Published in final edited form as:

J Parkinsons Dis. 2016 May 05; 6(2): 441–451. doi:10.3233/JPD-150753.

Cortical Implications of Advancing Age and Disease Duration in Parkinson's Disease Patients with Postural Instability and Gait Dysfunction

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Abstract

Background—Parkinson's Disease patients with predominant gait dysfunction appear to have reduced cortical thickness compared to other motor phenotypes. The extent to which advancing age or disease duration impact the pattern of these distinctions is unclear.

Objective—We examine if PD patients with predominant signs of postural instability and gait dysfunction are distinguished by distinct patterns of cerebral atrophy, and how these differences are influenced by age and disease duration.

Methods—The Unified Parkinson's Disease Rating Score (UPDRS) was administered to 196 PD patients (age = 61.4 ± 8.9 yrs) in the *Off* and *On* dopamine state. All completed a structural T1-weighted brain MRI. We defined 3 motor phenotypes: tremor dominant, akinetic-rigid, and postural instability with gait disorder. General linear modeling quantified cortical thickness in relation to disease duration, and motor improvement after dopaminergic therapy. Cortical thickness and subcortical volumes were compared between the three motor subtypes, after controlling for disease duration and age.

Results—We identified 177/196 patients who met criteria for a motor subtype. When corrected for disease duration, postural-instability patients had marked cortical thinning of the bilateral

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SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: <http://dx.doi.org/10.3233/JPD-150753>.

CONFLICT OF INTEREST

The authors have no relevant conflicts of interest to report and no other relevant financial relationships to disclose other than listed.

frontal-temporal and posterior cortical regions (cuneus/precuneus). After regressing for age, reduced frontal thickness was evident in patients with gait dysfunction. Widespread cortical thinning was associated with increasing disease duration and reduced motor improvement to dopaminergic therapy.

Conclusions—Results emphasize that the profile of motor signs, especially prominent gait manifestations, relate to cortical thinning in distinct regions. Unique patterns of atrophy appear to be driven by advancing pathology related to age and disease duration.

Keywords

Parkinson's disease; MRI; gait disorders; PIGD; tremor dominant; motor phenotypes

INTRODUCTION

Motor and cognitive symptoms in Parkinson's disease (PD) patients are more severe in older patients with long disease duration, where the emergence of progressive gait impairment and loss of postural reflexes is one such hallmark of advancing disease severity [1, 2]. Patients with predominant gait problems are phenotypically described as having “postural instability with gait disorder (PIGD) [1].” This clinical characterization emphasizes gait instability as the predominant (albeit not sole) motor sign, and is distinguished from other motor phenotypes such as tremor dominant (TD), akinetic-rigid (AR), and mixed presentations (in which a preeminent manifestation cannot be clearly distinguished) [3]. The dissociation of motor phenotypes is clinically important as accruing evidence suggests differential disease course, response to medication, and vulnerability to cognitive dysfunction [4–6]. For example, rigidity and tremor are highly responsive to alterations in the timing, amount, or type of dopamine therapy, but gait signs such as freezing and falls are most often unresponsive to alterations in dopaminergic therapies, associated with a more rapid disease course, and accompanied by more severe cognitive changes [2, 7].

Advancing age and disease duration are key to contributors to advancing symptomatology in PD. In particular, gait dysfunction is a result of progressive neurochemical and neuropathological changes that arise in older patients with longer disease duration. For instance, dopamine and cholinergic dysfunction, more evident in patients with longer duration of disease, manifests as gait instability, and is associated with the onset of PD related dementia [8, 9]. Additionally, neocortical β -amyloid deposition in the frontal, temporal, and posterior parietal areas is more common with advancing age, and is associated with greater severity of gait disturbances in PD [10]. Thus, one of the challenges in interpreting pathologic progression of PD patients with gait problems is that the proposed patterns of atrophy in anterior and posterior cortical regions may be a consequence of either accelerating age or disease duration [11].

Since patients defined as PIGD have a more rapid transition to dementia, increased presence of visual hallucinations, and increased rates of morbidity [5], we set out to define the location and magnitude of cortical distinctions between PIGD and other phenotypes, such as AR and TD, and determine how advancing age and disease duration influenced these phenotypes. We assessed regional cortical thickness differences across a large, well-

characterized, cohort of PD patients who were evaluated in both the Off and On dopamine state [12]. As cortical thinning is primarily responsible for reductions in gray matter volume [13], we took advantage of advancements in quantitative neuroimaging techniques that allow for increasingly precise measurements of cortical thickness. We determined whether disease duration and responsiveness to dopamine medications are associated with regional differences in cortical thickness. The purpose of our study was to test the hypothesis that motor phenotypes in PD are associated with regional distinctions in cortical thickness, where patients with PIGD will manifest a thinned cortex, as compared to AR and TD motor phenotypes.

METHODS

Clinical severity and motor subtype classification

This was a retrospective study that included PD patients evaluated between 2004 and 2013. All patients ($n = 196$, mean age = 61.4 ± 8.9 years) underwent a standardized clinical and motor examination during the pre-evaluation for deep-brain stimulation (DBS). All met UK Brain Bank Criteria for diagnosis of PD [14], and as part of the motor assessment, a UPDRS part III [15] was obtained in both the Off and On dopamine state by a single examiner and videotaped for reference. The On examination was performed in the optimal dopaminergic medication state, and Off examination was performed 12–16 hours (overnight withdrawal) post-dopaminergic medication administration. To account for disease severity, we determined disease duration (defined as the time from first motor signs to present exam, in years), UPDRS improvement from dopamine therapy (UPDRS part III Off – UPDRS part III On dopamine therapy), and levodopa equivalent daily dose (LEDD) [16]. The Vanderbilt Institutional Review Board approved the study.

Patients who met predetermined criteria for 1 of the 3 motor subtypes in the Off condition were included: Tremor dominant (TD), Akinetic-Rigid (AR), or Postural Instability with Gait (PIGD). Subtypes were defined based upon previous methods in Jankovic (1990) and Schiess (2000) [1, 3], using a formula incorporating essential elements of part III of the UPDRS: Tremor score (T) (mean of items 20 and 21), postural-instability and gait (P) (mean of items 27, 29, and 30), and akinesia-rigidity (A) (mean of items 22 and 31) [15]. To meet criteria for AR, both the A/T and A/P ratios were ≥ 1.5 . If either ratio was < 1.5 , the T/P ratio was used to determine TD or the PIGD subtype status. If T/P was ≥ 1.5 , the patient was classified as TD, while if it was < 1.0 the patient was placed in the PIGD subtype (see Table 1 for details of categorization). At the time of the motor exam, the UPDRS part III was used and not the newer MDS-UPDRS. Therefore, newer subtype classifications based on the MDS-UPDRS could not be performed.

Cognitive assessment

All patients underwent a standard neuropsychological battery within 90 days of the motor assessment as part of the DBS evaluation. The battery of tests is listed in Supplementary Table 1 and includes a global measure of function (Dementia Rating Scale) along with measures of executive function, attention, visuospatial function, memory, and language. References for these assessments are included in Supplementary Table 1. A scaled score was

recorded based on age and education norms, from 0–20, with 10 being the mean for a given age and education level. To determine if cognitive distinctions were present, we use a multivariate analysis of variance (MANOVA), and specific contrasts to determine if significant cognitive differences were present amongst motor subtypes (TD and AR were contrasted with PIGD).

Sedated MRI acquisition

As part of the DBS clinical protocol, all patients were anesthetized before the brain MRI to avoid discomfort from placement of the bone markers. Because of this, an absence of movement artifact in the brain MRI was considered an added benefit, but not the primary reason sedation was performed. Propofol was given to induce general anesthesia, and maintained using Sevoflurane during the entire procedure with an MRI-compatible anesthesia machine. Standard monitoring consisted of a five-lead ECG, noninvasive blood pressure, pulse oximetry and end-tidal CO₂ monitoring throughout the entire protocol. Variations in end-tidal CO₂ were minimized, and while it is possible that sedation could alter brain volume, all patients completed similar sedation protocol. The UPDRS evaluation occurred on a different day from MRI evaluation (at least 2 weeks in advance of MRI), thus the effects of sedation did not influence UPDRS score.

MRI scanning was performed on a 3T Philips Achieva scanner (Philips Medical Systems, Best, The Netherlands) using body coil transmission and eight-channel SENSE head-coil reception. Structural imaging was performed using a 3D T₁-weighted Magnetization-Prepared-Rapid-Gradient-Echo acquisition with spatial resolution = $1 \times 1 \times 1 \text{ mm}^3$, slices = 170, TR/TE = 7.92/3.65 ms.

Cortical thickness measurements

Cortical thickness was assessed using FreeSurfer (Version 5.3.0, <http://surfer.nmr.mgh.harvard.edu/>). The MRI anatomical brain images were preprocessed by performing intensity normalization and skull stripping. The extracted brain was then segmented into gray matter, white matter, and sub-cortical structures. The choice of imaging parameters closely matched the FreeSurfer recommended parameters and Han et al. showed that with these parameters, segmentation inaccuracies are minimal and do not affect study outcome [12]. Each subject's data was registered to the standard FreeSurfer brain (fsaverage). FreeSurfer provides a unique advantage of inflating the cortex, allowing larger surface-based smoothing kernels of full-width-half-maximum = 15 mm to be applied without any smearing effects across adjacent sulci and gyri. Cortical thickness was measured in 75 brain regions per hemisphere as defined by the Destrieux Atlas [17].

General linear modeling analysis

Our statistical approach incorporated a generalized linear modeling (GLM) regression-analysis in FreeSurfer using contrast matrices. Brain regions with significant ($p < 0.05$) correlation between the main effect and cortical thickness were recorded using the annotations already available in FreeSurfer. Cluster-wise correction ($p < 0.05$) for multiple comparisons was performed to determine regions with significant differences in cortical thickness using Monte-Carlo simulations in FreeSurfer with 10,000 iterations. Bonferroni

correction was implemented to account for separate comparisons across the two brain hemispheres. Mean cortical thickness and effect sizes for each cluster (using the gamma.mgh and rst.d.mgh maps in FreeSurfer) are reported.

The relationship between disease duration, defined as years from first motor signs to MR scan, and cortical thickness was determined using a covariate analysis within a generalized linear model statistical approach. The relationship between cortical thickness and motor improvement on dopamine therapy was assessed using similar procedures. Improvement on dopamine therapy was calculated as the change in UPDRS score (*Off*- *On* state), and correlated to cortical thickness. Region-wise differences in cortical thickness were evaluated between motor phenotypes defined in *Off* dopamine state. All group comparisons were first corrected for disease duration alone. Comparisons were then repeated with corrections for age alone.

Subcortical volume measurements

Subcortical volumes were measured using FSL's model-based segmentation and registration tool, FIRST. Deformable shape models were used to parameterize the subcortical volumes based on prior manual segmentations. To account for varying head sizes, the total intracranial volume (ICV) was calculated using FreeSurfer (eTIV), which includes the total gray matter, white matter, and CSF volumes. Before comparison, the subcortical volume of each subject was normalized using the respective intra-cranial volumes. Statistical comparison included a two-side *t*-test between each group, corrected for multiple comparisons for multiple regions and groups. Eleven subjects failed registration, and were therefore not included in the group comparison.

RESULTS

Clinical characteristics of motor subtypes

In the acute dopamine withdrawn (*Off*) state, 177/196 patients met criteria for one of three motor subtypes: PIGD ($n = 74$), AR ($n = 58$), and TD ($n = 45$). Clinical characteristics of this cohort are summarized in Table 1. PIGD patients had longer disease duration (12.1 years, versus 9.5 (AR) and 9.4 years (TD)), were slightly older at imaging and motor assessment (63.7 versus 61.5 AR and 60.0 TD), and had a larger UPDRS Off score. As expected, we found a strong correlation between the age of assessment and length of disease duration ($r = 0.29$, $p < 0.0001$).

Cognitive differences between motor subtypes

No significant differences were observed in the age and education normed Dementia Rating Scale (DRS) values (50th percentile score = 10). Data for DRS scores was not available in 29 patients as they were under the age of 55, and at the time of testing, age and education norms were not available for this age bracket. Supplementary Table 1 shows results from more extensive and focused neuropsychological assessments. All groups had a mean scaled score within 1 standard deviation of age and education level. In addition, no significant differences were seen between the subtypes, $F(28, 324) = 1.33$, $p = 0.127$ (not shown in table). Paired contrasts illustrated differences between PIGD patients in Picture Completion

and Word List 1. PIGD patients performed slightly lower in picture completion compared to TD patients (9.5 $\pm$ 2.7 versus 10.6 $\pm$ 3.3, $p = 0.04$), and lower than AR patients in Word List 1 (8.3 $\pm$ 3.6 versus 9.6 $\pm$ 3.2) $p = 0.03$. Of note, none of these contrasts survived the test for multiple comparisons, and the mean scores did not reach clinical criteria for MCI, as defined by greater than 1 standard deviation from normal (i.e. less than a scaled score of 7). Thus, conventional neuropsychology testing did not identify clinically meaningful distinctions between motor subtypes.

Cortical thinning correlations: Disease duration and dopamine therapy

Due to the finding that PIGD patients had longer mean disease duration, we tested the correlation between cortical atrophy and duration (time in years) of motor symptoms. Figure 1a displays the FreeSurfer GLM analysis results. Increasing disease duration was associated with significant widespread cortical thinning ($p < 0.0005$) in frontal, temporal, parietal, and occipital areas.

Since motor improvement *On* dopamine varied amongst patients, we assessed the relationship between UPDRS improvement and cortical thickness. Figure 1b displays areas of cortical thinning that correlate with the difference in UPDRS scores between medication states (*Off-On*). Smaller improvements in UPDRS scores were significantly associated ($p < 0.005$) with thinner prefrontal, temporal pole, occipital, primary motor, and primary sensory cortices. Of these, three major clusters of cortical thinning were weakly but significantly associated with smaller motor improvements: Left temporal-motor ($R = 0.19$, $R^2 = 0.038$), left lateral occipital ($R = 0.13$, $R^2 = 0.016$), and right motor cortex ($R = 0.19$, $R^2 = 0.038$).

Cortical thickness and motor subtypes

Imaging analysis identified group differences based on the motor phenotype classification, first after accounting for disease duration effects on cortical thickness. The largest cortical differences were between the PIGD and AR phenotypes (Fig. 2a), where PIGD patients have reduced cortical thickness in distinct regions: Substantial portions of the bilateral frontal lobes ($p < 0.0005$), superior parietal cortices ($p < 0.005$ left hemisphere, $p < 0.05$ right hemisphere), and posterior cortical regions (cuneus/precuneus, occipital) ($p < 0.005$). Both mean cortical thickness and mean effect sizes are outlined in detail in Table 2. Cortical cluster mean effect size differences ranged from 0.82 to 0.93, emphasizing the robust distinctions between these groups. Between PIGD and TD, similar regional distinctions were evident, notably the dorsolateral frontal lobes ($p < 0.05$), anterior temporal lobes ($p < 0.05$), and cuneus/precuneus ($p < 0.005$). Despite the smaller number of cortical clusters, mean effect sizes were large and ranged from 0.6 to 0.88. No cortical distinctions were seen between AR and TD groups.

Since advancing age is a risk factor for cortical thinning, we also assessed cortical differences between motor subgroups, controlling for age. Given a strong correlation between advancing age and disease duration, cortical differences would likely be less extensive than those described when controlling for disease duration alone, but illustrate which regions were more susceptible to age-effects in PD. We found that after controlling for age, cortical differences were most prominent between PIGD and TD patients, and

localized to the left frontal region (TD was greater than PIGD, $p < 0.005$; Fig. 2b). Furthermore, the effect size between TD and PIGD was remarkably high, at 3.12 (Table 2). No differences were evident between AR and PIGD, or TD and AR groups.

Subcortical volumes between motor Subtypes

Table 3 outlines the bilateral subcortical volumes for the thalamus, caudate, putamen, pallidum, hippocampus, amygdala, and nucleus accumbens. The average ICV for each group are also noted in this table. No significant subcortical differences were observed between the motor-subtypes of Parkinson's disease. Although not significant ($p = 0.07$ – 0.48), the TD group showed a trend for higher subcortical volumes than AR and PIGD. This observation mirrors the cortical thickness comparisons, where the TD group had higher cortical thickness compared to the PIGD group. In addition, disease duration showed poor correlation with subcortical volume: (Thalamus, $R = -0.03$; Caudate, $R = -0.01$; Putamen, $R = -0.01$; Pallidum, $R = 0.005$; HF, $R = 0.08$; Amygdala, $R = 0.07$; Nucleus Accumbens, $R = 0.12$).

DISCUSSION

Over the course of PD, patients often require an increasing daily dose of dopaminergic medications, and suffer from progressive midline motor signs, postural instability, and gait impairment. Here we evaluated the cortical thickness distinctions between PIGD and other motor subtypes in PD, and how these distinctions are driven by age or disease duration. After controlling for disease duration effects on cortical thinning, distinctions between PIGD and other motor subtypes were most prominent in anterior and posterior cortical regions, notably the bilateral dorsolateral frontal, and posterior parietal/occipital lobes. After controlling for age, left frontal cortical thickness was reduced in those patients classified as PIGD. In addition, we show that thinner cortices are associated with decreased motor improvement (UPDRS part III) with dopamine therapy. These results suggest that while cortical atrophy is greater in PD patients with predominant gait impairment, the neuropathological process arising from advancing disease duration and age-related effects differentially determine the location and extent of these cortical differences.

Cortical atrophy in PD is characteristic of advancing disease severity and progression [18], yet disease duration versus age-related effects on cortical thinning are poorly disassociated. Gray matter volume reduction in PD is linked to advancing manifestations of PD, such as cognitive impairment and dementia [19–24], and recent findings emphasize what appears to be a PD-specific pattern of decreasing anterior (frontal-temporal), and posterior cortical thickness. Even after controlling for disease duration, study results replicate a similar pattern of alterations to cortical thickness localized to the prefrontal, temporal, parietal, and cuneus/precuneus in PIGD phenotypic patients. Significant cortical clusters are consistent with prior work, where PIGD patients showed reductions in gray matter density in cuneal, cingulate, temporal, and frontal regions [25]. Importantly, other studies relate regional gray matter atrophy to gait disturbances in PD. Specifically, cuneus, precuneus, inferior parietal, and frontal atrophy correspond to freezing of gait symptoms in PD [26, 27].

One possible explanation for cortical differences in this cohort is that the groups differ based on cognitive dysfunction. Cortical thinning occurs as part of the normal aging process, and is generally not associated with cognitive decline [28, 29]. In PD, however, there is a known association between the PIGD subtype and worsening cognitive decline [1–6]. We found no significant cognitive differences between motor subtypes with an extensive neuropsychological battery. PIGD patients show a trend for lower scores on visual spatial integration, and executive function, and this seems to agree with the localization of cortical distinctions between these groups. Nonetheless, cognitive differences do not explain cortical differences seen in the imaging comparison. These results suggest conventional neuropsychological tools may fail to clinically differentiate PIGD patients, which may be due to the particular neuropsychological battery used in the clinical evaluation of these patients. More specific cognitive tests (for example, cognitive control tasks associated with deficiencies in the fronto-striatal network) may prove more sensitive in capturing cognitive distinctions in patients with PIGD. Selection bias may also play a role in our finding of no significant cognitive differences between subtypes. Since cognitive dysfunction is a contraindication to DBS surgery, only those with intact cognitive function may have been referred, therefore biasing the PIGD population towards normal cognitive function on average.

Cortical thinning in PD could be attributed to diverse etiologies, such as reductions in synaptic density or the presence of neuropathologic changes such as cortical Lewy Body and amyloid deposition, yet few studies have shown dissociable regional cortical differences in distinct motor phenotypes of PD. Based on the patterns of cortical differences between PIGD and other motor phenotypes, progressive neuropathologic changes may also contribute to regionally specific reductions in cortical thickness, along with associated clinical phenomena [30]. Regions that correlate with advancing disease duration replicate the proposed pattern of Lewy Body progression, with exception to the anteromedial temporal mesocortex [31]. Also, the distribution of cortical amyloid deposition mirrors regional differences that are associated with increased severity of midline motor manifestations [10].

We speculate that a combination of various neuropathological and neurochemical changes ultimately manifest with cortical changes evident in patients with postural instability and gait dysfunction. This process may begin with progressive monoamine and cholinergic dysfunction, and then accelerate with advancing extra-nigral lewy body and amyloid deposition. Progressive cholinergic deafferentation is linked to the posterior cortical differences in PIGD patients [8, 32, 33], while monoaminergic deafferentation may account for more anterior cortical distinctions (particularly prefrontal and temporal cortical thinning [33]). Poorly myelinated, long projection neurons are most susceptible to alpha-synuclein pathology [34]. These neurons include brainstem nuclei with diffuse cortical monoamine and cholinergic projections (e.g. ventral tegmental area, locus coeruleus, pedunculopontine nucleus, and the nucleus basalis of Meynert (nBM); all of which are involved in early stages of PD) [31]. Cortical projections from these nuclei innervate prefrontal, limbic, subcortical, and posterior cortical structures. The longest cholinergic axons extend from the nBM to the posterior cortical regions, including the cuneus, and these show the most severe and the earliest cholinergic denervation in PD [35, 36]. Cholinergic deficits emerge early in the course of PD and the cortical areas that we found to be more atrophic in the PIGD motor

subgroup receive robust cholinergic projections from the basal forebrain [36, 37]. However, this process may indeed be related to distant aging effects in certain PD populations. While we did not see clear subcortical distinctions between motor subtypes, there was a trend for greater subcortical atrophy in PIGD patients. Additional analysis of white matter tracts (e.g. Diffusion Tensor imaging) may illustrate additional structural changes associated with other motor phenotypes. We suspect that degeneration of cholinergic and monoaminergic projection neurons may in part account for the distinct pattern of cortical atrophy, with additive effects from extra-nigral Lewy Body and amyloid deposition, but additional studies are needed to test this hypothesis.

Since age and disease duration are inherently correlated, additional studies are needed to determine the trajectory of PD related cortical regions susceptible to increasing disease duration, independent of age [38]. Recent studies emphasize that age related cortical thinning is localized to the frontal, temporal, precentral and postcentral regions at a maximum rate of ~ 0.045 mm/decade [13, 39, 40]. Age related cortical changes might contribute to observed differences in PD patients. However, our study shows cortical thickness differences ranging from 0.03–0.12 mm. Given that the maximum age difference between groups is slightly less than 4 years, age alone cannot account for the observed cortical differences. When we control for age, temporal and posterior cortical differences that distinguish PIGD from other motor subtypes are not evident. This suggests that the aging process in PD may account for most of the temporal and posterior cortical changes described in patients with predominant midline motor signs. This would also agree with the recent PATH Through Life Study that examined longitudinal, as opposed to cross-sectional, cortical thinning in healthy controls [41]. They study patients in their 60's (similar to our mean age) and found significant age-related thinning (mean -0.3% per year) in heteromodal association cortices. Given the known association of advancing age with amyloid deposition [42] and acetylcholine denervation [43], the aging PD brain may be susceptible to faster rates of cortical atrophy in certain cortical regions. We recently reported data supporting this hypothesis [44]. When considering age-related changes, sub-regions of the frontal (pars opercularis), temporal (middle temporal gyrus, fusiform gyrus), parietal (precuneus), and occipital (lingual gyrus) regions appear to be susceptible to a non-linear, early decline course of atrophy in PD when compared to a linear decline in these areas in healthy controls. In sub-regions where PD patients and healthy controls both had linear rates of decline, steeper slopes of decline were seen in PD patients. In addition, advancing age and disease duration showed synergistic effects in PD, with older patients with longer disease duration showing the fastest rates of atrophy in frontal, temporal, and parietal sub-regions [43]. Future studies could determine how these patterns of atrophy in PD differ between specific motor subtypes and healthy controls.

The main limitation of this study was the inclusion of patients who presented for DBS surgery. While this may bias results to include patients with more severe motor signs, it likely explains why the majority of patients could be classified into defined motor subgroups. It may also explain the lack of cognitive differences between motor subtypes, as cognitive decline is a contraindication for DBS. Overall, our results further emphasize the role of frontal cortical changes in patients classified as PIGD. Recent data suggests cortical thinning begins early in disease progression, and early pathology of cortical afferents is

consistent with this observation [23]. Future studies are needed to determine if PIGD is an inevitable phenotype of PD, or represents a subset of PD. Cortical changes may prove a reliable quantitative biomarker of disease progression, and regional patterns of cortical involvement may predict emerging cognitive and motor phenotypes. Indeed, if postural instability and gait dysfunction are phenotypes of advancing PD and cortical atrophy, disease-modifying interventions in PD may be measured by time to gait dysfunction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank Ms. Lauren Griffin for assistance in compiling patient records for this study.

Study funding: Supported by R01-EB006136 to B.D., R01-NS078828 to M.J.D, K23-NS080988 to D.C., and the Ramie Tritt Family Foundation to J.H. and D.C.

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Fig. 1. Cortical thickness maps emphasizing cortical relationships with increasing disease duration and reduced motor response to dopamine therapy. (a) Areas of significant inverse correlation between disease duration and cortical thickness. (b) Areas of significant correlation between decreased motor response to dopamine therapy (UPDRS On – UPDRS Off) and decreased cortical thickness.

Fig. 2.

Cortical thinning distinguishes PIGD from other motor phenotypes in the *Off* Dopamine state. (a) Corrected for disease duration: When defining motor phenotypes in the *Off* dopamine state, widespread cortical distinctions separate PIGD ($n = 74$) from the other phenotypes (AR $n = 48$ and TD $n = 55$). Yellow: $p < 0.0005$, orange: $p < 0.005$, red: $p < 0.05$. (b) Corrected for age: Cortical distinctions in the frontal lobe separate PIGD ($n = 74$) from the TD ($p < 0.005$). No significant differences were observed between PIGD and AR phenotypes or between AR and TD phenotype.

Table 1

Patient Demographics of Motor Subtype Groups

	PIGD (<i>n</i> = 74)	Akinetic-rigid (<i>n</i> = 58)	Tremor dominant (<i>n</i> = 45)	Statistic
Age at Diagnosis	51.7 (10.1)	52.0 (9.2)	50.6 (9.3)	N.S.
Age at Assessment*	63.7 (8.8)	61.5 (9.0)	60.0 (9.2)	$F(2, 176) = 2.87, p = 0.06$
Disease Duration*	12.1 (6.9)	9.5 (4.3)	9.4 (4.1)	$F(2, 176) = 4.94, p < 0.01$
LEDD*	1310 (585)	1068 (558)	1121 (494)	$F(2, 176) = 3.32, p < 0.01$
UPDRS <i>Off</i> *	44.5 (13.5)	38.7 (13.7)	37.6 (10.4)	$F(2, 176) = 5.63, p < 0.005$
UPDRS <i>On</i> *	20.7 (10.8)	18.4 (9.9)	15.6 (7.7)	$F(2, 176) = 4.55, p < 0.012$
UPDRS Change	23.9 (10.0)	20.2 (11.5)	22.1 (10.0)	N.S.
DRS Scaled Score [range]	11.8 (2.5) <i>n</i> = 65; [5–15]	11.9 (2.6) <i>n</i> = 36; [4–15]	12.2 (2.4) <i>n</i> = 47; [4–15]	N.S.

Demographic and Disease characteristics of motor subtypes in the *Off* dopamine state. Mean (Standard Deviation). Significant ANOVA results are marked with an * (N.S.: Not Significant). DRS Scaled score is from 1–20, with 10 being a 50% age and education norm. Note, age and education norms were not available for patients <55 years of age. (LEDD: Levodopa equivalent daily dose, UPDRS: Unified Parkinson's Disease Rating Scale, DRS: Dementia Rating Scale).

Table 2

Quantified cortical thickness reduction in PIGD versus other motor subtypes

Group	Comparisons	Clusters in the left hemisphere			Clusters in the right hemisphere		
		Region	Thickness mm (mean $\pm$ sd)	Effect Size	Region	Thickness mm (mean $\pm$ sd)	Effect Size
Corrected for disease duration only	AR PIGD	Middle frontal	2.33 $\pm$ 0.19	0.84 $\pm$ 0.11	Lateral frontal	2.04 $\pm$ 0.16	0.82 $\pm$ 0.16
			2.27 $\pm$ 0.15			2.01 $\pm$ 0.15	
		Superior parietal-occipital	2.19 $\pm$ 0.16	0.93 $\pm$ 0.19	Occipital	2.15 $\pm$ 0.15	0.82 $\pm$ 0.25
	TD PIGD	Inferior frontal	2.12 $\pm$ 0.15	0.84 $\pm$ 0.12	Fronto-medial	2.08 $\pm$ 0.14	0.96 $\pm$ 0.31
			2.29 $\pm$ 0.18			2.50 $\pm$ 0.19	
			2.22 $\pm$ 0.13			2.42 $\pm$ 0.14	
Corrected for age	TD PIGD	Lateral prefrontal	2.71 $\pm$ 0.18	0.60 $\pm$ 0.25	Middle frontal	2.44 $\pm$ 0.17	0.80 $\pm$ 0.17
			2.61 $\pm$ 0.14			2.33 $\pm$ 0.15	
		Inferior frontal, temporal	2.14 $\pm$ 0.16	0.67 $\pm$ 0.23	Superior parietal-occipital	2.03 $\pm$ 0.14	0.75 $\pm$ 0.14
	TD PIGD	Superior parietal-occipital	2.07 $\pm$ 0.14			1.95 $\pm$ 0.16	
			2.24 $\pm$ 0.15	0.69 $\pm$ 0.31	Fronto-medial, inferior frontal	2.29 $\pm$ 0.15	0.88 $\pm$ 0.23
		Fronto-medial	2.19 $\pm$ 0.15			2.22 $\pm$ 0.13	
			2.22 $\pm$ 0.19	3.12 $\pm$ 0.55			
			2.14 $\pm$ 0.15				

Cortical thickness (mean $\pm$ std. deviation), and mean effect size values for significant cortical clusters. These data emphasize reduced cortical thickness in PIGD, and quantify patterns presented in the *Off-* medication state while correcting for the effects of disease duration (Fig. 2a) and age (Fig. 2b).

Table 3

Quantified subcortical volume comparison between AR, TD, and PIGD phenotype

Subcortical structure	Thalamus	Caudate	Putamen	Volumes (mm ³)	Pallidum	Hippocampus	Amygdala	Accumbens	ICV
Motor subtype									
AR	7181±1449	3128±575	4249±758	1669 ± 363		3805±653	1163 ± 249	409±102	1543633±137143
TD	7394±1499	3112 ± 601	4462±838	1657±352		3907 ± 662	1208±306	412±115	1585694±200300
PIGD	7246 ± 1223	30326±562	4181±747	1575±389		3761±600	1186±278	393 ± 103	1563758±198815
<i>p</i> -values									
Motor subtype									
AR vs TD	0.48	0.25	0.27	0.27		0.47	0.36	0.40	0.11
TDvs PIGD	0.47	0.40	0.08	0.23		0.29	0.46	0.32	0.29
ARvs PIGD	0.45	0.14	0.21	0.07		0.31	0.38	0.20	0.26

The top panel shows mean and standard deviation for subcortical volumes by structure and motor phenotype (ICV: Intra-Cranial Volume). The bottom panel shows *p*-values for standard *t*-test comparisons between motor subtypes for each subcortical structure and ICV.