlier was found in the inspection of the scatterplot for ventricular volume vs change in UPDRS 3. However, on further inspection this point had a small Cook's distance, and removal of this point did not cause a significant change in the outcome of the multiple linear regression, therefore it was not considered an outlier. Student's t-test was used to compare change in UPDRS 3 between upper and lower quartiles of thalamic and

Table 1
Patient demographics at date of surgery.

Number of participants	86
Age	62.9 ± 9.5
Years since onset	11.8 ± 4.4
Sex	Male: 58 Female: 28
Race	Caucasian: 78 African American: 3 American Indian or Alaskan Native: 4 Any Hispanic: 1
Level of education:	Less than high school: 7 Completed high school: 14 Some college or trade School: 25 Completed bachelor's degree: 10 Completed advanced degree: 21 Did not specify: 9
PD motor subtype:	Tremor dominant: 15 Postural instability gait disease dominant: 65 Mixed: 6

Relevant values reported as mean ± standard deviation

ventricular volume and volumes of thalamus and ventricles between TD and PIGD groups.

3. Results

Patient demographics in our cohort are summarized in Table 1. Postoperatively, UPDRS 3 decreased 43% (36.7 ± 10.2 to 21.0 ± 7.10) and daily levodopa equivalents (LED) also decreased by 28% (1765 ± 775 to 1277 ± 741). UPDRS3 scores quickly decreased after DBS implantation and programming, and remained generally stable over the 15-month postoperative period (Fig. 1).

Regional volumes of thalamus and ventricles significantly predicted motor response to STN DBS. After multiple regression analysis

Table 2
Volumetric measures vs change in UPDRS3 after STN DBS.

	β	p
Ventricle Volume	0.29	* < 0.001
Thalamus Volume	-0.30	* < 0.001
Caudate Volume	0.04	0.67
Putamen Volume	-0.15	0.09
Pallidum Volume	-0.06	0.43
Cortical Volume	-0.15	0.07
LP Volume	-0.17	0.04
PS Volume	-0.09	0.24
SM Volume	-0.17	0.04
HC Volume	-0.18	0.04
Cortical Thickness	-0.04	0.62
LP Thickness	-0.05	0.51
PS Thickness	0.02	0.82
SM Thickness	-0.02	0.77
periHC Thickness	-0.14	0.10

Values are reported as beta values (standardized regression coefficient) followed by p-values.

* indicates significance after correction for multiple comparisons at FDR < 0.05.

(Table 2), thalamic volume predicted postoperative change in UPDRS 3 ($\beta = -0.30$, $p < 0.001$); smaller thalamic volumes related to less UPDRS 3 improvement postoperatively. Volume of the lateral and 3rd ventricles also predicted postoperative improvement of UPDRS 3 ($\beta = 0.29$, $p < 0.001$); increased ventricular volume related to less improvement in UPDRS 3 scores after DBS. Volume of caudate, putamen, and pallidum did not predict change in UPDRS 3. Thalamic volume correlated strongly with ventricular volume ($R = -0.536$, $p < 0.001$, Fig. 2). Global cortical volume did not predict post-operative improvement of UPDRS 3 ($\beta = -0.154$, $p = 0.067$). Non-significant trends that did not meet multiple comparisons correction were observed with lateral parietal ($\beta = -0.174$, $p = 0.039$), sensorimotor ($\beta = -0.174$, $p = 0.039$) and hippocampal ($\beta = -0.180$, $p = -0.043$) volumes predicting change in UPDRS 3, while perisylvian volume ($\beta = -0.093$, $p = 0.237$) did not produce any notable trend. Global cortical thickness had no significant relationship with UPDRS 3 (β

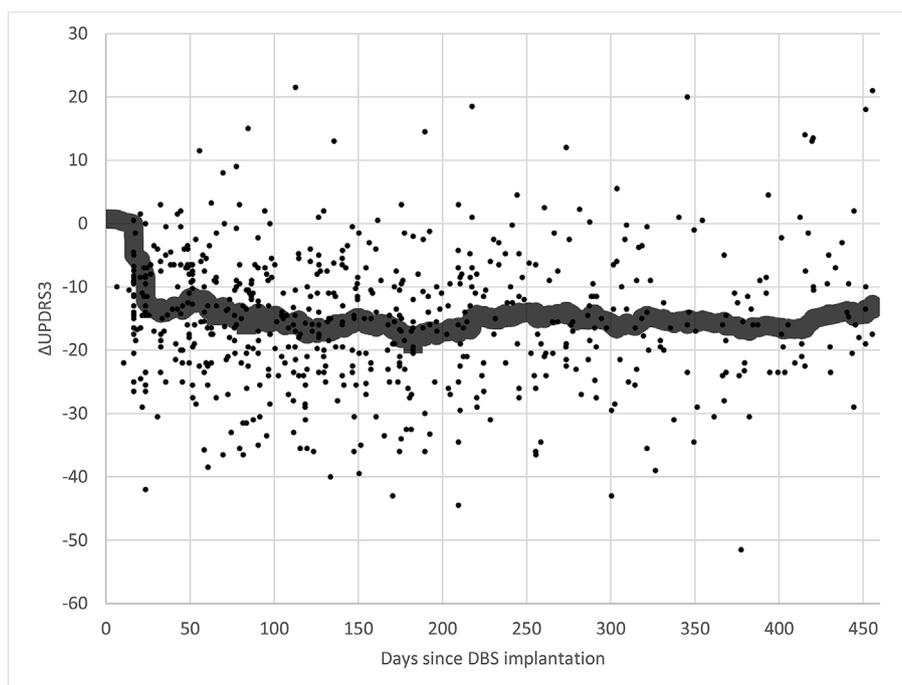


Fig. 1. Change in UPDRS3 from baseline over time after DBS implantation, with running average.

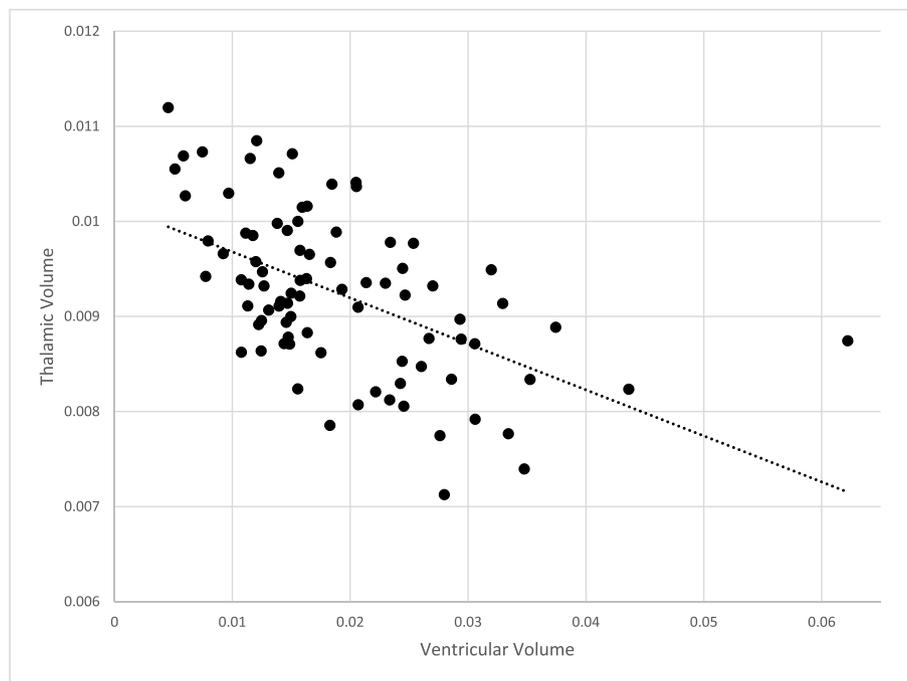


Fig. 2. Ventricular vs thalamic volume.

$= -0.042$, $p = 0.607$) or UPDRS 1 ($\beta = -0.086$, $p = 0.308$). Thickness of lateral parietal, sensorimotor, perisylvian and parahippocampal cortical regions did not significantly relate to change in UPDRS scores.

Thalamic and ventricular volumes were separated by quartiles to quantify the difference between high and low atrophy in terms of motor response. A 30% reduction in UPDRS 3 was used as a threshold for a desirable response, as this approximates the minimum reduction in UPDRS 3 with levodopa typically considered to support candidacy for DBS [21]. UPDRS 3 reduction for 1st quartile thalamic volumes (corresponding to the most atrophy) averaged 28.4%, significantly less than 47.5% in the 4th quartile ($p = 0.019$). Similarly, UPDRS 3 reduction for 1st quartile ventricular volumes (corresponding to the least enlargement) averaged 47.9% compared to 4th quartile reduction of 35.2%, though this difference did not reach significance ($p = 0.14$). Of the 1st quartile thalamic volumes, 52% experienced at least a 30% reduction of UPDRS3 after DBS, while 90% of participants with 4th quartile thalamic volumes reached that mark. Among 1st quartile ventricular volumes, 90% had at least 30% reduction in UPDRS 3, while this was true for 67% of those in the 4th quartile. TD and PIGD groups did not significantly differ with regard to change in UPDRS 3 ($p = 0.74$), thalamic volume ($p = 0.52$), or ventricular volume ($p = 0.59$).

4. Discussion

We demonstrate, in a large consecutive cohort of PD patients undergoing STN DBS, that presurgical thalamic and ventricular volumes predicted degree of improvement in motor scores after DBS. Non-significant associations were seen for sensorimotor and lateral parietal regional volumes, while global measures of cortical volume and thickness did not predict outcomes after STN DBS. These data indicate that MRI volumetrics may contribute to PD patient selection for STN electrode implantation.

Thalamic and ventricular size had a strong relationship with postoperative motor outcomes in our data even after accounting for other relevant clinical variables. Smaller thalamic and increased ventricular volumes predicted a less robust motor benefit from DBS, while subjects in the quartiles corresponding with the most thalamic atrophy and most ventricular enlargement in these regions were less likely to benefit substantially from DBS. Ventricular volume is commonly used as a

marker of global brain atrophy but may be particularly influenced by atrophy of adjacent subcortical structures such as caudate and thalamus, supported by the high degree of correlation between thalamic and ventricular volumes in our study, therefore it is not surprising that thalamic and ventricular volumes would predict motor outcomes to a similar degree [22]. The effect of thalamic and ventricular volume here was also much stronger than the effect of cortical volume and cortical thickness on either motor or non-motor outcomes. Cortical areas previously reported to atrophy in PD were more strongly associated with motor outcomes than was global cortical volume, although these associations did not reach significance.

Several possible explanations exist for the stronger relationship between thalamic and ventricular volumes and DBS motor outcomes compared to selected cortical regions. Technically, increased ventricular size may contribute to difficulty with surgical targeting of the STN and may predispose patients to electrode shift [23]. Additionally, thalamus is typically penetrated by electrodes *en route* to the STN, making this a possible contributor to structural causes of inaccuracy [24]. Furthermore, the ventricles are typically avoided in surgical planning, thus particularly large ventricles may add difficulty to accurate electrode placement. While each patient in this study received CT verification of electrode placement postoperatively, differences in accuracy sufficient to cause clinical change may occur on millimeter scale and therefore evade this quality check [25]. As the ventroanterior and ventrolateral nuclei of the thalamus are major downstream outputs of the STN and internal globus pallidus, structural changes in the thalamus may also hypothetically affect the functional pathways by which DBS exerts its therapeutic effects [26]. The mechanism by which STN DBS affects motor function in PD remains somewhat controversial, with modulation of pallidothalamic activity, antidromic stimulation of direct STN to cortex connections bypassing pallidothalamic connections (the “hyperdirect” pathway”), and alteration of functional connectivity in downstream networks all implicated in various studies [26–29]. The strong relationship between thalamic structure and clinical effects in DBS supports mechanistic models that include modulation of thalamic activity.

Other studies have previously demonstrated that brain volumes at the time of DBS surgery affect postoperative outcomes. Mesencephalic surfaces inversely correlated with improvement in activities of daily

living (ADL) after STN DBS [3] whereas volumes of cortex, caudate and putamen did not predict motor outcomes, as we found. We did not include mesencephalic measures as this region is not isolated in our processing pipeline. Another group reported that small subregions of paracentral, superior frontal, and superior and inferior parietal cortex predicted motor outcomes and voltage required to achieve maximum effect [4]. We did not test whether such small isolated clusters as those seen in this study predict motor response to STN DBS, though we did not find that cortical thickness at the regional level can predict DBS outcomes. However, the significant clusters in their study largely fall within the sensorimotor and lateral parietal regions in our analysis, regions showing the strongest relationship with motor outcomes of any cortical area, although cortical thickness of these regions produced no significant results in our study. None of these other studies included analyses of thalamic or ventricular volumes, which we found predict motor outcomes. Furthermore, these MRI-based measurements of ventricular and thalamic volumes are easily performed and may be useful components of presurgical workup for DBS [30]. Although those in the quartiles corresponding to the highest degree of atrophy in thalamus and enlargement of ventricles were less likely to have a robust response to STN DBS, there was no degree of atrophy in our data that suggested a complete lack of benefit or a threshold to be used as a contraindication to DBS. If confirmed in another cohort, volumetric analysis of these regions may be useful for the decision-making process between clinicians and patients.

The main limitation of this study was its retrospective nature. This permitted analysis of a large sample but limited accounting for potentially confounding variables, such as socioeconomic factors and recruitment bias. However, most potentially confounding variables were addressed with multiple regression of clinical and demographic covariates. More importantly, these findings require replication in an independent cohort to confirm that these variables can be useful for predicting STN DBS outcomes, preferably using longitudinal data able to track volume measures over time to test the role of atrophy on DBS outcomes. Our population included relatively few TD compared to PIGD patients, although the groups were similar in atrophy and motor outcomes despite the more reliable historical response of tremor to STN DBS compared with gait and postural symptoms [21]. We limited this study to motor outcomes and did not address nonmotor manifestations. Future study of the effect of atrophy to predict outcomes for DBS of the internal globus pallidus may reveal differences from DBS targeting STN since the targets may have different side effect thresholds and cognitive effects [2].

5. Conclusion

We demonstrate here that thalamic and ventricular volumes predict degree of motor response to STN DBS for PD. Use of preoperative structural MRI to identify patients with high degrees of atrophy in these regions may be useful to inform physicians and patients during presurgical planning.

Conflicts of interest

The authors have no conflicts of interest to report.

Acknowledgements

This work was supported by NIH NINDS/NIA/NIBIB (NS075321 [JSP, MCC], NS41509 [JSP], NS097799 [MCC], NS097437 [MCC], R44AG054405 [MCC], T32EB021955-01A1 [JRY]), the Barnes-Jewish Hospital Foundation (Elliot Stein Family Fund and Parkinson Disease Research Fund); the American Parkinson Disease Association (APDA) Advanced Research Center for Parkinson Disease at Washington University in St. Louis; the Greater St. Louis Chapter of the APDA; the Barbara & Sam Murphy Fund; the McDonnell Center for Systems

Neuroscience; and the Oertli Fund for Parkinson Disease Research.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.parkreldis.2018.11.026>.

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