Corpus callosal atrophy and associations with cognitive impairment in Parkinson disease

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ABSTRACT

Objective: To investigate atrophy of the corpus callosum on MRI in Parkinson disease (PD) and its relationship to cognitive impairment.

Methods: One hundred patients with PD and 24 healthy control participants underwent clinical and neuropsychological evaluations and structural MRI brain scans. Participants with PD were classified as cognitively normal (PD-NC; $n = 28$), having mild cognitive impairment (PD-MCI; $n = 47$), or having dementia (PDD; $n = 25$) by Movement Disorder Society criteria. Cognitive domain (attention/working memory, executive function, memory, language, visuospatial function) z scores were calculated. With the use of FreeSurfer image processing, volumes for total corpus callosum and its subsections (anterior, midanterior, central, midposterior, posterior) were computed and normalized by total intracranial volume. Callosal volumes were compared between participants with PD and controls and among PD cognitive groups, covarying for age, sex, and PD duration and with multiple comparison corrections. Regression analyses were performed to evaluate relationships between callosal volumes and performance in cognitive domains.

Results: Participants with PD had reduced corpus callosum volumes in midanterior and central regions compared to healthy controls. Participants with PDD demonstrated decreased callosal volumes involving multiple subsections spanning anterior to posterior compared to participants with PD-MCI and PD-NC. Regional callosal atrophy predicted cognitive domain performance such that central volumes were associated with the attention/working memory domain; midposterior volumes with executive function, language, and memory domains; and posterior volumes with memory and visuospatial domains.

Conclusions: Notable volume loss occurs in the corpus callosum in PD, with specific neuroanatomic distributions in PDD and relationships of regional atrophy to different cognitive domains. Callosal volume loss may contribute to clinical manifestations of PD cognitive impairment.

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GLOSSARY

AD = Alzheimer disease; **ANCOVA** = analysis of covariance; **CC** = corpus callosum; **DSM-IV** = *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*; **DTI** = diffusion tensor imaging; **HC** = healthy controls; **MCI** = mild cognitive impairment; **MDS-UPDRS** = Movement Disorder Society–Unified Parkinson's Disease Rating Scale; **MMSE** = Mini-Mental State Examination; **NC** = normal cognition; **PD** = Parkinson disease; **PDD** = Parkinson disease dementia; **SMA** = supplementary motor area.

Cognitive impairment in Parkinson disease (PD) can be a debilitating feature, reducing quality of life¹ and increasing mortality.² Longitudinal studies reveal that up to 80% of patients with PD will develop dementia (PDD) over the disease course,³ and this may be preceded by prodromal mild cognitive impairment (PD-MCI).⁴ Cerebral gray matter atrophy detected on structural MRI has been recognized as a correlate of neurodegenerative processes underlying PD cognitive impairment.^{5,6} However, white matter changes also have been described, with diffusion tensor imaging (DTI) studies demonstrating altered white matter microstructural integrity in PD-MCI and PDD, including the corpus callosum (CC).^{7–9} Abnormalities in the CC are of particular

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Figure 1 Corpus callosum segmentation into its 5 subsections with FreeSurfer processing methods

T1-weighted MRI scan of a healthy control subject.

interest in terms of cognitive impairment given the central role of this large white matter fiber bundle in interhemispheric connectivity and coordination of cognitive function.¹⁰

Little is known, however, about macrostructural changes in the CC in PD and whether such changes are associated with cognitive status. The few prior morphometric MRI studies of the CC in PD examined small participant numbers, had limited focus on cognition, and investigated the CC in only the midsagittal plane using area¹¹ or thickness¹² measurements. The aim of our study was therefore 3-fold: first, to investigate CC volume, in total and different subregions, on MRI in a large PD cohort compared to healthy controls (HC); second, to evaluate the relationship of CC volume to cognitive impairment by comparing callosal volumes on MRI across the PD cognitive spectrum (i.e., PD with normal cognition [PD-NC], PD-MCI, and PDD); and third, to examine the relationship of callosal volumes to performance measures of different cognitive domains to determine topographical effects of atrophy on PD cognitive profiles.

METHODS Participants. We studied 100 participants with PD and 24 HC who were enrolled in a prospective study of clinical and neuroimaging markers of PD cognitive impairment at Rush University Medical Center.^{13–15} Participants with PD were selected to capture the full cognitive spectrum with $\approx 25\%$ PD-NC and PDD and 50% PD-MCI. Participants with PD were 60 to 90 years of age, met UK Parkinson's Disease Society Brain Bank criteria,¹⁶ and had disease durations ≥ 4 years at initial study evaluation, stable

medication regimens, and examinations by a movement disorders neurologist (J.G.G.). Exclusionary criteria were atypical or secondary parkinsonism, severe or unstable depression, anticholinergic medication (e.g., trihexyphenidyl, benztropine, tricyclic antidepressants), medical or neurologic causes of cognitive impairment (e.g., seizures, strokes, head trauma), or MRI contraindications (e.g., cardiac pacemaker, metallic implants). HC participants were recruited from the community and had no cognitive complaints, Mini-Mental State Examination (MMSE)¹⁷ scores ≥ 28 , and normal cognition and neurologic examinations.

Standard protocol approvals, registrations, and patient consents. The study was approved by the Rush University Medical Center Institutional Review Board, Chicago, IL. Participants provided written informed consent.

Evaluations and cognitive classification. Participants underwent clinical evaluations, neuropsychological testing, and structural MRI brain scans. Clinical evaluations recorded demographics, medications, and for participants with PD, disease-related features, including the Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) in the “on” state and Hoehn and Yahr stage.¹⁸

Neuropsychological assessments included the MMSE, Hamilton Depression Rating Scale, and a cognitive test battery representing 5 cognitive domains (attention/working memory, executive function, language, memory, and visuospatial function) using MDS Task Force recommendations¹⁹ and methodology previously described in our cohort (table e-1 at Neurology.org).^{14,15,20} Raw scores were transformed to *z* scores on the basis of normative data from HC at our center.^{15,21} Composite scores for each memory test (e.g., Consortium to Establish a Registry for Alzheimer's Disease, Free and Cued Selective Reminding Test, Figural Memory, Logical Memory) were computed by averaging individual subcomponent *z* scores (e.g., list learning, delayed recall). Cognitive domain scores were calculated by averaging *z* scores for neuropsychological tests within each of the specific domains.

Participants with PD were classified into cognitive groups (PD-NC, PD-MCI, PDD) with MDS Task Force criteria for PD-MCI¹⁹ and PDD²² and previously published consensus conference and cognitive classification methodology.^{15,20} Participants with PD without dementia who did not fulfill MDS PD-MCI criteria were classified as PD-NC.

MRI acquisition and processing. Participants underwent brain MRI scans on a 1.5T General Electric Signa scanner (Fairfield, CT) at Rush University Medical Center with a research protocol including structural T1-weighted magnetization-prepared rapid gradient-echo or fast spoiled gradient echo sequence with the following parameters: 166 contiguous sagittal images, thickness = 1.2 mm, matrix = 192×192 , field of view = 24 cm, echo time = minimum full, repetition time = 1,000 milliseconds, flip angle = 8° , number of excitations (average) = 1, phase field of view = 1, and bandwidth = 15.63 Hz.²³

All scans were processed with FreeSurfer version 5.1 software (<http://freesurfer.net>) and inspected by the study team (J.G.G., D.M., V.D.). The CC was identified and divided into 5 subsections (anterior, midanterior, central, midposterior, posterior) with FreeSurfer's automatic labeling for subcortical segmentation and demarcation by the `mri_cc` command as callosal segments.²⁴ The 5 subsections were derived from evenly spaced partitions along the primary eigenaxis, closely corresponding to the longitudinal axis (figure 1). Subsection volumes were computed in FreeSurfer and then summed for total CC volume. To control for individual variation in head size, total and subsection CC volumes were normalized by dividing each volume by the total intracranial volume

obtained from FreeSurfer (labeled as eTIV and estimated from a relationship between intracranial volume and the linear transform of the image to Montreal Neurological Institute 305 space).²⁵

Statistical analyses. Clinical characteristics. Clinical features were compared across groups (HC, PD-NC, PD-MCI, PDD) using analyses of variance for age, disease duration, motor scores, MMSE scores, and cognitive domain *z* score comparisons, as well as nonparametric tests for sex, Hoehn and Yahr stage, and Hamilton Depression Rating Scale. Post hoc comparisons were adjusted for multiple comparisons with the Scheffé correction, allowing comparisons of each group with all other groups.

CC volumetric measurements. Normalized CC volumes (total and 5 subsections) were compared between the entire PD cohort and HC participants with analyses of covariance (ANCOVAs) with age and sex as covariates and Bonferroni correction for multiple comparisons, yielding an adjusted α level of $p \leq 0.01$. Total CC and subsection volumes were examined across PD cognitive groups (PD-NC, PD-MCI, PDD), with separate ANCOVAs for each volume, with age, sex, and PD duration as covariates, and post hoc comparisons using Bonferroni correction.

Relationship between CC volumes and cognitive domain scores. Regression analyses were performed to evaluate the relationship between CC subsection volumes and cognitive domain *z* scores in PD. Separate regression models were performed for each cognitive domain. In each model, age, sex, and PD duration were included as forced-entry independent variables, after which callosal subsection volumes were entered as independent variables with

a stepwise method, providing adjusted R^2 outputs accounting for the number of predictors in the model.

RESULTS Participant characteristics. Demographic features of participants are presented in table 1. There were no significant differences across the groups (HC, PD-NC, PD-MCI, PDD) regarding sex or years of education. Age differed significantly across the groups ($F_{3,120} = 3.55$, $p = 0.017$), with post hoc comparisons revealing older age in participants with PDD compared to PD-NC ($p = 0.04$). Disease duration differed among the PD groups ($F_{2,97} = 11.40$, $p < 0.0005$), with longer duration in PDD compared to participants with PD-MCI ($p = 0.001$) and PD-NC ($p < 0.0005$). MDS-UPDRS total motor scores and Hoehn and Yahr staging differed significantly among PD groups, with worse motor severity in participants with PDD compared to PD-MCI and PD-NC and in those with PD-MCI compared to PD-NC. Mean daily levodopa-equivalent doses did not differ significantly among PD groups. Depression was absent or mild in the groups as reflected by low Hamilton Depression Rating Scores, but the PD group scored significantly higher than HC. MMSE scores differed significantly

Table 1 Demographic features of the study cohort

	PD-NC (n = 28)	PD-MCI (n = 47)	PDD (n = 25)	HC (n = 24)	p Values
Age, y	70.6 ± 4.7	74.0 ± 6.4	75.5 ± 6.8	71.8 ± 6.1	0.017 ^a
Male, n (%)	24 (85.7)	34 (72.3)	17 (68.0)	14 (56.0)	0.17
Education, y	16.3 ± 2.6	14.7 ± 3.4	15.2 ± 3.0	16.4 ± 2.7	0.56
Hamilton Depression Rating Scale	5.1 ± 3.1	6.0 ± 3.9	7.6 ± 3.9	2.3 ± 2.4	<0.0005 ^b
PD duration, y	8.5 ± 2.9	9.9 ± 4.3	13.8 ± 5.1	—	<0.0005 ^c
MDS-UPDRS Part 3 motor score	30.1 ± 7.8	37.57 ± 11.4	45.52 ± 13.9	—	<0.0005 ^d
Hoehn and Yahr stage, median (range)	2 (2-3)	2 (2-5)	3 (2-5)	—	<0.0005 ^e
Levodopa-equivalent doses, mg/d	772.3 ± 462.7	773.3 ± 419.6	831.9 ± 306.0	—	0.82
MMSE scores	28.96 ± 0.99	27.51 ± 1.6	21.0 ± 4.6	29.29 ± 0.91	<0.0005 ^f
Attention/working memory <i>z</i> score	-0.27 ± 0.52	-1.37 ± 0.80	-2.911 ± 0.54	-0.07 ± 0.65	<0.0005 ^g
Memory <i>z</i> score	-0.22 ± 0.45	-1.35 ± 0.71	-3.10 ± 0.91	-0.019 ± 0.56	<0.0005 ^h
Executive function <i>z</i> score	-0.28 ± 0.56	-1.57 ± 0.95	-2.67 ± 0.83	-0.02 ± 0.52	<0.0005 ⁱ
Language <i>z</i> score	-0.12 ± 0.64	-0.84 ± 0.68	-2.10 ± 1.02	0.04 ± 0.64	<0.0005 ^j
Visuospatial <i>z</i> score	0.03 ± 0.50	-1.64 ± 1.72	-4.84 ± 2.98	0.06 ± 0.69	<0.0005 ^k

Abbreviations: HC = healthy controls; MCI = mild cognitive impairment; MDS-UPDRS = Movement Disorder Society-Unified Parkinson's Disease Rating Scale; MMSE = Mini-Mental State Examination; NC = normal cognition; PD = Parkinson disease; PDD = Parkinson disease dementia.

Data presented as mean ± SD unless noted.

^aPD-NC vs PDD, $p = 0.043$.

^bHC vs PD-NC, $p = 0.001$; HC vs PD-MCI, $p < 0.0005$; HC vs PDD, $p < 0.0005$.

^cPD-NC vs PDD, $p < 0.0005$; PD-MCI vs PDD, $p = 0.001$.

^dPD-NC vs PD-MCI, $p = 0.025$; PD-NC vs PDD, $p < 0.0005$; PD-MCI vs PDD, $p = 0.021$.

^ePD-NC vs PD-MCI, $p = 0.001$; PD-NC vs PDD, $p < 0.0005$; PD-MCI vs PDD, $p < 0.0005$.

^fHC vs PD-MCI, $p = 0.033$; HC vs PDD, $p < 0.0005$; PD-NC vs PDD, $p < 0.0005$; PD-MCI vs PDD, $p < 0.0005$.

^gHC vs PD-MCI, $p < 0.0005$; HC vs PDD, $p < 0.0005$; PD-NC vs PD-MCI, $p < 0.0005$; PD-NC vs PDD, $p < 0.0005$; PD-MCI vs PDD, $p < 0.0005$.

^hHC vs PD-MCI, $p < 0.0005$; HC vs PDD, $p < 0.0005$; PD-NC vs PD-MCI, $p < 0.0005$; PD-NC vs PDD, $p < 0.0005$; PD-MCI vs PDD, $p < 0.0005$.

ⁱHC vs PD-MCI, $p < 0.0005$; HC vs PDD, $p < 0.0005$; PD-NC vs PD-MCI, $p < 0.0005$; PD-NC vs PDD, $p < 0.0005$; PD-MCI vs PDD, $p < 0.0005$.

^jHC vs PD-MCI, $p < 0.0005$; HC vs PDD, $p < 0.0005$; PD-NC vs PD-MCI, $p = 0.002$; PD-NC vs PDD, $p < 0.0005$; PD-MCI vs PDD, $p < 0.0005$.

^kHC vs PD-MCI, $p = 0.003$; HC vs PDD, $p < 0.0005$; PD-NC vs PD-MCI, $p = 0.002$; PD-NC vs PDD, $p < 0.0005$; PD-MCI vs PDD, $p < 0.0005$.

Figure 2 ANCOVA comparing corpus callosum subsection volumes in participants with PD and HC, covarying for age and sex

Error bars represent 95% confidence intervals. *Significant ANCOVA, covarying for age and sex and Bonferroni corrected for multiple comparisons. ANCOVA = analysis of covariance; HC = healthy control; ICV = intracranial volume; PD = Parkinson disease.

across the groups ($F_{3,120} = 68.35, p < 0.0005$), with worse performance in participants with PDD compared to PD-MCI ($p < 0.0005$), PD-NC ($p < 0.0005$), and HC ($p < 0.0005$) and in those with PD-MCI compared to HC ($p = 0.033$). MMSE scores did not differ between participants with PD-NC and HC ($p = 0.97$). All cognitive domain z scores differed significantly across PD groups (all $p < 0.0005$). Participants with PDD performed significantly worse in all cognitive domains (all $p < 0.0005$). Participants with PD-MCI had significantly lower cognitive domain z scores than those with PD-NC and HC (all $p < 0.0005$ except language [$p = 0.002$] and visuospatial domains [HC vs PD-MCI, $p = 0.003$; PD-NC vs PD-MCI, $p = 0.002$]). There were no significant differences in cognitive domain z scores between participants with PD-NC and HC (all $p > 0.5$).

CC volumetric measurements. Comparisons between participants with PD and HC. The ANCOVA for the normalized total CC volume, controlling for age and sex, was significant ($F_{3,120} = 11.66, p < 0.0005$), with diagnostic grouping (PD vs HC) trending toward significance in the model ($F_{1,120} = 3.86, p = 0.052$) (figure 2). For the normalized CC subsection volumes, the ANCOVA, controlling for age and sex, was significant for all callosal segments ($F_{3,120} = 7.41$ [anterior], 11.77 [midanterior], 10.97 [central], 5.52 [midposterior], 7.88 [posterior]; all $p < 0.0005$). Diagnostic

grouping was significant for several callosal subsections, with smaller volumes in participants with PD compared to HC, controlling for age and sex, specifically midanterior ($F_{1,120} = 3.97, p = 0.049$) and central ($F_{1,120} = 5.47, p = 0.021$) segments, with a trend of statistical significance for the midposterior segment ($F_{1,120} = 3.66, p = 0.058$).

Comparisons among PD cognitive groups. The ANCOVA for the normalized total CC volume, controlling for age, sex, and PD duration, was significant ($F_{5,94} = 8.96, p < 0.0005$), with differences among PD cognitive groups ($F_{2,94} = 7.17, p = 0.001$) (figures 3 and 4). Post hoc comparisons revealed smaller total CC volumes in participants with PDD compared to PD-NC ($p = 0.001$) and PD-MCI ($p = 0.013$) but no significant differences between participants with PD-NC and PD-MCI. For normalized CC subsection volumes, the ANCOVA, controlling for age, sex, and PD duration, was significant for all callosal segments ($F_{5,94} = 6.11$ [anterior], 7.52 [midanterior], 7.23 [central], 4.44 [midposterior], 6.04 [posterior]; all $p < 0.0005$ except midposterior [$p = 0.001$]). Among PD cognitive groups, volumes were decreased across all callosal regions, with post hoc comparisons showing reduced volumes in participants with PDD compared to PD-NC in 4 of the CC segments: anterior ($F_{2,94} = 4.53, p = 0.013$, post hoc $p = 0.011$), midanterior ($F_{2,94} = 4.90, p = 0.009$, post hoc $p = 0.008$), central ($F_{2,94} = 5.74, p = 0.004$, post hoc $p = 0.003$), and posterior ($F_{2,94} = 3.76, p = 0.027$, post-hoc $p = 0.026$). Reduced volumes also occurred in the midposterior CC segment ($F_{2,94} = 5.83, p = 0.004$), with post hoc comparisons showing reduced volumes in participants with PDD compared to PD-NC ($p = 0.004$) and PD-MCI ($p = 0.021$). Callosal subsection volumes did not differ significantly between the PD-NC and PD-MCI groups.

Relationship between CC volumes and cognitive domain scores. In the PD cohort, using a hierarchical linear regression model with age, sex, and PD duration forced entered on the first step as covariates, we found significant associations among normalized CC subsection volumes and different cognitive domain z scores. Specifically, attention/working memory domain was significantly associated with central subsection volumes ($F_{4,95} = 10.94, p < 0.0005$, adjusted $R^2 = 0.287$; central subsection volume $\beta = 0.331, p = 0.001$). Executive function domain was associated with midposterior subsection volumes ($F_{4,95} = 9.179, p < 0.0005$, adjusted $R^2 = 0.248$; midposterior subsection volume $\beta = 0.307, p = 0.001$), as was language domain ($F_{4,95} = 9.937, p < 0.0005$, adjusted $R^2 = 0.265$; midposterior subsection volume $\beta = 0.254, p = 0.006$). Memory domain was associated with both posterior and midposterior subsection volumes

Figure 3 ANCOVA comparing total corpus callosum volumes among the PD cognitive groups, covarying for age, sex, and PD duration

Error bars represent 95% confidence intervals. *Significant ANCOVA, covarying for age, sex, and PD duration and Bonferroni corrected for multiple comparisons. ANCOVA = analysis of covariance; ICV = intracranial volume; MCI = mild cognitive impairment; NC = normal cognition; PD = Parkinson disease; PDD = Parkinson disease dementia.

($F_{5,94} = 10.644$, $p < 0.0005$, adjusted $R^2 = 0.328$; posterior subsection volume $\beta = 0.222$, $p = 0.041$; midposterior subsection volume $\beta = 0.204$, $p = 0.047$). Visuospatial domain was associated with posterior subsection volume ($F_{4,95} = 9.29$, $p < 0.0005$,

Figure 4 ANCOVA comparing corpus callosum subsection volumes among PD cognitive groups, covarying for age, sex, and PD duration

Error bars represent 95% confidence intervals. *Significant ANCOVA, covarying for age, sex, and PD duration and Bonferroni corrected for multiple comparisons. ANCOVA = analysis of covariance; ICV = intracranial volume; MCI = mild cognitive impairment; NC = normal cognition; PD = Parkinson disease; PDD = Parkinson disease dementia.

adjusted $R^2 = 0.251$; posterior subsection volume $\beta = 0.248$, $p = 0.012$). No significant associations between the other CC subsection volumes (anterior, midanterior) and cognitive domains were found.

DISCUSSION Our study revealed volume loss of the CC on MRI in participants with PD compared to HC, especially midanterior and central callosal segments, and significantly greater callosal volume loss in cognitively impaired participants with PD. Callosal atrophy, particularly evident in those with PDD, spans multiple segments from anterior to posterior and demonstrates regional specificity with certain cognitive deficits.

We found that the most cognitively impaired participants with PD (those with PDD) were distinguished from cognitively intact participants with PD by volume loss across multiple callosal segments. Such abnormalities are of interest given the role of the CC in coordinating cognitive function, its interhemispheric connectivity, and the highly topographic organization of its projections.¹⁰ DTI tractography maps demonstrate connectivity of anterior callosal regions with frontal cortical areas and posterior callosal regions with parietal and occipital cortical areas, along with associated brain-behavioral links to cognitive, motor, and sensory functions.^{26,27} Given anterior and midanterior CC region projections to frontal lobes, anterior callosal volume loss in PDD may be related to frontal cortical atrophy described in MRI studies focused on gray matter atrophy in cognitively impaired patients with PD.^{5,6} Interestingly, the anterior CC is histologically distinct from other portions, with higher concentrations of small and unmyelinated fibers,²⁸ later myelination compared to more posterior segments, and potential greater susceptibility to myelin breakdown.^{28,29} Greater volume loss of the central CC region in PD and PD with cognitive impairment may signify involvement of this area, and its projections to premotor, supplementary motor area (SMA), and primary motor cortex, in both cognitive and motor function. Given midposterior and posterior CC projections to parietal, temporal, and occipital lobes, atrophy in these CC regions in our PDD group may be related to posterior cortical region atrophy described in MRI studies of gray matter volumes or cortical thickness and associated with clinical features of PDD.^{5,6}

Our results of CC volume loss in PD and its association with PDD differ from a prior study that demonstrated CC atrophy and correlations with cognitive impairment severity in Alzheimer disease (AD) but not PD or PDD.¹¹ Differences in clinical definitions and cognitive characterizations of participants with PD (e.g., PDD defined by DSM-IV criteria and MMSE vs the MDS PDD criteria and detailed

neuropsychological testing plus representation of the full PD cognitive spectrum in our study) and imaging analyses (CC measurements of area based on midsagittal view, 5-mm slice thickness, and division into 4 subsections vs the CC measurements of volume from multiple slices in FreeSurfer, 1.2-mm slice thickness, and division into 5 subsections in our study) may explain the differing results.

The clinical profile of PD cognitive impairment includes attention/working memory and executive function deficits but also deficits in memory, language, and visuospatial function, often referred to as posterior cortical dysfunction.³⁰ In our study, we demonstrated relationships between regional CC volume loss and specific cognitive deficits in PD. We found smaller anterior and central CC volumes in cognitively impaired participants with PD and associations between central CC atrophy and worse performance in attention/working memory domain. Attention/working memory tasks engage frontal brain regions to which anterior and central CC regions project, and regional callosal atrophy may affect structural connections to those cortical regions. In support of this link, anterior-predominant CC atrophy has been associated with cognitive dysfunction in normal aging³¹ and diseases (e.g., AD, amnesic MCI, vascular dementia, multiple sclerosis) manifesting cognitive deficits,^{29,32–34} including worse MMSE scores,³⁵ verbal fluency,³² attention, executive function, processing speed,^{33,34} working memory,³¹ and global cognition.³⁶ In our PD cohort, we also found associations of volume loss in more posterior CC regions with executive function, language, memory, and visuospatial domain deficits. The midposterior callosal segment, as delineated in FreeSurfer and with callosal-cortical projections inferred from anatomic landmarks, parcellation schema, and tractography studies, may project to the SMA, primary motor cortex, and parietal lobe.³⁷ These connections may be highly relevant given contributions of the SMA and parietal lobe to a frontoparietal “attention” network.³⁸ The parietal lobe also has been implicated in dementias, including AD and PDD.^{30,39} Volume loss in posterior CC segments and potentially altered projections to parietal-occipital regions may underlie memory, language, and visuospatial deficits found in PDD and the recognized association of parieto-occipital gray matter atrophy on MRI and posterior cortical deficits in PD.³⁰ Moreover, parietal-dominant subtypes of AD have been associated with distinct neuroanatomic patterns of cortical thinning on MRI and may help explain clinical heterogeneity.⁴⁰

Mechanisms leading to callosal atrophy are not fully understood but may include effects of wallerian degeneration (e.g., die-back process resulting from atrophy of connected cortical regions) or primary white matter

changes (e.g., myelin injury), both of which have been hypothesized to drive callosal volume loss in dementias such as AD.²⁹ Several DTI studies in PD demonstrating altered white matter microstructural integrity (e.g., decreased fractional anisotropy, increased mean diffusivity) in white matter pathways, including the CC, support the involvement of white matter in PD-related neurodegenerative processes.^{7,8} While underlying mechanisms of CC volume loss in PD cannot be fully elucidated by the present neuroimaging findings or techniques, this is an important area for future neuroimaging and clinicopathologic studies.

Strengths of our study include a large, well-characterized PD cohort with clinical diagnoses made by movement disorders experts and use of a comprehensive, robust cognitive test battery in accordance with MDS criteria for PD-MCI¹⁹ and PDD.²² The FreeSurfer program offers an unbiased imaging method for CC segmentation, and imaging analyses measuring total and CC subsection volumes offer 3-dimensional information, thereby extending CC characterization beyond just the midsagittal plane as is typical for 2-dimensional area or thickness measurements. We acknowledge potential limitations of our study. While the FreeSurfer segmentation schema, which evenly divides the CC regions, has been frequently used, other parcellations propose alternative CC divisions and distributions of callosal-cortical projections.^{27,37} Currently, these neuroimaging analyses represent research, rather than clinical, tools. At present, the underlying neuropathology associated with CC atrophy detected on MRI cannot be established, but future postmortem studies and clinicopathologic correlates will be informative. Finally, given the trend of decreasing callosal volumes with increasing cognitive impairment in PD at a cross-sectional level, longitudinal follow-up is needed to determine CC volume changes over time and to offer insight into predictors of cognitive decline in PD.

AUTHOR CONTRIBUTIONS

Jennifer G. Goldman, MD, MS, and Ian O. Bledsoe, MD, MS: design/conceptualization of the study, analysis/interpretation of the data, drafting/revising the manuscript for intellectual content. Doug Merkitch, BA, Vy Dinh, BA, and Bryan Bernard, PhD: analysis/interpretation of the data. Glenn T. Stebbins, PhD: design/conceptualization of the study, analysis/interpretation of the data, drafting/revising the manuscript for intellectual content.

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DISCLOSURE

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