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Intraindividual Variability in Neuropsychological Performance Predicts Longitudinal Cortical Volume Loss in Early Parkinson's Disease

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Abstract

Objective: Cognitive impairment is common among individuals with Parkinson's Disease (PD). Intraindividual variability (IIV) is a measure of variability across multiple tasks of cognitive functioning. Due to the limited amount of research, particularly among individuals with PD, IIV has been an underutilized metric of cognitive functioning both in research and clinical practice. Previous research demonstrated that individuals with PD have greater variability in cognitive performance relative to controls, and that IIV is predictive of future cognitive impairments. The aim of this study is to investigate the association between baseline IIV and change in cortical and subcortical volumes among individuals with PD.

Methods: The current study used data from 80 newly diagnosed PD patients who were part of a longitudinal cohort study (Parkinson Progression Marker Initiative; PPMI). Participants completed neuropsychological measures and underwent T1 MRI at baseline and the first annual follow-up. Neuropsychological tests assessed attention, processing speed, visuospatial functioning, verbal fluency learning, and memory. T1 scans were processed using standard Freesurfer protocols for extraction of regional volumes.

Results: Greater IIV at baseline was predictive of change in cortical volume in posterior temporal/parietal regions over the one-year period. Baseline IIV predicted cortical volume changes above and beyond the main effect of motor severity and the baseline statistical mean/global cognition score.

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Conflicts of Interest: none

Ethics approval: The study was approved by the institutional review board at each site. Consent to participate: Participants provided informed consent prior to all study activities. Consent for publication: Not applicable

Conclusion: Our results provide initial evidence that IIV is a marker of longitudinal cortical volume loss. Evidence is building that IIV is a sensitive marker of cognitive impairment and the underlying neurodegeneration among individuals with PD.

Keywords

Parkinson's disease; cognitive impairment; early detection; intra-individual variability; neuroimaging

Introduction

Parkinson's disease (PD) is a movement disorder characterized by degeneration of dopamine in the substantia nigra. Common motor deficits include tremors, stiffness, and slow movement. Cognitive impairment is also common and can include deficits in several domains including executive functioning, learning and memory, attention, and language (Williams-Gray & Worth, 2016). Cognitive impairment is associated with deterioration in quality of life (Klepac et al., 2008). Up to 80% of PD patients develop PD dementia (Hely et al., 2008). However, detection of cognitive impairment in PD is challenging, as several studies have indicated diverse patterns of impairment (Kehagia et al., 2010). Some studies suggest that cognitive impairment in PD is attributed to frontal-striatum disruption, which gives rise to executive dysfunction. Conversely other studies state that a "posterior" cognitive pattern characterized by verbal (semantic fluency) and visuospatial (pentagon copy) impairments is predictive of early cognitive impairment (Kehagia et al., 2010; Pal et al., 2018). Furthermore, other studies have suggested that memory impairment was the most prevalent cognitive domain impaired followed by visuospatial, and attention/executive ability impairment in PD patients with mild cognitive impairments (PD-MCI) (Aarsland et al., 2010). Specifically, the Aarsland et al., (2010) study utilized a pooled sample from multiple centers and domains consisted of a mix of tests; for example the "memory" domain include impairments in either scores of immediate recall, delayed recall or delayed recognition across a variety of verbal and visual tests. Therefore, it is not clear whether these findings support the conceptualization of a "frontal" or "posterior" pattern. Regardless, these variations suggest it is a challenge to identify which cognitive domains are most affected by PD and how to detect individuals at risk for decline.

Intraindividual variability (IIV) is predictive of future cognitive impairments in normal-aging adults and individuals with PD (Jones et al., 2020). IIV is measured by either examining inconsistency or dispersion in an individual's performance within or between neuropsychological tasks or cognitive domains (Jones et al., 2018; Tractenberg & Pietrzak, 2011). Inconsistency is defined as the trial-to-trial variability or fluctuation of an individual's performance within a single task (Koffer et al., 2018). Several studies have found that older adults display higher inconsistency, mainly in tasks requiring attention (Bunce et al., 2004). On the other hand, dispersion is the variability across multiple test scores within a single testing occasion (Jones et al., 2018; Stuss et al., 2003).

Intraindividual variability, particularly dispersion, may potentially be an important metric of cognitive testing among neurologic populations (Tractenberg & Pietrzak, 2011). Multiple

studies show that IIV is a relevant measure of cognitive functioning in HIV populations. There is greater dispersion in HIV seropositive older adults compared to older HIV- and younger HIV+ individuals (Morgan et al., 2011). Furthermore, HIV+ individuals with greater dispersion are at increased risk of future neurocognitive impairments and white matter degradation (Jones et al., 2018; Anderson et al., 2018). In addition to the HIV population, individuals with Alzheimer's disease (AD) or PD display greater IIV than healthy adults (Burton et al., 2006). Among individuals with PD, greater IIV is a risk factor for future PD-MCI and Parkinson's disease dementia (PDD) over a five-year period (Jones et al., 2020).

A number of studies have shown IIV is associated with neuroimaging abnormalities among the healthy aging population (MacDonald et al., 2009). To the best of our knowledge, most neuroimaging studies of IIV have focused on white matter integrity as opposed to grey matter metrics. In a review, lesions to prefrontal structures were strongly associated with higher IIV (MacDonald et al., 2009). Another study found that white matter integrity declines in prefrontal regions in normal aging individuals and is associated with cognitive performance variability (Madden et al., 2009). More specifically, the central portion of the genu, and splenium-parietal fibers in the right hemisphere were significant predictors of cognitive variability (Madden et al., 2009). A recent study found that greater IIV among healthy aging individuals was correlated with less intact white matter in the anterior, superior, and posterior corona radiata bilaterally, the internal capsule bilaterally, external capsule bilaterally, bilateral fornix, genu of the corpus callosum, and inferior longitudinal fasciculus, bilaterally (Halliday et al., 2019). Similarly, dispersion was positively correlated with white matter hypointensities on T1 imaging (Manning et al., 2021). Of note, this sample largely consisted of individuals with late-life major depression (n=94) and, to a lesser extent, non-depressed healthy controls (n=35). One study examining cortical brain atrophy and IIV among individuals living with HIV found that greater IIV was associated with grey matter atrophy in the inferior frontal gyrus, inferior temporal/supramarginal gyrus, superior parietal labule and posterior regions of the transverse temporal gyrus (Hines et al., 2015).

Despite the fact that IIV can be easily calculated and incorporated into research/clinical practice, IIV remains an underutilized metric particularly in the Parkinson's literature. This may be due to the limited number of studies on IIV (Jones et al., 2020; Burton et al., 2006; de Frias et al., 2007) and because the neural mechanisms of IIV have not been thoroughly examined in PD. The aim of this study is to investigate the association between IIV and longitudinal cortical and subcortical volumes among individuals newly diagnosed with PD. If IIV is an early marker of neurologic compromise in PD, then we expect that greater IIV at baseline will predict longitudinal volume loss.

Methods

Design

The present study utilized data from the Parkinson's Progression Markers Initiative (PPMI; http://www.ppmi-info.org; Marek et al., 2011). The PPMI is a longitudinal multisite study of untreated and newly diagnosed PD patients from North America, Europe and the Middle

East. The study was approved by the institutional review board at each site and participants provided informed consent. Data from 10 national or international sites from were utilized in the current sample (see https://www.ppmi-info.org/about-ppmi/ppmi-clinical-sites for a complete list of sites). Sample size per site ranged from one to 21 participants. Data was downloaded from the PPMI repository in February 2019.

Neurocognitive Tests

Participants completed five neuropsychological tests, resulting in six scores. Attention/working memory was assessed with Letter-Number Sequencing, a test requiring participant to recall a string of letter/numbers in numerical and alphabetical order (Wechsler, 2008). Processing speed was assessed with Symbol Digit Modalities Test, a timed tests of matching numbers to symbols (Smith, 1982). Visuospatial functioning was measured with the Judgement of Line Orientation test that required participants to match lines to target lines based on the angle of the line (Benton et al., 1983). Verbal fluency was assessed with animal fluencythe number of animals produced in one minute (Gladsjo, et al., 1999). Learning and delayed recall was assessed with a word-list memory test where participants are required to recall words immediate (Trials 1–3 total) and after a 20-minute delay without cues (Hopkins Verbal Learning Test-Revised; Brandt & Benedict, 2001). Scores were converted into demographically-normed z-scores.

IIV and a global cognition composite scores were calculated for each individual at baseline. Global cognition was calculated as the statistical average of the six normative scores. IIV was calculated as the dispersion cognitive scores. Specifically, the standard deviation of the six normative scores relative to the participant's mean (Jones et al., 2020).

$$IIV = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N}\left(x_i - \bar{X}\right)^2} \quad (1)$$

Neuroimaging

T1 MRI scans were collected at baseline and the year 1 follow-up. Quality control procedures are available at https://www.ppmi-info.org/study-design/research-documents-andsops. MRI parameters can be found at http://www.ppmi-info.org. Briefly, parameters were field strength 3.0T, repetition time 5–11 ms; echo time 2–6 ms; slice thickness 1–1.5 mm; inter slice gap 0 mm; voxel size 1*1*1.2 mm; matrix 256 * minimum 160. MR images were visually inspected and quality controlled before further processing. Freesurfer version 7.1.0 (http://surfer.nmr.mgh.harvard.edu) was used to reconstruct and segment T1-weighted images. This involved standard Freesurfer preprocessing procedures and longitudinal processing, which resulted in automated parcellation of cortical/subcortical surfaces defined by the Harvard-Oxford cortical and subcortical atlases (Fischl, 2012; Thames et al., 2017). Regional volume of each cortical and subcortical parcellation was calculated for each participant. Total intracranial volume (ICV) was calculated as the total of entire brain and cerebral spinal. The inner table of the skull was the outer boundary of the segmented image (Fischl, 2012). All regions were examined for skewness/kurtosis. Two

regions (Frontal Medial Cortex, Subcallosal Cortex) had skewness or kurtosis values >2 and were log transformed. This resulted in skewness/kurtosis values ≤2.

Statistical Analyses

Raw data is available at http://www.ppmi-info.org. Multilevel models (MLMs) were used to analyze the association between IIV and volume of regions. All models were conducted in IBM SPSS version 25. Analytic plans were not pre-registered; output/syntax is available from the corresponding author upon request. A model was conducted separately for each cortical and subcortical region (Supplemental Table 1), resulting in 46 total models. Benjamini-Hochberg false discovery rate (FDR) adjustments were utilized to determine statistical significance and correct for multiple comparisons (Benjamini & Hochberg, 1995; Radua & Eizagirre, 2010). The dependent variables were the regions of interest volumes at baseline and the year 1 follow-up. Age at baseline, occasion (baseline or year 1 follow-up), motor severity, baseline ICV, baseline global cognition, baseline IIV and an IIV x occasion interaction were entered into models as predictors.

The above analyses were repeated with subcortical regions (accumbens, amygdala, caudate, hippocampus, pallidum, putamen and thalamus) entered as the dependent variable. Models were conducted separately for each subcortical region, resulting in seven models.

Results

For the current study, we queried individuals with PD who underwent T1 scans at both baseline and the first annual follow-up. From the initial pool of 487 participants with PD, the query resulted in a subsample of 80 participants. Demographic and clinical characteristics are displayed in Table 1. Individuals who underwent neuroimaging during the first two assessment had less education (mean difference = 1.5 years, $p<0.001$) relative to individuals who did not undergo neuroimaging, but there were no group differences (those with imaging vs. those without imaging) in age, motor severity, global cognition or IIV (Supplemental Table 2).

Intra-Individual Variability and Cortical Volume.

Analyses are summarized in Table 2. After FDR adjustment for multiple comparisons, the IIV X Occasion interaction term significantly predicted change in volume of the following regions: 1) temporal occipital middle temporal gyrus, 2) posterior supramarginal gyrus, and 3) planum temporale. The interaction term revealed that individuals with higher IIV at baseline experienced less preservation of cortical volume over the one-year period (Figure 1). Cortical volumes in these regions were also associated with older age and smaller intra-cranial volumes. Motor severity and global cognition were not statistically significant predictors.

No additional cortical regions were significantly predicted by either the main effect of baseline IIV or the IIV X Occasion interaction term.

Intra-Individual Variability and Subcortical Volume.

Analyses were repeated for subcortical volumes. Neither the main effect of baseline IIV, nor the interaction effect (IIV X Occasion) significant predicted any subcortical region following FDR-correction. There was a near-significant main effect of IIV (standardized estimate = −0.769; FDR-corrected $p = 0.117$) and interaction effect (standardized estimate = −0.639; FDR-corrected $p = 0.117$) predicting bilateral thalamic volumes.

Discussion

The present study supports IIV as a marker of neurologic disruption among individuals newly diagnosed with PD. Specifically, greater variability in neuropsychological performance at baseline was associated with cortical volume loss in posterior temporal-parietal regions over the first year of diagnosis. Additionally, IIV predicted cortical volume loss above and beyond motor severity and baseline global cognitive functioning.

Findings from the current study are consistent with past studies supporting the utility of IIV as a marker of early neurologic compromise among individuals with PD. Early cross-sectional studies showed greater IIV, as measured by inconsistency across attention/processing speed tasks, among individuals with PD relative to healthy controls (Burton et al., 2006; de Frias et al., 2007). Among individuals newly diagnosed with PD, greater IIV/dispersion across neuropsychological tests predicted increased risk of PD-MCI and PDD within 5-years of diagnosis (Jones et al., 2020). The current study expands upon the literature by demonstrating an association between IIV and structural cortical changes.

Past neuroimaging studies of individuals with HIV or Alzheimer's disease have generally conceptualized IIV as a measure highly influenced by frontal-executive functioning and frontal cortical-basal ganglia circuitry (Hines et al., 2015; Jackson et al., 2012; Jones et al., 2018). We are unaware of previous neuroimaging studies of IIV among individuals with PD. However, it is well-known that striatal dopamine depletion leads to disruption of frontal-basal ganglia circuitry, and this is traditionally considered an important mechanism of cognitive impairment in PD (Kehagia et al., 2013). Therefore, it would be reasonable to hypothesize that IIV would be associated with frontal cortical or subcortical areas among individuals with PD.

Interestingly, the current study found that IIV was associated with cortical volume changes in posterior temporal/parietal regions but not frontal-cortical or subcortical basal ganglia regions. This is consistent with the more recent appreciation that individuals with a "posterior" cognitive profile (e.g. impairments in semantic fluency or visuospatial functioning) are at risk for cognitive impairment, particularly early in the disease process (Williams-Gray et al., 2013; Kehagia et al., 2013). It may be worth considering that there is some heterogeneity in terms of when PD patients develop cognitive impairment. Longitudinal cohort studies have reported that roughly 20% of individuals with PD will develop PDD within the first five years of diagnosis, with the rate climbing to about 50% within 10 years, and 80% within 20 years of diagnosis (Hely et al., 2008; Williams-Gray et al., 2013). The development of dementia early versus late in the disease process may reflect heterogeneous mechanisms of cognitive impairment. Non-dopaminergic mechanisms

have been proposed to be particularly key mechanisms of dementia early in the course of PD. Among individuals newly diagnosed with PD, degeneration of cholinergic pathways projecting from the basal forebrain to posterior temporal/parietal regions predicted early cognitive impairment (Barrett et al., 2019; Pereira et al., 2020). In a 10 year longitudinal cohort study of individuals newly diagnosed with PD, dementia was predicted by genes (MAPT) important for the regulation of tau, but not genes (COMT) involved in dopamine regulation (Williams-Gray et al., 2013). Post-mortem findings have also suggested that Alzheimer pathologies (neuritic Braak stage, cortical amyloid plaque load, and cerebral amyloid angiopathy) more robustly differentiate PDD from non-dementia PD patients (Jellinger & Attems 2008; Horvath et al., 2013). Overall, a hypothesis that IIV is a neuropsychological marker of non-dopaminergic mechanisms of cognitive impairment early in PD would be a reasonable integration of the current finding with the existing knowledge base. IIV may be less sensitive to frontal-basal ganglia disruption secondary to striatal dopamine depletion in early PD. However, future studies consisting of individuals with longer disease duration are needed to determine if IIV is a marker of frontal-basal ganglia disruption in later stages of PD.

More specifically than a frontal vs posterior pattern of cognitive impairment, the current study found that IIV was associated with volume reduction in the temporal occipital middle temporal gyrus, posterior supramarginal gyrus and planum temporale. A study by Melzer et al. (2011) found lower grey matter volumes in various temporal regions, including the planum temporale, among PD patients with cognitive impairment (PD-MCI or PDD). Similarly, separate studies showed that transition from cognitive intact to PD-MCI was associated cortical thinning in the supramarginal gyri (Filippi et al.; 2020) and the middle temporal gyrus (Tard et al., 2015). These studies provide evidence that the three significant regions (temporal occipital middle temporal gyrus, posterior supramarginal gyrus and planum temporale) associated with IIV in the current study may indeed be important for cognitive functioning in PD. However, they do not address the question of why these regions are important for response variability or IIV. IIV has traditionally been viewed as reflecting frontal-subcortical networks important for self-monitoring and other aspects of executive functioning. This raises the question of why temporal-parietal regions are associated with IIV in the current study. One speculation is that learning/memory tests and language (verbal fluency) tests account for half of the cognitive measures administered. Therefore, impairments on these tests but relatively intact performance on other tests would lead to higher IIV and thus a positive association with the three significant regions. Ultimately, future studies utilizing a more complete cognitive battery, including measures of executive functioning, would be best suited to explore neural correlates of IIV.

The finding that IIV predicted cortical volume loss independent of global cognitive functioning is consistent with past studies examining clinical outcomes in PD, and neuroimaging outcomes in other neurologic populations (Anderson et al., 2018; Jones et al., 2020; Jones et al., 2018). Considering the PD population, IIV was previously shown to predict risk of cognitive impairment above and beyond a global cognition composite/average score and performance of any individual neuropsychological measure (Jones et al., 2020). This pattern of findings suggest that IIV may represent a unique and separate construct that is not fully captured by traditional neuropsychological metrics. Additionally, the

significant interaction term (IIV X occasion) in the context of an insignificant main effect of IIV suggests that IIV may be of greater utility for identifying future risk of neurologic compromise in the early years of PD, rather than a marker of concurrent neurologic health that is likely influenced by both the early PD process and pre-existing conditions.

Limitations were present in the current study. The sample consisted of newly diagnosed PD patients. Although this provides a unique and clinically important opportunity to study early predictors of cognitive impairment, findings may not generalize to later stages of PD. Similarly, the sample is predominantly Caucasian and findings may not generalize to more diverse samples. The neuropsychological battery utilized in the parent study (PPMI) was limited in tests of executive functioning. The battery of cognitive tests does assess certain constructs that are commonly subsumed under the term executive functioning (i.e. semantic fluency, working memory), but other aspects of executive functioning were not assessed (e.g. set-shifting, letter fluency, behavioral inhibition, problem solving). Due to relatively limited sample size and strict correction for multiple-comparisons, the current study included age but excluded other demographics (gender or education) in the statistical models. To the best of our knowledge, gender and education have either not been included or were non-significant predictors of past studies of IIV among individuals with PD (Burton et al., 2006; Jones et al., 2020) or imaging studies of IIV from other populations (Hines et al., 2016; Jones et al., 2018; MacDonald et al., 2009; Madden et al., 2009. The lack of thorough measures of executive functioning may contribute to the null findings of an association between IIV and frontal cortical regions. The current study was underpowered to statistically covary for differences in the study site (10 separate study sites). There may be minor differences between study sites/scanners that may potentially confound the current results. However, one past study of the PPMI cohort failed to find significant differences in grey matter volumes as a function of the research site/scanner (Schulz et al., 2018). The current study utilized a cortical and subcortical structural volume to operationalize neurologic health. Additional neuroimaging approaches (voxel-based measures, cortical thickness, diffusion or functional imaging) could potentially provide valuable contributions/findings regarding the neuroanatomical mechanisms of IIV among individuals with PD. Future investigation is encouraged.

Overall, findings support the utility of IIV as an early cognitive marker of neurologic compromise in PD. Due to the limited amount of research, particularly among individuals with PD, IIV has been an underutilized metric of cognitive functioning both in research and clinical practice. However, evidence is building that IIV is a sensitive marker of neurologic compromise across various populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Availability of data:

data is available at ppmi-info.org.

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Key Points

Questions:

Does Intra-individual Variability (IIV) predict longitudinal volumetric changes among individuals with Parkinson's disease?

Findings:

Baseline IIV predicted cortical volume loss in posterior regions following the first year of diagnosis.

Importance:

Evidence is building that IIV is a sensitive marker of cognitive impairment and the underlying neurodegeneration among individuals with Parkinson's Disease.

Next Steps:

Examine if utilization of IIV is associated with positive outcomes in clinical settings.

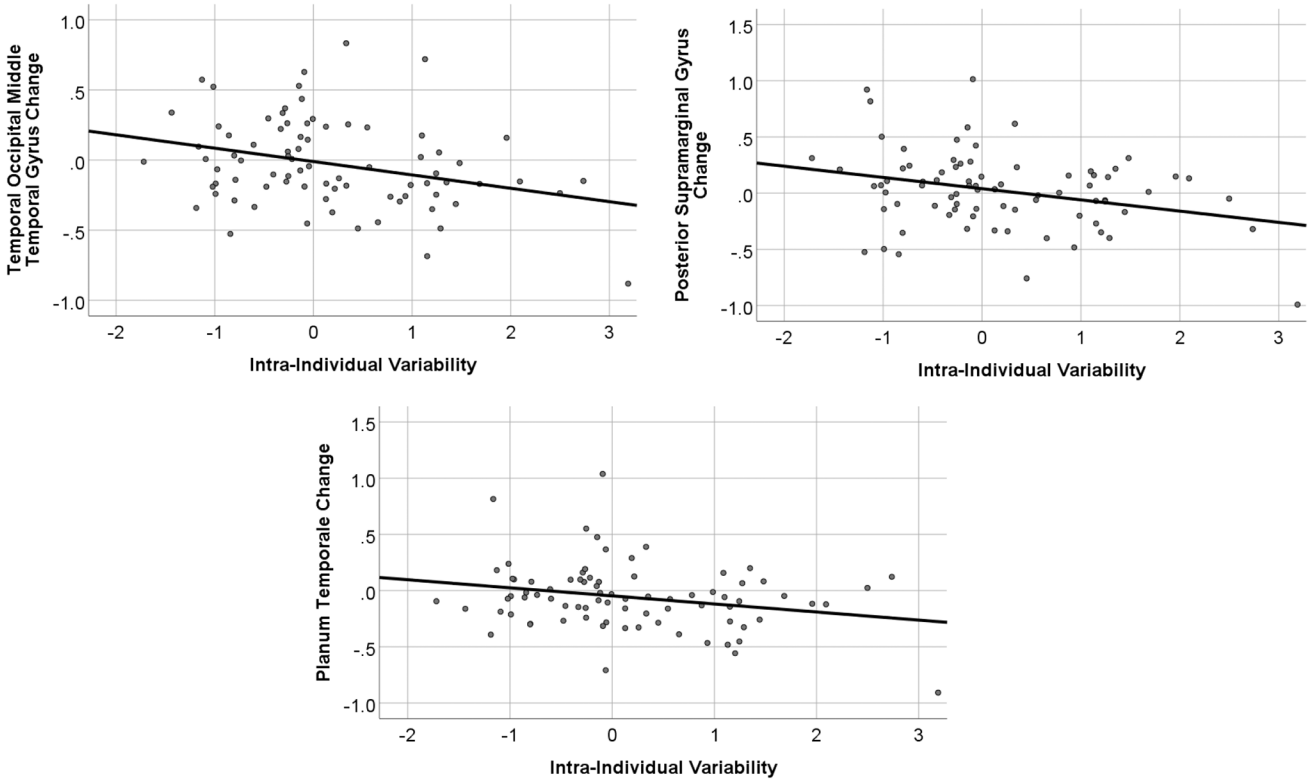

Figure 1.

Association between Cortical Volume Change and Intra-Individual Variability (IIV) at Baseline. All variables displayed in a z-score metric. The y-axis depicts change in volume of the region of interest (time 2 – time 1). Regional volume was entered as time-varying data, the change score was calculated solely for the purpose of depicting IIV X Occasion interaction effect.

Table 1.

Baseline Characteristics (n=80)

	Mean	SD	IQR
Age	59.9	9.7	54 – 68
Education	14.3	3.2	14 – 18
% Male	68.8%	--	--
% Caucasian	97.5%	--	--
UPDRS-III Motor	19.5	8.2	13 – 25
% Hoehn Yahr Stage 1	47.5%	--	--
% Hoehn Yahr Stage 1	52.5%	--	--
LED	304	230	152 – 396
IIV (Z score)	1.0	0.4	0.7 – 1.2
Global Cognition (Z score)	0.02	0.6	−0.36 – 0.38

SD = Standard deviation; IQR = Inter-Quartile Range; UPDRS = Unified Parkinson's Disease Rating Scale- part III; LED = levodopa equivalency dose; IIV = Intra-Individual Variability.

Table 2.

Intra-Individual Variability Predicts Regional Cortical Volumes.

	Temporal Occipital Middle Temporal Gyrus			Posterior Supramarginal Gyrus			Planum Temporale		
	Standardized Estimate	**SE**	***p***	**Standardized Estimate**	**SE**	***p***	**Standardized Estimate**	**SE**	***p***
Age	−0.30	.07	0.003	−0.40	.09	0.001	−0.38	.09	0.002
Motor Severity	−0.05	.06	0.628	−0.09	.06	0.312	−0.06	.06	0.553
ICV	0.26	.06	0.001	0.24	.07	0.005	0.05	.06	0.670
Global Cognition	0.09	.06	0.551	0.10	.10	0.553	0.14	.10	0.365
Occasion	−0.01	.06	0.951	0.10	.06	0.294	−0.10	.05	0.193
IIV	−0.05	.09	0.761	−0.12	.11	0.523	−0.07	.10	0.716
IIV X Occasion	−0.19	.05	0.009	−0.17	.06	0.036	−0.14	.05	0.050

P values are adjusted with Benjamini-Hochberg false discovery rate. SE = standard error; ICV = intracranial volume; IIV = intra-individual variability.