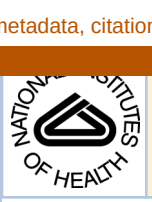

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Asymmetrical lateral ventricular enlargement in Parkinson's disease

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Abstract

Background—A recent case report suggested the presence of asymmetrical lateral ventricular enlargement associated with motor asymmetry in Parkinson's disease (PD). The current study explored these associations further.

Methods—Magnetic resonance imaging (3T) scans were obtained on 17 PD and 15 healthy Control subjects at baseline and 12–30 months later. Baseline and longitudinal lateral ventricular volumetric changes were compared between contralateral and ipsilateral ventricles in PD subjects relative to symptom onset side and in Controls relative to their dominant hand. Correlations between changes in ventricular volume and United Parkinson's Disease Rating Scale motor scores (UPDRS-III) while on medication were determined.

Results—The lateral ventricle contralateral to symptom onset side displayed a faster rate of enlargement compared to the ipsilateral ($p=0.004$) in PD subjects, with no such asymmetry detected ($p=0.312$) in Controls. There was a positive correlation between ventricular enlargement and worsening motor function assessed by UPDRS-III scores ($r=0.96$, $p<0.001$).

Discussion—There is asymmetrical lateral ventricular enlargement that is associated with PD motor asymmetry and progression. Further studies are warranted to investigate the underlying mechanism(s), as well as the potential of using volumetric measurements as a marker for PD progression.

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Keywords

Structural magnetic resonance imaging; semi-automatic segmentation; lateral ventricular volume; motor asymmetry; Parkinson's disease

Background

Parkinson's disease (PD) is marked clinically by asymmetrical presentation of motor dysfunction. Among other changes, PD is characterized pathologically by loss of dopamine neurons in the substantia nigra par compacta (SNc) of the basal ganglia (BG), and often is accompanied by cognitive deficits related to frontal lobe dysfunction. Like other neurodegenerative disorders [1,2], accelerated generalized/selective brain atrophy may occur and be useful to reflect cell loss in PD during its progression. Previous studies of brain structural changes, however, have yielded inconsistent and/or nonspecific findings in PD [1–4].

As the site of primary PD pathology [5], the SN has been intensively studied using many imaging technologies, including most recently transcranial ultrasound [6]. Several lines of evidence, however, suggest that structural changes at the SN level will not be very useful to reflect PD-specific cell loss during disease progression. First, it is difficult to define the SN boundary precisely using current imaging technology [7,8]. Second, the volume of the SN is so small that it accounts for only 0.5–0.6% of the total brain volume. Lastly, there is a long asymptomatic period before PD is manifested clinically, by which time patients may have lost 50%–80% of their dopamine neurons [9,10].

Although nigral dopamine neuron loss could have far reaching effects on the downstream structures of the striatum (caudate, putamen), most studies on striatal volumetric changes have yielded inconsistent results [3,7,11,12]. For example, some studies have reported caudate atrophy in PD compared to control subjects [1,11], whereas others have reported no change [3,7,12,13]. Similarly, there have been reports of putamen atrophy in PD compared to control subjects [7,11,14], but others that have reported no distinction between the groups [13]. These inconsistent findings may be due to small sample sizes, cross sectional design, and/or variability in imaging analysis methods that are highly rater-dependant [1–4].

The lateral ventricles surround both the BG and its downstream (e.g. frontal cortex) structures that may be influenced by PD. The lateral ventricles are large compared to the SN and striatal structures, and the segmentation method is relatively mature, straightforward, and has good reliability [15]. These factors, coupled with recent knowledge of the diffuse nature of the PD process [16], suggested that lateral ventricular volume enlargement may be sensitively associated with PD-related cell loss. Previous results on lateral ventricle volume changes in PD have, again, been equivocal, with some studies reporting increased lateral ventricle volume in PD [1], and others no change [3,4]. Some studies [17,18] have associated lateral ventricular changes with cognitive decline in PD, but not with PD-specific motor changes. One recent case report [19] suggested the possibility of the association of asymmetrical lateral ventricular enlargement with PD-specific motor asymmetry. In order to explore this association further, we collected longitudinal structural MRI data on 17 PD and 15 control subjects to determine whether changes in lateral ventricle volume may encode PD-specific information (i.e., asymmetry and motor progression).

Methods

Study subjects

Seventeen early-stage PD patients [Hoehn and Yahr (HY) stage I–II] [20] and 15 healthy control subjects participated in the study (see Table 1 for detailed demographic information). The shortest follow up visit for PD and control subjects occurred at 12.4 and 11.8 months after baseline, respectively, and the longest at 30.5 and 42.8 months, respectively. The mean time (SD) between scans was 20.3 (5.4) months for PD and 21.0 (8.4) months for control subjects. The time from diagnosis of PD to initial study time had a range of 0–95.8 months. The average UPDRS score for subjects at baseline was 9.4 and that at follow up was 10.8. All PD patients received medical treatment for their PD, which was optimized by a movement disorder specialist (X.H.) during the course of the study. PD subjects were identified through a tertiary-care movement disorders clinic, and all PD subjects met published diagnostic criteria for PD [21]. The study protocol received Institution Review Board approval, complied with all tenets of the Helsinki accords, and written informed consent was obtained from all subjects.

All subjects were screened to be free from other major medical illnesses, as well as liver, kidney, or electrolyte abnormality, or B12 or folate deficiency. Mini-Mental Status Exam (MMSE) scores of all study subjects were above 27 at the baseline of the study.

Structural MRI acquisition

The structural MRI for subjects were acquired on a 3.0 T Siemens scanner (Siemens, Erlangen, Germany) with a birdcage type standard quadrature head coil and an advanced nuclear magnetic resonance echoplanar system. The imaging protocol was comprised of a high-resolution T1 weighted anatomical image (3D SPGR, TR=14 ms, TE=7.7 ms, flip angle=25°, voxel dimensions 1.0 × 1.0 × 1.0 mm, 176 × 256 voxels, 160 slices) for each subject.

Image Processing

All MRI analyses were performed at the University of North Carolina Neuro Image Analysis Laboratory (NIAL, UNC-Chapel Hill, NC). All datasets were first processed by a rater-independent, fully-automatic tissue-segmentation method [22] that generates detailed maps of gray matter, white matter, and cerebrospinal fluid (CSF). This processing step includes a correction for mainly RF coil induced intensity inhomogeneities, as well as skull stripping and intensity calibration. A semi-automatic, rater-initialized method was employed to segment the lateral ventricles based on the probabilistic CSF map [23]. The lateral ventricular volume consisted of the lateral ventricles surrounding both the BG and its downstream (e.g. frontal cortex) structures, excluding the temporal horn, third, and fourth ventricles. A detailed protocol is accessible at http://www.ia.unc.edu/dev/tutorials/Documents/UNC-NeuroimagingLab-Manual.pdf. All scans (both baseline and follow up for each subject) were coded with a random number that was not shared with the personnel performing the analysis. As such, personnel were blinded to the time of subjects' scans (baseline or follow up) or any other personal information concerning the subjects. The coefficient of variation (CV) from this study was less than 1% for the measurements [24]. This level of reliability has not been achieved via pure manual segmentations of brain structures, with the latter generally yielding considerably larger CVs (4–5 times larger than the automated method) [25].

Motor function evaluation for PD subjects

The side of symptom onset was determined by patients' reports that were all corroborated by motor exam (the symptom onset side remained the more symptomatic side during the course

of PD [26]). The motor function in PD subjects was quantified by the United Parkinson's Disease Rating Scale motor part (UPDRS-III) score that was obtained while the PD patients were on medication. This provided a clinical estimation for the severity of motor function deficits that are not alleviated by medication, a factor that might have relevance to intrinsic brain structural atrophy. The UPDRS was administered to all subjects by the same movement disorders specialist (XH) who also had optimized PD subjects' medications. All authors involved in volumetric calculations were blind to subject identity until final statistical analyses were performed.

Statistical analysis

Single-point analysis comparing the 17 PD or 15 control subjects at either baseline or follow up was done using t-tests. Longitudinal comparison of the age trajectories for PD subjects was completed using the quadratic growth curve model (PROC MIXED). We then compared the longitudinal trend of lateral ventricle volume changes in 17 PD subjects during disease progression between the contralateral and ipsilateral side relative to PD symptom onset. A random coefficient growth curve model (PROC MIXED) was used to fit the evolving trends with duration of disease. Lateral ventricle volume (in mm^3) was entered as the dependent variable, years since diagnosis, quadratic term of years since diagnosis, side (contralateral vs. ipsilateral), and the interaction of time since diagnosis and side were entered as fixed effects. To account for heterogeneity between subjects, the model included a subject-specific intercept and years since diagnosis as random effects with variance-covariance structure of compound symmetry for multiple observations within subjects. A similar analysis was completed for the 15 control subjects with contralateral defined as the side opposite their dominant hand and without the inclusion of the PD-specific terms.

The positive finding of asymmetric atrophy trajectories was followed by ad hoc paired t-tests between contralateral and ipsilateral ventricle volumes at baseline and follow up. Pearson correlation coefficient (r) was calculated for the association between annual change rates in total lateral ventricle volume and rates in UPDRS-III scores. A conservative robust correlation procedure also was employed to evaluate the association while constraining the impact of an influence data point. Statistical analyses were performed with SAS v.9.1 (SAS Institute Inc., Cary, NC).

Results

For control subjects, single-time-point analysis revealed no significant difference between their contralateral and ipsilateral ventricle volumes at either baseline or follow up (see Table 2). In addition, there were no significant differences in the rate of lateral ventricular volumetric changes in normal subjects between ventricles ipsilateral and contralateral to the dominant hand ($p=0.312$).

In contrast, the single-time-point analysis at baseline and follow up visits in PD subjects showed an asymmetric enlargement in lateral ventricles between the contralateral and ipsilateral ventricles relative to side of symptom onset. The paired t-test showed the lateral ventricle on the contralateral side was 1253 (2659.6) mm^3 [mean (SEM)] larger than the ipsilateral side ($t(16)=1.94$, $p=0.070$) at study baseline. At follow up, the difference increased to 1496 (2875.7) mm^3 [mean (SEM), $t(16)=2.14$, $p=0.048$; Table 2)].

Analysis of the longitudinal trajectories revealed that PD subjects showed a significantly more rapid ventricular increase contralateral to symptom side onset compared to the ipsilateral side of the brain [$F(3, 46.6)=5.00$, $p=0.004$)]. As shown in Figure 1, the enlargement in the lateral ventricle contralateral to symptom side started right after disease diagnosis and continued almost linearly afterwards. The enlargement in the lateral ventricle

ipsilateral to symptom side, on the other hand, progressed much slower, with no obvious change in the first 3 years but gradually picked up speed and reached a similar level after 8 years.

The annual rate of ventricular enlargement was associated with the rate of worsening motor function (while “on” medication), as measured by the UPDRS-III score. The scatter plot of this association is shown in Figure 2, and follows a linear trend with faster ventricle enlargement associated with significantly hastening deterioration in the UPDRS-III score ($r=0.96$, $p<0.001$). Even with the exclusion of an influential data point at the far end of the distribution, a conservative robust correlation procedure replicated the significant association with $r=0.77$, $p<0.001$.

Discussion

In this longitudinal structural MRI study we found asymmetrical lateral ventricular enlargement in PD subjects, with faster lateral ventricular enlargement on the contralateral side relative to symptom onset. Such a change was not seen in healthy Control subjects. PD is characterized as an asymmetrical disease, with one side (the side on which symptoms start) always affected more than the other [26,27]. The finding of asymmetrical lateral ventricular enlargement following the same pattern as motor asymmetry in PD is consistent with a prior case report of asymmetrical lateral ventricular enlargement in a pair of discordant monozygotic PD twins [19].

The strength of the study includes longitudinal design, semi-automatic segmentation methods, and using the less affected side of the PD patients as a reference. The results raise interesting questions about the neuroanatomical and pathological mechanisms underlying asymmetric ventricular increase in PD. Moreover, it also raises the possibility of using lateral ventricle volumetric measurements as a possible marker of disease progression.

Ventricular enlargement is often considered a non-specific marker for neurodegeneration and has only been associated with cognitive deficits in PD in the past [18,28–30]. Changes in surrounding structures may contribute to this ventricular enlargement, as some studies have demonstrated decreased volume in hippocampus [2,31], caudate [1,11], putamen [11,32], thalamus [11], and cortex [11,33] in PD subjects, whereas other studies have failed to detect any differences [3,7,12,13]. Neuropathologically, there is clear evidence of a loss of projections to the caudate and putamen in PD [34]. In addition, in PD there is decreased serotonergic, noradrenergic, and cholinergic content [35–38], such that the dysfunction of these neurotransmitters and their associated neuromodulators (trophic factors or peptides) also may cause atrophic changes in regions that surround the lateral ventricles. Although the current study could not address the exact mechanism(s) that contribute to ventricular enlargement, the asymmetry of lateral ventricular enlargement supports the idea that lateral ventricular volume may encode PD-specific information. Ideally, PD subjects would be “off” medication when we assessed the structural lateralization and the lateralized motor subscores. This was not done, however, in the current study for practical reasons, especially the ethical issues in withholding effective medical treatment for long-periods of time. In addition, there is evidence that a true “off” state cannot be achieved with an acceptable period [39].

Instead, the motor end point (UPDRS-III) was obtained with subjects on optimized dopaminergic drug therapy that is known to modulate the lateralized subscores of the UPDRS-III (tremor, rigidity, finger dexterity) [40]. Future studies that record the lateralized motor score in the “off” drug state will be useful to clarify these issues further. Nevertheless, we found a significant association between changes in total lateral ventricular volume and

PD motor progression as reflected by changes of total UPDRS motor scores while subjects were “on” medication. Because residual UPDRS-III scores that we measured may reflect a non-dopamine-responsive component of motor dysfunction, this finding suggests that overall lateral ventricular volume changes also may be related to an extranigral, non-dopaminergic-related PD process. This is consistent with a previous report of an association of axial signs of PD motor dysfunction with ventricular volume [4].

Although motor asymmetry is a well-known clinical phenomenon, cognitive asymmetry also has been described in PD. For example, Tomer et al. [41] demonstrated that only PD subjects whose symptoms started on the left, not the right, displayed decreases on the Wisconsin Card Sorting Test. In addition, PD subjects with initial left side symptoms were more impaired on spontaneous flexibility tests (assessed by the Alternate Uses test), whereas initial right side subjects commit more reversal errors. In a study on the effect of left vs. right subthalamic nucleus deep brain stimulation (DBS) on speech, those subjects requiring left side DBS had reduced articulatory accuracy and speaking rates at baseline compared to subjects needing right side DBS [42]. Future studies to correlate the progressions of these non-motor asymmetry symptoms with localized brain atrophy will be especially usefully to guide our understanding of the neuroanatomical and pathological mechanisms underlying the asymmetric ventricular increase in PD.

Structural measures that could reflect disease-specific information may have utility in following disease progression *in vivo*. First, structural measurements may reveal directly the consequence of cell loss that is not easily modulated by symptomatic treatments. Second, PD is known to have diffuse cell loss beyond the nigrostriatal dopamine system [16] that may not be reflected adequately by limited clinical evaluations focused on one or a few aspects of the disease, or by the simple measurement of nigrostriatal dopaminergic terminal integrity. For these reasons, future studies on the structural substrates contributing to the lateralized ventricular enlargement and their correlation to PD-specific functional changes (motor and non-motor measurements) appear warranted.

In summary, this longitudinal MRI study supports the hypothesis that there are PD-specific structural changes that may be reflected by lateralized ventricular volumetric changes in PD. Further studies (e.g., correlating the structural changes with both motor and non-motor functions in both the “on” and “off” drug states, in both early and later stage PD patients) are warranted to investigate the underlying mechanism(s) of these relationships, as well as the potential of using volumetric measurements as a marker for PD progression.

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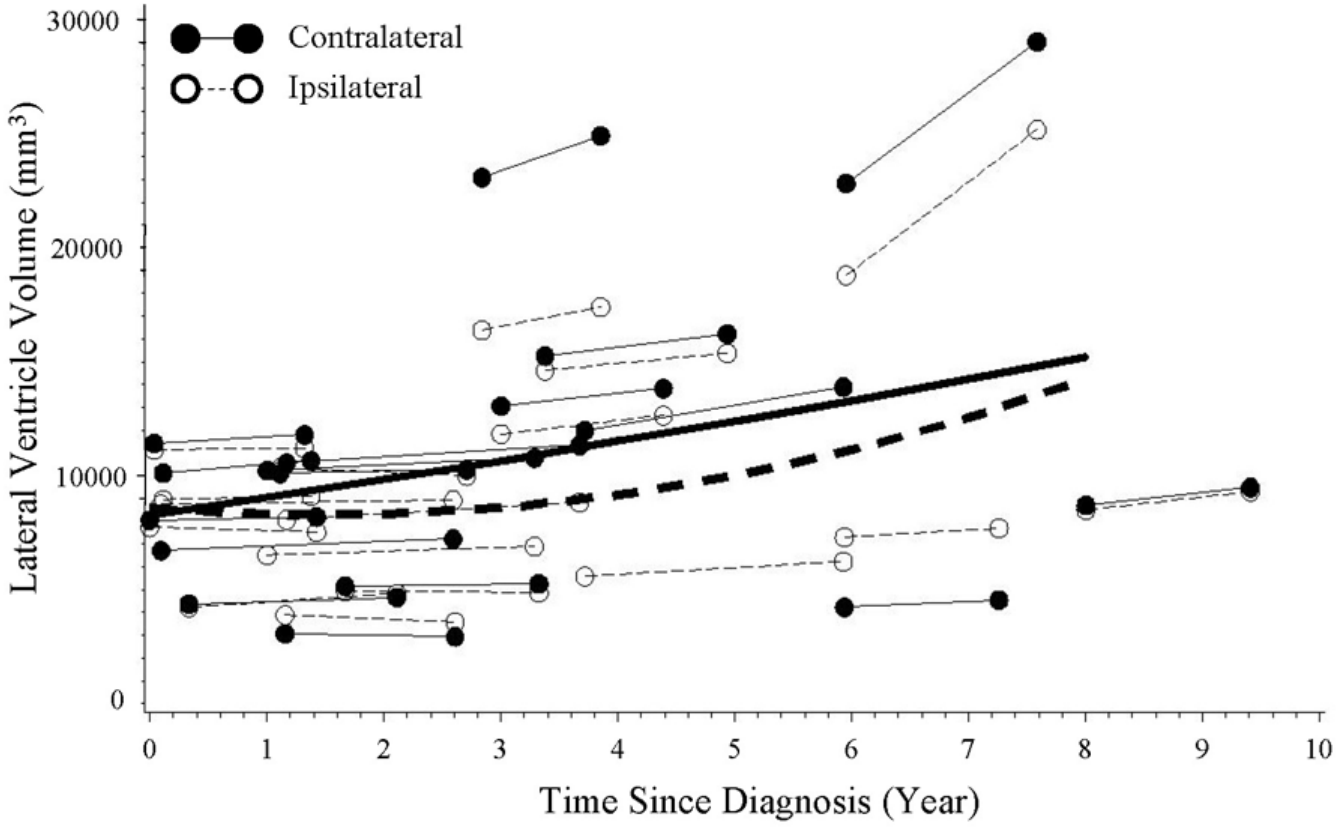

Figure 1.

The longitudinal course of lateralized volumetric changes in ipsilateral (open circles, dashed lines) and contralateral (closed circles, solid lines) lateral ventricles relative to side of symptom onset in PD subjects. The equations for the lines are as follows (where DA = duration of illness in years):

Lateral ventricle $volume_{contra} = 8253.6 + 795.78*DA + 13.8*DA^2$;

Lateral $ventricle_{ipsi} = 8571.0 - 421.5*DA + 141.2*DA^2$.

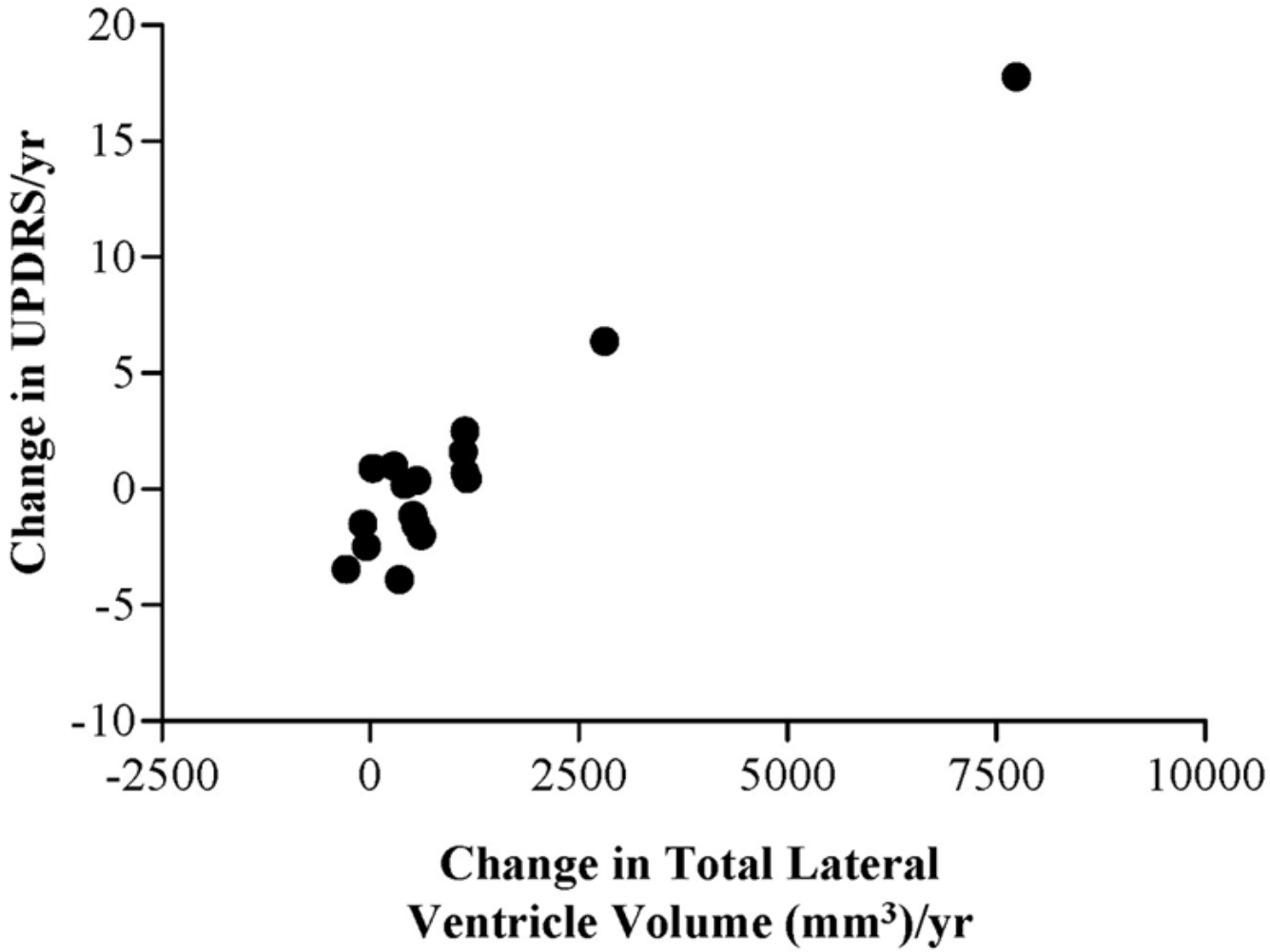

Figure 2.
Scatter plot of the association between changes in total ventricular volume and changes in UPDRS-III scores in PD subjects.

Table 1

Demographic information for study subjects

	Controls (N=15)	PD (N=17)	P*
Mean age at Baseline, yr (SD)	58.2 (12.3)	59.9 (13.0)	0.748
Male, n (%)	11 (73%)	10 (59%)	0.259
Right Handedness, n (%)	14 (93%)	16 (94%)	0.274
Right Side PD Symptom, n (%)	n.a.	11 (65%)	n.a.
Mean duration of illness, mo (SD)	n.a	30.0 (29.3)	n.a

P-values by Wilcoxon test for baseline age, and Fisher's exact test for gender and handedness.

Table 2

Mean volumes for the contralateral and ipsilateral lateral ventricles at baseline and follow up.

Subjects	Timepoint	Contralateral (mm^3)* Mean (SEM)	Ipsilateral (mm^3) Mean (SEM)	P value**
Healthy Controls (N=15)	Baseline	9393 (1288)	9071 (1283)	0.537
	Follow up	9886 (1388)	9511 (1386)	0.446
Parkinson's disease (N=17)	Baseline	10530 (1393)	9277 (1023)	0.070
	Follow up	11480 (1678)	9984 (1296)	0.048

*For control subjects, contralateral was defined as the side opposite the dominant hand; for PD subjects it was the side opposite to symptom onset side.

**P value is based on two tailed paired t-tests.