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Lateral ventricle volume is poor predictor of post unilateral DBS motor change for Parkinson's disease☆

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ABSTRACT

Background: Deep Brain Stimulation (DBS) surgery can effectively treat many debilitating motor symptoms of Parkinson's disease (PD), but axial symptom improvement is variable. Predictors for post-DBS axial symptom performance have yet to be identified. Pre-surgery ventricle volume may be one predictor, for increasing ventricular size has been associated with worsening gait disturbance. In PD, ventricle size may also increase with the advancement of motor symptoms.
Objective: To examine the hypotheses that 1) lateral ventricular volumes would predict motor and axial motor symptom change from pre to four months post unilateral DBS, and 2) PD patients have larger ventricle volumes contralateral to side of symptom onset.
Methods: Idiopathic PD patients ($n = 37$) completed pre-surgery volumetric brain scans and UPDRS motor testing (off-medication), unilateral DBS (Globus Pallidus interna, $n = 11$; subthalamic nucleus, $n = 26$), and 4-month follow-up motor assessments (on-stimulation). Ventricle volumes were normalized using total intracranial volume.
Results: Total ventricular volume as well as measurements of contralateral/ipsilateral volumes to side of symptom onset or DBS lead placement did not predict outcome motor measures or correlate to axial motor change. Patients improving at least 2 standard errors of measurement ($n = 6$) did not have smaller ventricles relative to those without significant change. Post-operative hemorrhage ($n = 1$) had ventricle volumes similar to the group average. There was no asymmetry in ventricular volume by side of onset or side of lead placement.
Conclusion: Ventricular volume was a poor predictor of acute motor change following DBS. Asymmetrical ventricles may not be a consistent imaging marker for PD motor dysfunction.

1. Introduction

Axial disability is a troubling motor manifestation of Parkinson's disease (PD) [1]. Gait dysfunction and postural instability can lead to an increased risk of falls and fall related injuries [2]. Over 68% of PD patients have been reported to fall annually with over 51% of patients falling two or more times a year [3]. Gait difficulty and fear of falling are significantly associated with worsened quality of life for individuals with Parkinson's disease [4]. PD patients with both postural instability and gait disturbance early in the course of the illness also have high rates of mortality (up to 80% higher than PD peers without these difficulties [5]).

Deep Brain Stimulation (DBS) can effectively treat many debilitating symptoms of PD [6–8]. DBS outcome data with regard to axial symptom improvement, however, remain variable for both

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unilateral and bilateral stimulation studies. Using subjective and objective measurements of gait, Kelly and colleagues [9] identified minimal changes in axial symptoms (either increase or decrease) with unilateral subthalamic nucleus (STN) placement, and chance levels of improvement (50% of patients improved) for those with bilateral STN stimulation. Visser and colleagues [10] reported that bilateral STN stimulation failed to improve postural stability over that of optimally dosed levodopa. Okun and colleagues [11] with a randomized unilateral placement study (STN versus globus pallidus interna, GPi) showed that both sites resulted in seven month post-DBS improvement for UPDRS rigidity, bradykinesia, and tremor items, but not postural stability or gait. Walker and colleagues [12], however, reported significant post-STN improvement for UPDRS axial symptoms at three, six, and 12 months post-surgery, although a proportion of the patients also began to develop more gait disturbance and difficulty standing from the seated position at 12 months. Why some individuals demonstrate post-DBS axial improvement while others do not remains unclear in the literature.

Presurgical lateral ventricular size may be an anatomical marker with predictive value for DBS related motor changes and specifically gait and postural instability. Ventricular dilation is hypothesized to impact the integrity of the basal ganglia structures, frontal lobe white matter pathways, and corticospinal tract integrity [13,14]. Ventricular dilation occurs with normal pressure hydrocephalus, which involves gait disturbance [13] and might be related to gait disturbances in PD [15]. Moreover, lateral ventricle asymmetry is suggested to be an important consideration for motor symptom progression. Lewis and colleagues [14] showed that lateral ventricles contralateral to symptom onset enlarged faster than ipsilateral ventricles in PD with this enlargement associated with motor worsening. Huang and colleagues [16] reported a larger lateral ventricle contralateral to the more symptomatic side in a PD twin, but not a non-PD twin. Moreover, examining ventricular size might have practical DBS surgical implications [17]. Larger ventricles might result in a greater chance of breaching the ventricles and resulting in intraventricular hemorrhage.

For this study, we investigated the role of pre-surgical lateral ventricular volumes on post-DBS motor (specifically gait and postural improvement), and the relative size of lateral ventricles to motor symptom onset and DBS lead placement. We hypothesized that pre-surgical lateral ventricular volume would predict motor and axial symptom change following DBS surgery with larger volumes predicting poorer motor outcomes. We secondarily examined the hypothesis that ventricular volume contralateral to self-reported side of symptom onset would be larger than the ipsilateral side in our sample, with these volumes predicting outcome. This hypothesis was also examined with ventricles on the same side of DBS lead placement, for DBS placement is often performed contralateral to the side of the body most affected.

2. Methods

2.1. Study design and participant sample

A retrospective study conducted in accordance with the University of Florida's Movement Disorder Center, Institutional Review Board, and the Declaration of Helsinki. Participants completed consent forms to have their baseline, operative, and post-operative data used for research purposes. Chart and MRI data were pulled (years 2002–2007) for consecutive patients who had a diagnosis of "probable" PD, had pre-operative cognitive testing, had completed a pre-surgery MRI on one of two scanners, had completed a unilateral DBS and had 4-month motor outcome data. Probable PD diagnosis was made by one of three fellowship trained Movement Disorder Specialists and determined by: (1) the presence of two out of three motor features of PD (tremor, rigidity, and bradykinesia), (2) and the absence of any features that would suggest other forms of Parkinsonism including lack of a substantial response to levadopa therapy. Exclusion criteria included known secondary causes of PD and prior neurosurgical treatment.

2.2. Surgery protocol

Surgeries were completed by a single surgeon (K.D.F.)/neurologist (M.S.O.) team with multipass electrode mapping [18]. DBS devices were activated one month after intracranial lead implantation. Follow-up evaluations were performed as needed until the optimal chronic stimulation parameters and adjunctive PD medication regimen were determined. All patients were kept on their optimized DBS setting and medication regimen for a minimum of 30 days before repeat motor evaluations were completed.

2.3. Imaging protocol and variables of interest

Participants had completed a pre-DBS volumetric brain scan via 1.5 T General Electric ($n = 10$) or Siemens ($n = 28$) MR clinical scanners using a T1-weighted three-dimensional volumetric sequence that allowed reconfiguration into any plane (typical protocol: TR = 11 ms, TE = 3.87 ms, Flip Angle = 15°, Inversion time = 600; 1.5 mm thick, 120 slices).

2.4. Lateral ventricular volumes

Lateral ventricular volumes were measured from 3D T_1-weighted magnetization prepared rapid acquisition gradient echo (MP-RAGE) or spoiled gradient recalled (SPGR) images acquired in the axial plane. For pre-processing the voxel intensity range was restricted to better delineate ventricles from non-ventricle. Trained raters used a semi-automated segmentation method with scans in native space (ITK-SNAP;http://www.itksnap.org [19]; Intra- and inter-rater spatial overlap and reliability were excellent; inter-rater grand Dice Similarity Coefficient (DSC) = .92 ± .04; ICC = .98, Pearson $r = .99$; intra-rater grand DSC = .96 ± .03, all $p < .001$). Origin seed bubbles were placed within each lateral ventricle, and an intensity algorithm governed by parameters optimized to minimize error and manual modification expanded the bubbles in 3D space to the periventricular tissue margin. Extraneous voxels were manually removed. Visual inspection confirmed left-right ventricles which were then separated. Variables of interest included 1) total lateral ventricular volume (mm^3) and 2) contralateral and ipsilateral volume relative to patient reported onset. Contralateral and ipsilateral volume to lead placement were calculated, for side of symptom onset did not always correspond to side of lead placement due to severity of symptoms at time of surgery.

2.5. Intracranial volume

Volumetric T1-weighted images were processed in BrainSuite by an automated method of quantifying total intracranial volume [20]. A horizontal plane demarcating the superior cerebellar border was applied as a standardized inferior margin for all cranial volumes. Extraneous voxels were manually removed from the 3D volume; visual inspection of the 3D volume confirmed the accuracy of the volumetric assessment.

2.6. Corrected lateral ventricular volumes

Corrected lateral ventricular volumes were calculated by dividing lateral ventricular volumes by intracranial volumes in order to account for intersubject head volume variability [21]. Final primary predictor variables of interest were: 1) Total lateral ventricular volume corrected for intracranial volume (TLVc), 2) Contralateral ventricle to symptom onset corrected for intracranial volume (CLV symptom_c and Ipsilateral ventricle volume to symptom onset corrected for intracranial volume (ILV symptom_c), and 3) Contralateral ventricle to lead corrected for intracranial volume (CLV lead_c) and Ipsilateral ventricle to lead corrected for intracranial volume (ILV lead_c).

2.7. Motor outcome measure

Unified Parkinson's Disease Rating Scale (UPDRS; [22]) – baseline and four-month post-DBS UPDRS scores were completed by a fellowship trained movement disorder neurologist. Baseline data were collected "off" medication. Four-month post-DBS data were collected "off" medication and optimal "on" electrode stimulation. Primary outcome variables were: UPDRS section III (motor subscale of the Unified Parkinson's Disease Rating Scale; higher = worse), with specific sub-items for axial motor symptoms including "arising from chair" (UPDRS item 27; 0–4), "posture" (UPDRS item 28; 0–4), "gait" (UPDRS item 29; 0–4), and "postural stability" (UPDRS item 30; 0–4).

2.8. Covariates considered

Age, education, duration of PD symptoms (defined as months between first symptoms of PD and baseline evaluation), pre-surgery disease severity (Hoehn and Yahr; H&Y [23]), and baseline general cognitive status as measured by the Mattis Dementia Rating Scale (DRS-2) [24], were considered variables that may alter the expected relationship between lateral ventricular volume and motor scores.