Regional Analysis of Cortical Atrophy in Non-Demented Parkinson’s Disease Patients

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Parkinson’s disease is a neurodegenerative disorder characterized by tremors, rigidity, and bradykinesia. Parkinson’s disease primarily affects subcortical brain structures and networks, but cortical atrophy also occurs in the disease, particularly in late stages and Parkinson’s disease with dementia. There is more controversy regarding cortical atrophy during earlier stages of Parkinson’s disease and in patients without dementia. To identify the atrophied brain regions in patients without dementia, we used FreeSurfer neuroimaging software to compare the average thicknesses of parcellated cortical regions between healthy controls and Parkinson’s patients. Our results revealed thinner left superior frontal and precentral cortex in Parkinson’s disease. There were also suggestions of thinner bilateral temporal, left parietal, right prefrontal, and bilateral occipital cortex in Parkinson’s disease patients compared to controls. These results demonstrate Parkinson’s disease patients without dementia have less cortical atrophy in regions associated with higher cognitive functioning; instead, they primarily have thinning in regions associated with planning and control of motor function.

INTRODUCTION

Parkinson’s disease is a chronic and progressive movement disorder typically characterized by a tremor or tremors in the hands, arms, legs, jaw, and face; bradykinesia (slowed movement); rigidity of the limbs and trunk; and postural instability. Motor symptoms primarily result from dopaminergic cell loss in the substantia nigra, a basal ganglia structure in the midbrain essential to movement and many other brain functions.

But the neurologic effects of Parkinson’s disease are not limited to the substantia nigra, as Lim, Fox, and Lang’s 2009 study shows. “In recent years,” they deemed, “there has been increasing recognition of the features of Parkinson’s disease that are not related to nigrostriatal dopamine deficiency,” which both precede and follow the disease’s more widely recognized motor symptoms. Several investigations into these features have revealed varied cortical changes correlated with Parkinson’s disease, among them thinner hippocampal and prefrontal regions, occipital and temporal regions, and thinning of the olfactory bulb relative to non-PD matched peers (Bruck, Kurki, Kaasinen, Vahlberg, & Rinne, 2004; Burton, McKeith, Burn, Williams, & O’Brien, 2004; Wattendorf et al., 2009).

Cortical atrophy has consequences that extend beyond impaired motor functioning since these regions are responsible for separate physical and cognitive functions (Lim et al., 2009). As a result, PD — varying with the duration and severity of the disease — is often accompanied by cognitive decline. More specifically, according to a 2011 study conducted by Song and colleagues, cortical thickness correlates strongly with the extent of cognitive decline within and across disease durations and severities, meaning patients with thinner cortices tend to experience more severe cognitive disability (Song et al., 2011). From this we raise the question: does cortical atrophy always accompany some degree of dementia, or do non-demented Parkinson’s patients experience cortical atrophy?

The Song et al. (2011) study dug into this question (among others), comparing gray matter densities of non-demented Parkinson’s patients with those of healthy controls. They found cortical differences, namely less gray matter in left occipital areas in non-demented PD patients and less gray matter in bilateral temporal, left prefrontal and insular, and right occipital areas in PD patients with mild cognitive impairment. Other researchers report different cortical areas affected by PD, including areas involved in higher cognitive functions (see Crowley et al., 2017, for a review and analyses). In PD without dementia, however, the disease primarily affects subcortical structures and pathways (Price et al., 2016) but might result in areas of limited cortical atrophy.

Heterogeneity of PD samples, MRI analysis methodologies, and statistical approaches results in contradictory cortical atrophy in PD findings. For example, there are some issues with Song et al.’s (2011) study that warrant brief discussion. To measure differences in cortical integrity between patients, Song and his team used a technique called voxel-based morphometry (VBM). While generally reliable, VBM measures gray matter density as a value between 0 (no gray matter) and 1 (full gray matter) in a three-dimensional cross section of the brain. One spurious effect is certain voxels in border regions containing gray and white matter will register low gray matter densities, somewhat confounding findings of low gray matter density averages across the brain. As a result, gray matter densities can drop in VBM regardless of whether or not there has been an actual loss of gray matter in the region. Other
issues affect VBM analyses (see Crowley et al., 2017, for a review).

To combat problems associated with VBM analyses in PD, our research used a surface-based thickness analysis; thickness is measured only locally, tracking the folding patterns of white surface underneath, which avoids finding reduced gray matter densities where none may lie. This way, we have a clearer, easier to interpret value for the degree of cortical atrophy in Parkinson’s patients. Using a thickness-based method to analyze cortex in non-demented Parkinson’s patients, we hypothesized we would not find differences between Parkinson’s patients and matched controls, because most nerve cell death for non-demented patients should predominantly occur subcortically.

**METHODS**

**Participants**

This retrospective analysis utilized a federally funded dataset for investigating neuroanatomical and cognitive profiles in idiopathic PD (n = 81) relative to non-PD matched peers (n = 50). The study was IRB approved for human participant investigation, required consent, and followed the protocol of the Declaration of Helsinki. Recruitment for individuals with PD involved a combination of: 1) brochure mailings to individuals identified through a research database within the UF Center for Neurorestoration and Movement Disorders (UF CNMDC), 2) UF CNMDC direct neurology referrals, and 3) advertisement at different PD support symposiums. Control participants were recruited through community fliers, free community memory screenings, and mail-outs to targeted individuals in local counties who met demographic inclusion criteria. All individuals were screened via telephone or in person and completed baseline cognitive testing to ensure they met cognitive screening criteria.

All participants were required to be right-handed, speak fluent English, and show no signs of dementia (Telephone Screening for Cognitive Status [TICS]; >34 [Cook et al., 2009]; Dementia Rating Scale-Revised [DRS-R] score in the average range [age and education scale score > 8]; Mini Mental State Exam [MMSE] >27 [Folstein et al., 1975]). Individuals with PD were diagnosed by a movement disorder fellowship trained neurologist, met criteria outlined by the UK Parkinson’s Disease Society Brain Bank Clinical Diagnostic Criteria (Hughes et al., 1992) and had a Hoehn and Yahr (1967) scale ranging from 1 to 3. Medical exclusions from the study included cancer (other than non-melanoma skin cancer) requiring treatment in the past 5 years, serious infectious diseases (e.g., self-reported HIV), myocardial infarction or cerebrovascular accident in the last six months, congestive heart failure, chronic hepatitis, history of organ transplantation, seizure disorders and head trauma resulting in intensive care, and any other medical condition likely to limit lifespan. Additional exclusion criteria included existence of a deep brain stimulator; secondary or atypical Parkinsonism as a result of 1) history of major stroke(s) associated with cognitive sequelae, 2) exposure to toxins or neuroleptics, 3) history of encephalitis, or 4) neurological signs of upper motor neuron disease, cerebellar involvement, supranuclear palsy, or significant orthostatic hypertension; signs of dementia as indicated by the neurological/neuropsychological assessment (DSM-IV criteria and DRS corrected scale score < 8); major psychiatric disorder as assessed by the psychiatric and neurological team with the Structured Clinical Interview for DSM-IV; and a history of Major Depressive Disorder. We did not exclude patients reporting mild depression or anxiety because many PD patients report such symptoms. Other exclusions included less than five years of normal education, inability to read or write, self-reported hearing difficulty that interferes with standardized test administration, claustrophobia, non-medical bodily metal, and presence of a pace-maker device.

**MRI**

Neuroimaging data were prospectively acquired with a Siemens 3 T Verio scanner using an 8-channel head coil. For gray and white matter analyses, we acquired 2 T1-weighted scans (176 contiguous sagittal slices, 1mmx3 voxels, 256 x 256 matrix, TR/TE = 2500/3.77 ms, 7/8 Partial Fourier, acquisition time 9:22). Images were visually examined for excessive motion, and images showing more than a moderate degree of motion were excluded from the analyses.

Cortical reconstruction and volumetric segmentation were performed with the Freesurfer image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures are described in prior publications (Dale, Fischl, & Sereno, 1999; Dale & Sereno, 1993; Fischl & Dale, 2000; Fischl, Liu, & Dale, 2001; Fischl et al., 2002; Fischl et al., 2004a; Fischl, Sereno, & Dale, 1999a; Fischl, Sereno, Tootell, & Dale, 1999b; Fischl et al., 2004b; Han et al., 2006; Jovicich et al., 2006; Reuter, Rosas, & Fischl, 2010; Reuter, Schmansky, Rosas, & Fischl, 2012; Segonne et al., 2004). Briefly, this processing includes motion correction and averaging (Reuter et al., 2010) of multiple volumetric T1 weighted images (when more than one is available), removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Segonne et al., 2004), automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (including hippocampus, amygdala, caudate, putamen, and ventricles) (Fischl et al., 2002; Fischl et al., 2004a), intensity normalization (Sled, Zijdenbos, & Evans, 1998), tessellation of the gray matter white matter boundary, automated topology correction (Fischl et al., 2001; Segonne, Pacheco, & Fischl, 2007), and surface deformation following intensity gradients to
optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale et al., 1999; Dale & Sereno, 1993; Fischl & Dale, 2000).

Once the cortical models are complete, a number of deformable procedures can be performed for further data processing and analysis. Such procedures include surface inflation (Fischl et al., 1999a), registration to a spherical atlas based on individual cortical folding patterns to match cortical geometry across subjects (Fischl et al., 1999b), parcellation of the cerebral cortex into units with respect to gyral and sulcal structure (Desikan et al., 2006; Fischl et al., 2004b), and creation of a variety of surface-based data including maps of curvature and sulcal depth. This method uses both intensity and continuity information from the entire three dimensional MR volume in segmentation and deformation procedures to produce representations of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface (Fischl & Dale, 2000).

The maps are created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity. The maps produced are not restricted to the voxel resolution of the original data and thus are capable of detecting submillimeter differences between groups. Procedures for the measurement of cortical thickness have been validated against histological analysis (Rosas et al., 2002) and manual measurements (Kuperberg et al., 2003; Salat et al., 2004). Freesurfer morphometric procedures have been demonstrated to show good test-retest reliability across scanner manufacturers and field strengths (Han et al., 2006; Reuter et al., 2012).

**Statistical Analyses**

Once cortex analyses were complete and data gathered concerning cortical thickness in PD patients and controls, we used FreeSurfer’s QDEC (Query, Design, Estimate, Contrast) interface to generate statistical maps and visual representations for comparison across groups. FreeSurfer’s documentation describes QDEC as a “single-binary application in the FreeSurfer distribution...[that] can be used to perform inter-subject/group averaging and inference on the cortical surface” based on data produced by the FreeSurfer processing stream.

We compared cortical thickness between the PD group and controls using a General Linear Model (GLM). The GLM was computed vertex-by-vertex for analysis of cortical thickness in each hemisphere. QDEC provides for creating a design matrix using two different methods: DOSS, standing for different offsets, same slope; and DODS, standing for different offsets, different slopes. We used the DODS procedure to model potential between-group differences in slopes and intercepts. We visualized our results by displaying regions containing significant cortical thickness differences across groups onto semi-inflated cortical surfaces, which were smoothed using a 10mm full width at half max Gaussian kernel. After visualization without correcting for multiple comparisons, we then corrected for multiple comparisons (False Discovery Rate). P values were set at <0.05.

**RESULTS**

**Participant Demographic Characteristics**

Details of participant characteristics for the PD vs. controls comparison are found in Table 1. PD and controls were statistically similar in demographics, comorbidity, premorbid intellect, and general cognition estimates. All participants were independent in instrumental activities of daily living (i.e., telephone, financial management), and all but one PD individual independently managed their medications. In the PD group, the sample was largely unilateral tremor dominant (70% Hoehn & Yahr stage ≤ 1.5).

<table>
<thead>
<tr>
<th>Participant Characteristics</th>
<th>PD-ND (n=81)</th>
<th>Control (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>67.46 (6.27)</td>
<td>68.06 (4.90)</td>
</tr>
<tr>
<td>Education</td>
<td>16.36 (2.59)</td>
<td>16.84 (2.21)</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>59:22</td>
<td>37:12</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>0.30 (0.63)</td>
<td>0.31 (0.66)</td>
</tr>
<tr>
<td>Disease Duration</td>
<td>6.79 (4.82)</td>
<td>--</td>
</tr>
<tr>
<td>Under 10 years duration</td>
<td>67 of 81; 83%</td>
<td>--</td>
</tr>
<tr>
<td>UPDRS Part 3</td>
<td>18.55 (10.13)</td>
<td>2.91 (3.54)</td>
</tr>
<tr>
<td>Hoehn &amp; Yahr</td>
<td>0.30 (0.63)</td>
<td>--</td>
</tr>
</tbody>
</table>

Note. Charlson Comorbidity Index is a measure of comorbidities and their severities; UPDRS Total: United Parkinson’s Disease Rating Scale total score; H&Y Hoehn and Yahr stage; cc Cubic Centimeters

**Uncorrected PD vs. Controls**

Our results before correcting for multiple comparisons are shown in Fig. 1. We observed cortical thickness differences in the bilateral temporal, left parietal, right prefrontal, and bilateral occipital regions of non-demented Parkinson’s patients relative to non-PD matched peers.

**Corrected PD vs. Controls**

As seen in Fig. 2, after correcting for multiple comparisons, however, almost all of these differences disappeared. There were mild but statistically robust...
regions of thickness differences in the left superior frontal and left precentral cortices in PD patients relative to matched peers.

![Image](image1)

**Figure 1. FDR uncorrected analysis results**

![Image](image2)

**Figure 2. FDR corrected analysis results**

**DISCUSSION**

We ran an analysis comparing average cortical thickness for parcellated regions of the cortex of non-demented PD patients relative to non-PD matched peers. Before correcting for multiple comparisons (which potentially results in many false positives), we found several areas of thinner cortex, particularly in the bilateral temporal, left parietal, right prefrontal, and bilateral occipital lobes.

After correcting for multiple comparisons, however, all but a small region of difference in the superior frontal and precentral cortex disappeared. Our results contrast with volume-based cortical studies, which typically demonstrate more widespread cortical atrophy in PD (e.g., Song et al., 2011). However, because PD pathology has a subcortical to cortical progression (Braak, Ghebremedhin, Rüb, Bratzke, & Del Tredici, et al., 2004) and should not result in much if any cortical atrophy in the absence of dementia (Price et al., 2016; Pereira et al., 2014).

We found minor differences in cortical thickness in the premotor region of the left superior frontal lobe, which roughly matches a result reported by Jubault and colleagues (2011). The premotor cortex is involved in motor planning, among other functions, and the major early symptoms of PD are movement-related. Therefore, one possible explanation for thinner premotor cortices in PD patients is that thinning results from a lack of signaling from the basal ganglia. The substantia nigra and basal ganglia are involved in many behaviors including signaling to the motor cortex, so as subcortical neurons dysfunction and/or die secondary to Parkinson’s disease pathology, ‘downstream’ and ‘upstream’ areas of cortex will receive reduced signal. Specifically, over time in PD, a weaker and weaker signal is broadcast to the regions of the premotor cortex responsible for planning movement.

This result demonstrates that PD patients without dementia experience little cortical atrophy in regions associated with higher cognitive functioning. Instead, they primarily show thinning in regions associated with planning and control of motor function.

While our results without correcting for multiple comparisons are not statistically robust, the patterns of temporal and posterior cingulate atrophy in PD are similar to previous publications with a subset of participants from this dataset (e.g., Tanner et al., 2015; Crowley et al., 2017).

It must be stated as a limitation that the multiple comparison corrected differences observed occurred only in a constrained section of the superior frontal cortex and represented only slight differences in thickness compared to non-PD controls. Statistically significant, such minor differences could result from noise produced in the MRI scan and/or processing stream. PD is a heterogenous disease (e.g., Gratwicke, Jahanshahi, & Foltynie, 2015) where a subset of participants possibly drive the difference.

**REFERENCES**


nuisance variables in brain voxel based morphometry in idiopathic PD. *Brain Imaging and Behavior*, 1-12.


