


Midsagittal corpus callosal thickness and cognitive impairment in Parkinson's disease

Conor Owens-Walton^{1,2}  | Chris Adamson³ | Mark Walterfang^{4,5} | Sara Hall^{6,7} | Danielle van Westen^{8,9} | Oskar Hansson^{6,7} | Marnie Shaw¹⁰ | Jeffrey C. L. Looi¹

¹Research Centre for the Neurosciences of Ageing, Academic Unit of Psychiatry and Addiction Medicine, School of Clinical Medicine, Medical School, Australian National University, Canberra, ACT, Australia

²Imaging Genetics Center, Mark and Mary Stevens Neuroimaging and Neuroinformatics Institute, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

³Developmental Imaging, Murdoch Children's Research Institute, Parkville, Victoria, Australia

⁴Neuropsychiatry Unit, Royal Melbourne Hospital, Melbourne Neuropsychiatry Centre, University of Melbourne and Melbourne Health, Melbourne, Victoria, Australia

⁵Florey Institute of Neurosciences and Mental Health, University of Melbourne, Melbourne, Australia

⁶Memory Clinic, Skåne University Hospital, Malmö, Sweden

⁷Department of Clinical Sciences, Lund University, Malmö, Sweden

⁸Centre for Medical Imaging and Physiology, Skåne University Hospital, Lund, Sweden

⁹Diagnostic Radiology, Department of Clinical Sciences, Lund University, Lund, Sweden

¹⁰College of Engineering and Computer Science, The Australian National University, Canberra, ACT, Australia

Correspondence

Conor Owens-Walton, Imaging Genetics Center, Mark and Mary Stevens Neuroimaging and Neuroinformatics Institute, Keck School of Medicine, University of Southern California, 1975 Zonal Ave, Los Angeles, CA 90033, USA. Email: conor.owens-walton@loni.usc.edu

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Abstract

People diagnosed with Parkinson's disease (PD) can experience significant neuropsychiatric symptoms, including cognitive impairment and dementia, the neuroanatomical substrates of which are not fully characterised. Symptoms associated with cognitive impairment and dementia in PD may relate to direct structural changes to the corpus callosum via primary white matter pathology or as a secondary outcome due to the degeneration of cortical regions. Using magnetic resonance imaging, the corpus callosum can be investigated at the midsagittal plane, where it converges to a contiguous mass and is not intertwined with other tracts. The objective of this project was thus two-fold: First, we investigated possible changes in the thickness of the midsagittal corpus callosum and cortex in patients with PD with varying levels of cognitive impairment; and secondly, we investigated the relationship between the thickness of the midsagittal corpus callosum and the thickness of the cortex. Study participants included cognitively unimpaired PD participants ($n = 35$), PD

Marnie Shaw and Jeffrey C.L. Looi are co-senior authors.

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participants with mild cognitive impairment ($n = 22$), PD participants with dementia ($n = 17$) and healthy controls ($n = 27$). We found thinning of the callosum in PD-related dementia compared with PD-related mild cognitive impairment and cognitively unimpaired PD participants. Regression analyses found thickness of the left medial orbitofrontal cortex to be positively correlated with thickness of the anterior callosum in PD-related mild cognitive impairment. This study suggests that a midsagittal thickness model can uncover changes to the corpus callosum in PD-related dementia, which occur in line with changes to the cortex in this advanced disease stage.

KEYWORDS

corpus callosum, dementia, mild cognitive impairment, Parkinson's disease

1 | INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease in the world, diagnosed in 2–3% of the population over the age of 65 (Poewe et al., 2017). Longitudinal research has indicated that up to 80% of people with PD will develop dementia (Hely et al., 2005), significantly impacting patients and caregivers. Mild cognitive impairment (MCI) in PD has emerged as an important clinical diagnosis and research focus, as it may represent an intermediate stage in the progression of the disease from cognitively unimpaired PD to PD-related dementia (PDD) (Litvan et al., 2012). PD-related MCI identifies patients with impairment in attention, working memory, executive function and language or visuospatial function (Litvan et al., 2012). While significant attention has been paid to grey matter changes in the brain that may underline these impairments in PD, the role of white matter damage is important as it may precede grey matter changes (Rektor et al., 2018). All domains of cognitive function require the integration of distributed neural activity via white matter connections (van den Heuvel & Sporns, 2013), and the corpus callosum is crucial in facilitating the interhemispheric processes associated with cognitive function (Doron & Gazzaniga, 2008). The callosum is the largest white matter structure in the brain, comprising over 100 million topographically arranged neurons (Schmahmann et al., 2009). In normal functioning, the corpus callosum contributes to a comprehensive set of cognitive measures linked to intelligence, working memory, executive function, attention and processing speed (Martín-Loeches et al., 2013). Given that the majority of interhemispheric fibres from cortical regions converge to a contiguous mass at the midsagittal corpus callosum, the structure is seen as attractive target for research as regional cortical brain changes may be reflected in regional changes to the

morphology of the callosum (Walterfang et al., 2014). Information on the relationship between the structure of the callosum and clinical function can also be investigated, as it has been argued that the integrity and density of the callosal axons reflects the functional capacity of the brain regions they connect (Hofer & Frahm, 2006).

The midsagittal callosum is an attractive candidate for structural brain imaging analyses in neuroimaging research due to its high contrast at its boundaries on sagittal magnetic resonance imaging (MRI). Numerous schemes have been proposed to describe the morphology of the structure, including areal subdivision (Witelson, 1989), cortical endpoint (Hofer & Frahm, 2006), boundary tangent (Joshi et al., 2013) and cross-sectional thickness models (Adamson et al., 2011; Walterfang et al., 2009). The current work uses the cross-sectional thickness model (Adamson et al., 2011) to model callosal morphology. Firstly, the method produces a contour that bisects the callosum on an anterior–posterior trajectory from the splenium to the genu. From this contour, 100 perpendicular and non-intersecting curvilinear contours are generated that connect the inferior and superior boundaries. The length of these contours is interpreted as callosal ‘thickness’. Such a fine-grained approach may uncover greater detail about how the regional structure of the callosum is impacted in PD early in the disease course, when putative morphological alterations may be harder to detect with traditional volumetric approaches. This approach may also yield important information on how the structure of the callosum informs on changes to the cerebral cortex and measures of clinical function, opening up avenues for the development of clinical translation tools. Several different studies investigated callosal structure in PD, yielding varied results, as outlined in Table 1. Overall, due to evidence of callosal thinning in PD participants with dementia, coupled with research showing that greater thickness of

TABLE 1 Summary of literature

Study	Method	Finding
Wiltshire et al. (2005)	Manual segmentation with areal subdivisions.	No significant differences in areas of the total callosum, or in evenly spaced subdivisions of the structure, in PD or PD-dementia cohorts compared with controls.
Goldman et al. (2017)	Semi-automated 3-dimensional volumetric analyses.	No difference in total volume of the callosum in PD compared with controls. Analysis of callosal subdivisions found significant thinning in PD, driven by changes in PD-dementia participants. Changes in volumes of the callosum correlated with measures of clinical function.
Lenka et al. (2017)	Semi-automated 3-dimensional volumetric analyses.	No differences in total callosal volumes, or callosal subdivisions, in PD compared with controls.
Vasconcellos et al. (2018)	Semi-automated 3-dimensional volumetric analyses.	Thinning of callosal subdivisions in PD.

Note: Summary of the key studies in this field of research, the method used to quantify corpus callosal morphometry and the core findings from each work.

the callosum is linked to measures of general cognitive ability (Luders et al., 2007), we thus hypothesised that callosal thickness would be reduced in PD, being more pronounced in PD subgroups with increased levels of cognitive impairment. We also hypothesised that there would be a positive correlation between thickness of the callosum and thickness of the cortex and that thickness of the callosum would be associated with clinical functioning.

2 | MATERIALS AND METHODS

2.1 | Participants

Participants in this study ($n = 101$) were from the Swedish BioFinder study (www.biofinder.se) and gave informed written consent. This research was performed in accordance with the World Medical Association's Declaration of Helsinki, and ethical approval was obtained through the Ethical Review Board of Lund, Sweden, and the Human Research Ethics Committee at the Australian National University, Canberra, Australia.

2.2 | PD disease groups: Cognitive impairment

Diagnosis of PD was made by an experienced movement disorders neurologist using the National Institute of Neurological and Stroke Diagnostic Criteria (Gelb et al., 1999). PD participants were divided into three

cognitive impairment disease groups, the first comprising cognitively unimpaired PD patients (PD-CU; $n = 35$); the second comprising PD patients with MCI (PD-MCI; $n = 22$), with the diagnosis based on the Movement Disorder Society Task force guidelines (Litvan et al., 2012). This criterion is met when patients score at least one standard deviation below the normative mean in at least two cognitive tests in the executive function, attention, visuospatial, memory and language domains. The third subgroup consists of PD participants also diagnosed with PDD ($n = 17$) (Emre et al., 2007). The core features of this diagnosis include a dementia syndrome with insidious onset and slow progression, developing during the course of established PD and diagnosed by history, clinical and mental examination. Patients must have impairment in more than one cognitive domain declining from a premorbid level, and the deficits are severe enough to significantly impair daily life independent of impairment associated with motor or autonomic symptoms. A control group (Controls; $n = 27$) was used for comparative purposes. Exclusion criteria for this study included significant unstable systemic illness or organ failure, such as terminal cancer, significant alcohol or substance misuse, significant neurological or psychiatric illness and poor knowledge of the Swedish language.

All participants underwent a cognitive and neurological examination by a medical doctor with extensive clinical experience with movement disorders. PD participants remained on their usual medication regimen during all assessments. Clinical functioning of participants was quantified using the Hoehn and Yahr staging, assessing the progression of the disorder, the Unified Parkinson's

Disease Rating Scale Part-III test (UPDRS-III), assessing the motor signs of PD (Fahn & Elton, 1987); the Mini Mental State Examination (MMSE), assessing cognitive mental state (Folstein et al., 1975); the A Quick Test of Cognitive Speed (AQT) assessing perceptual and cognitive speed (Jacobson et al., 2004); and the ‘Letter S Fluency’ (LSF) and ‘Animal Fluency’ (AF) tests, assessing the verbal fluency aspect of executive function (Tombaugh et al., 1999).

2.3 | MRI

MRI data were obtained on a 3T scanner (Trio, Siemens Magnetom, Erlangen, Germany) with a 20-channel head-coil. High resolution T_1 -weighted three-dimensional anatomical brain images were acquired using a magnetisation-prepared rapid acquisition technique with gradient-echo sequence (repetition time = 7 ms; echo time = 3 ms; flip angle = 90° ; voxel size = isotropic 1 mm^3). Image matrix size was 356 voxels in the coronal and sagittal planes and 176 voxels in the axial plane.

2.4 | Thickness of the corpus callosum

Thickness of the corpus callosum was estimated using a semi-automated pipeline (<https://github.com/chrisadamsonmcri/CCSegThickness>), explained in detail in previously published works (Adamson et al., 2011, 2014). Steps in the pipeline include the identification of the mid-sagittal plane in subjects T_1 -weighted MRI data, followed by template guided segmentation of the corpus callosum,

topological error fixing and the removal of pericallosal blood vessels. After the structure has been segmented, thickness profile generation is performed using the following steps: The callosum is split into left (posterior) and right (anterior) halves with an endpoint selected at the bottom right and left extrema. A midline equipotential contour is created between these end points, as a solution to Laplace’s equation, maximising the length of the midline contour of the callosum and subdividing the outside boundary of the structure into superior and inferior contours. Streamlines are then generated at evenly spaced intervals along the centre contour, which are non-overlapping nominally parallel lines intersecting the superior and inferior contours orthogonally along an anterior–posterior trajectory. One hundred streamlines per subject were created for this study, with the first and last 10 removed during statistical analyses as comparing and interpreting the lengths of these highly curved streamlines may be problematic (see ends of callosal structure in Figure 1b).

2.5 | Cortical grey matter thickness analysis

Cortical reconstruction and segmentation of grey matter were performed with the FreeSurfer image analysis suite (v6.00). Technical details of these procedures are described in published works (Dale et al., 1999; Fischl et al., 1999). Briefly, processing includes motion correction and averaging of multiple volumetric T_1 -weighted images (Reuter et al., 2010), removal of non-brain tissue using a deformation procedure, automated Talairach

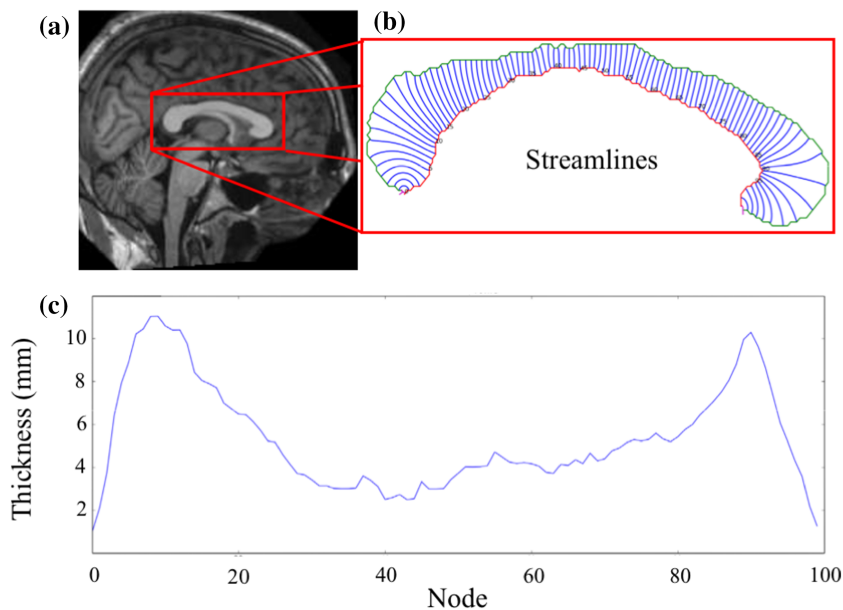


FIGURE 1 Generation of mid-sagittal thickness streamlines. (a) Mid-sagittal callosal segmentation in an example subject; (b) non-overlapping cross-sectional contour lengths (streamlines) numbered from 0 at the intersection of the inferior and superior contours of the corpus callosum, moving anteriorly to node 100 at the most rostral end of the corpus callosum; (c) thickness of each streamline at the 100 nodes

transformation, intensity normalisation (Sled et al., 1998), tessellation of the grey matter–white matter boundary, automated topology correction (Fischl et al., 2001; Ségonne et al., 2004), surface deformation along intensity gradients to optimally define cortical surface borders, registration to a spherical atlas using individual cortical folding patterns to align cortical anatomy between subjects (Fischl et al., 1999) and, finally, the parcellation of the cerebral cortex into units with respect to gyral and sulcal structure based on the Desikan–Killiany atlas (Desikan et al., 2006; Fischl et al., 2004).

2.6 | Statistical analyses

Statistical analyses of the between-group differences in callosal thickness were performed using IBM SPSS Statistics for Macintosh (IBM Corporation, Somers, New York, USA, Version 22.0). Analyses of the relationship between callosal thickness, cortical thickness and clinical function were performed using open-source Python packages Pandas, Matplotlib, Numpy, Statsmodels and Seaborn.

2.6.1 | Group differences in callosal thickness

To investigate group differences in the callosal thickness at the 80 streamlines, we performed a series of multivariate analyses of covariance. Group membership was the fixed factor, with average callosal thickness for each group at each streamline serving as the dependent variable. Estimated total intracranial volume (eTIV), age and sex were entered as nuisance variables. An adjustment for multiple comparisons was performed using the Bonferroni method, whereby SPSS multiplies the p value of the least significant differences by the number of tests, producing a corrected p value.

2.6.2 | Group differences in cortical thickness

Average cortical thicknesses for the 31 regions of interest (ROIs) (per hemisphere) for each participant were used as dependent variables in a multivariate analysis of covariance, with experimental group as the fixed factor, age, eTIV and sex as nuisance variables. An adjustment for multiple comparisons was performed using the Bonferroni method above.

2.6.3 | Correlation between corpus callosum thickness and cortical thickness

To investigate the relationship between callosal thickness and cortical thickness at the 62 ROIs, we ran a series of multiple regressions for each experimental group. These analyses controlled for age, eTIV and sex, producing beta correlation coefficients indicating the magnitude and directionality of the relationship for each group and p value $n \times m$ matrices, where n is the number of callosal thickness measurements ($n = 80$) and m is the number of cortical thickness measurements ($m = 62$). An adjustment for multiple comparisons was performed using the Bonferroni method, with a significant alpha set at $p < 0.01$.

2.6.4 | Correlation between callosal thickness and clinical variables

To investigate the relationship between callosal thickness and clinical variables, we ran a series of multiple regressions within each experimental group. These analyses controlled for age, eTIV and sex, producing beta correlation coefficients indicating the directionality of the relationship for each group and p value $n \times m$ matrices, where n is the number of callosal thickness measurements ($n = 80$) and m is the number of clinical function measurements ($m = 6$). Clinical variables included years of education, AF and LSF, MMSE, AQT and disease duration. An adjustment for multiple comparisons was performed using the Bonferroni method, with a significant alpha set at $p < 0.01$.

3 | RESULTS

Participant characteristics in this research are displayed in Table 2. A χ^2 test for independence found no significant difference in sex between the groups ($\chi^2(3, n = 98) = 0.83, p = 0.84$). One-way analyses of variance found no significant difference in age ($F(3, 97) = 2.17, p = 0.097$), years of education ($F(3, 82) = 1.159, p = 0.331$) or eTIV ($F(3, 97) = 0.036, p = 0.991$) between experimental groups (Table 2). There was a significant difference in disease duration between the PD cohorts ($F(2, 71) = 10.299, p \leq 0.001$), with post hoc analyses of variance showing that the PDD cohort had a significantly longer duration than the PD and PD-MCI cohorts. As expected, there were significant differences in UPDRS-III ($F(3, 97) = 47.96, p < 0.001$), MMSE ($F(3, 97) = 4.049, p < 0.001$), AF ($F(3, 96) = 17.28, p < 0.001$), LSF ($F(3, 94) = 11.37,$

$p < 0.001$) and AQT ($F(3,94) = 18.59, p < 0.001$) scores between experimental groups.

A visual display of the estimated callosal thickness profile for each experimental group, after controlling for head size and age, is presented in Figure 2.

3.1 | Callosal thickness: Pairwise analyses

We found no significant differences in callosal thickness when comparing Controls, PD-CU and PD-MCI participants. There were also no differences in callosal thickness between PDD and Control participants. PDD participants

demonstrated reduced thickness at streamlines 42 ($p = 0.024$), 51 ($p = 0.047$) and 55 ($p = 0.029$) compared with PD-CU participants and reduced thickness at thickness at streamlines 42 ($p = 0.04$), 54 ($p = 0.033$), 55 ($p = 0.026$) and 56 ($p = 0.045$) compared with PD-MCI participants (Figure 3).

3.2 | Cortical thickness: Pairwise analyses

After controlling for multiple comparisons, there were no significant differences in cortical thickness in PD-CU or PD-MCI participants compared with Controls (Figure 4).

TABLE 2 Participant characteristics

Item	Controls	PD-CU	PD-MCI	PDD	<i>p</i> value
Number of participants	27	35	22	17	-
Female/male	12/15	17/18	12/10	7/10	0.843
Average age in years	69.47 (6.09)	69.45 (6.18)	70.53 (5.38)	73.70 (6.67)	0.097
eTIV (cm ³)	1572.64 (157.37)	1584.91 (192.19)	1570.74 (179.15)	1580.79 (222.55)	0.991
Years of education	12.54 (3.47)	11.68 (5.35)	9.66 (6.807)	11.5 (4.52)	0.331
Years since diagnosis	-	6.17 (5.14)	5.45 (3.56)	11.88 (5.48)	-
H&Y	-	1.73 (0.72)	2 (0.72)	2.85 (0.77)	-
UPDRS-III	2.26 (2.28)	12.37 (9.54)	14.28 (9.07)	33 (10.21)	<0.001
MMSE	28.56 (1.34)	28.83 (1.01)	27.41 (1.65)	22.88 (3.77)	<0.001
AF	23.56 (6.26)	23.57 (5.79)	18.86 (6.24)	11.81 (4.18)	<0.001
LSF	18.56 (6.26)	16.15 (5.33)	12.5 (5.62)	9.31 (4.24)	<0.001
AQT	60.41 (15.73)	63.37 (11.49)	78.32 (28.01)	132.93 (73.26)	<0.001

Note: Participant data presented as mean (standard deviation). All data correct to two decimal places.

Abbreviations: AF, 'Animal Fluency Test'; AQT, 'A Quick Test of Cognitive Speed'; eTIV, estimated total intracranial volume; H&Y, Hoehn and Yahr Scale; LSF, 'Letter S Fluency Test'; MMSE, Mini Mental-state Examination; UPDRS-III, Unified Parkinson's Disease Rating Scale part III.

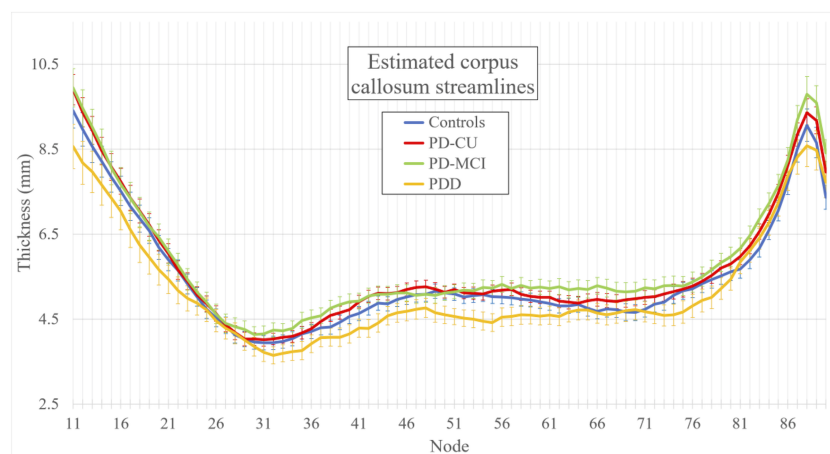
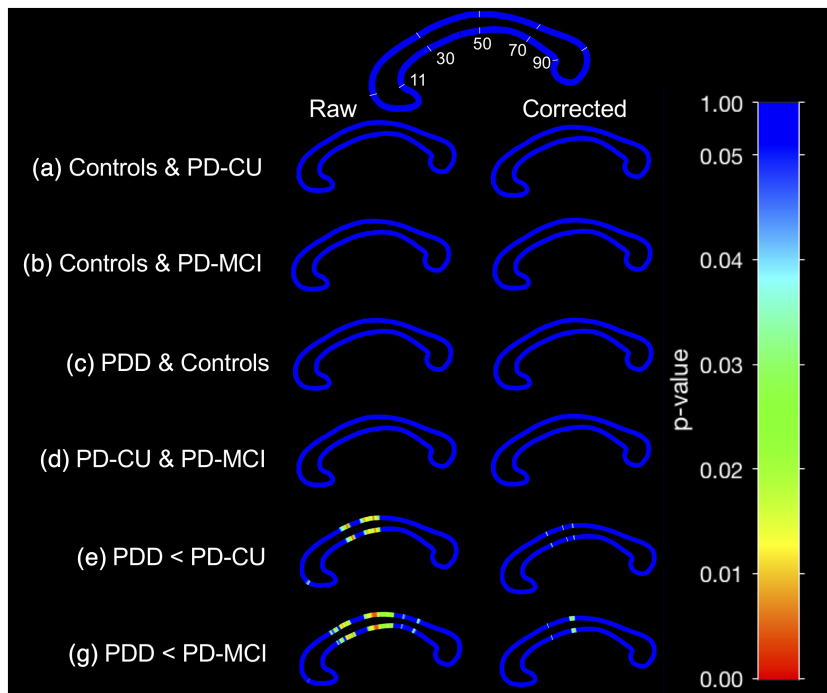


FIGURE 2 Summary corpus callosum thickness profiles for all experimental groups. Streamline data represent the estimated averages for each group after controlling for head size and age, with error bars representing standard error of the mean

FIGURE 3 Group differences in midsagittal plane corpus callosum thickness. Areas of the corpus callosum where the thickness is reduced in one group compared with the other. Significant p values (<0.05) appear in light blue, becoming warmer in colour with lower values. Raw p values are presented in the left column, with Bonferroni corrected p values presented on the right. Positioning of streamlines is guided by the image at the top. The genu of the corpus callosum points to the right of the image, whereas the splenium faces left



There were also no significant differences in cortical thickness in PD-CU participants compared with PD-MCI participants (Figure 5). Significant reductions in left hemisphere cortical thickness were found in PDD participants compared with Controls at the entorhinal cortex ($p = 0.002$), fusiform gyrus ($p < 0.001$), insula cortex ($p = 0.024$), inferior temporal cortex ($p = 0.005$), lateral orbitofrontal cortex ($p = 0.029$), middle temporal cortex ($p = 0.045$) and superior temporal cortex ($p = 0.015$). In the right hemisphere, cortical thickness was reduced at the fusiform gyrus ($p < 0.001$), inferior parietal cortex ($p = 0.015$), inferior temporal cortex ($p < 0.001$), lateral orbitofrontal cortex ($p < 0.001$), middle temporal cortex ($p = 0.009$), pars triangularis ($p = 0.035$) and supramarginal cortex ($p = 0.011$) (Figure 4).

Significant reductions in left hemisphere cortical thickness were found in PDD participants compared with PD-CU participants at the left entorhinal cortex ($p = 0.012$), fusiform gyrus ($p = 0.004$), inferior temporal cortex ($p = 0.041$) and superior temporal cortex ($p = 0.006$) (Figure 5). In the right hemisphere, cortical thickness was reduced in PDD participants at the fusiform gyrus ($p < 0.001$), inferior temporal cortex ($p < 0.001$), lateral orbitofrontal cortex ($p = 0.018$), middle temporal cortex ($p = 0.01$), pars triangularis ($p = 0.005$) and the rostral middle frontal cortex ($p = 0.007$) (Figure 5). Significant reductions in left hemisphere cortical thickness were found in PDD participants compared with PD-MCI participants at the inferior parietal cortex ($p = 0.002$), inferior temporal cortex

($p = 0.026$), superior temporal cortex ($p = 0.003$) and transverse temporal cortex ($p = 0.041$) (Figure 5). In the right hemisphere, cortical thickness was reduced in PDD participants at the fusiform gyrus ($p = 0.005$), inferior temporal cortex ($p = 0.007$) and lateral orbitofrontal cortex ($p = 0.019$) (Figure 5).

3.3 | Correlation between thickness of the corpus callosum and thickness of the cortex

When correlating callosal and cortical thicknesses within each experimental group, we found that the thickness of the left medial orbitofrontal cortex was significantly positively correlated with thickness of the corpus callosum at streamlines 78, 79 and 80 in the PD-MCI group (Figures 6 and S1). While significant, we would not expect the medial orbitofrontal cortex to be anatomically connected with posterior regions of the corpus callosum, so these results should be interpreted with caution. All other correlations were non-significant after controlling for multiple comparisons.

3.4 | Correlation between callosal thickness and clinical function

We found no significant correlations between callosal thickness and clinical variables, after controlling for multiple comparisons (Figure S2).

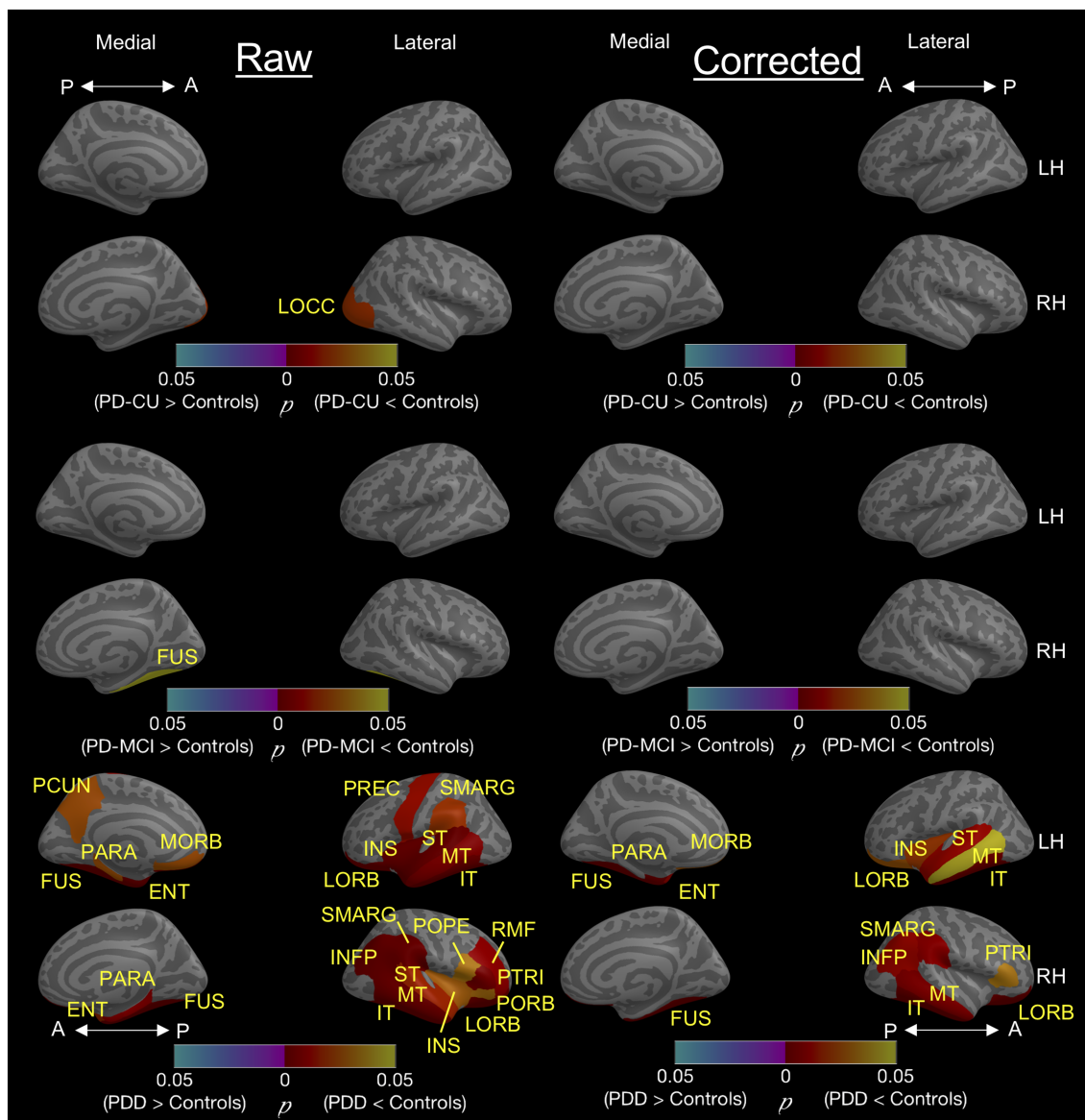


FIGURE 4 Group differences in cortical thickness, Controls and Parkinson's disease (PD) groups. Areas of the cortex where the thickness is reduced in one group compared with the other. Raw p values are presented in the left column, with Bonferroni corrected p values presented on the right. Abbreviations: ENT, entorhinal cortex; FUS, fusiform cortex; INFP, inferior parietal cortex; IT, inferior temporal cortex; LOCC, lateral occipital cortex; LORB, lateral orbitofrontal cortex; MORB, medial orbitofrontal cortex; MT, middle temporal cortex; PARA, parahippocampal cortex; PREC, precentral cortex; PCUN, precuneus; POPE, pars opercularis; PROB, pars orbitalis; PTRI, pars triangularis; RMF, rostral middle frontal; ST, superior temporal cortex; SMARG, supramarginal gyrus; INS, insula cortex

4 | DISCUSSION

This study uses an advanced midsagittal corpus callosal morphology technique to investigate changes to the thickness of the structure in PD patients with varying levels of cognitive impairment. This was followed by an analysis of the thickness of cortical ROIs across experimental subgroups and an investigation of the usefulness of this callosal thickness metric as a predictor of cortical thicknesses and clinical variables.

This study demonstrated no significant differences in thickness of callosal streamlines in PD-CU subjects compared with Controls, supporting early two-dimensional area-based findings (Wiltshire et al., 2005) as well as more recent three-dimensional volumetric work (Lenka et al., 2017). Two studies showed volumes of callosal subdivisions are reduced in a total PD cohort comprising participants with and without cognitive impairment and also dementia, compared with controls (Goldman et al., 2017; Vasconcellos et al., 2018). Analyses between PD-disease subgroups in Goldman et al. (2017) indicate

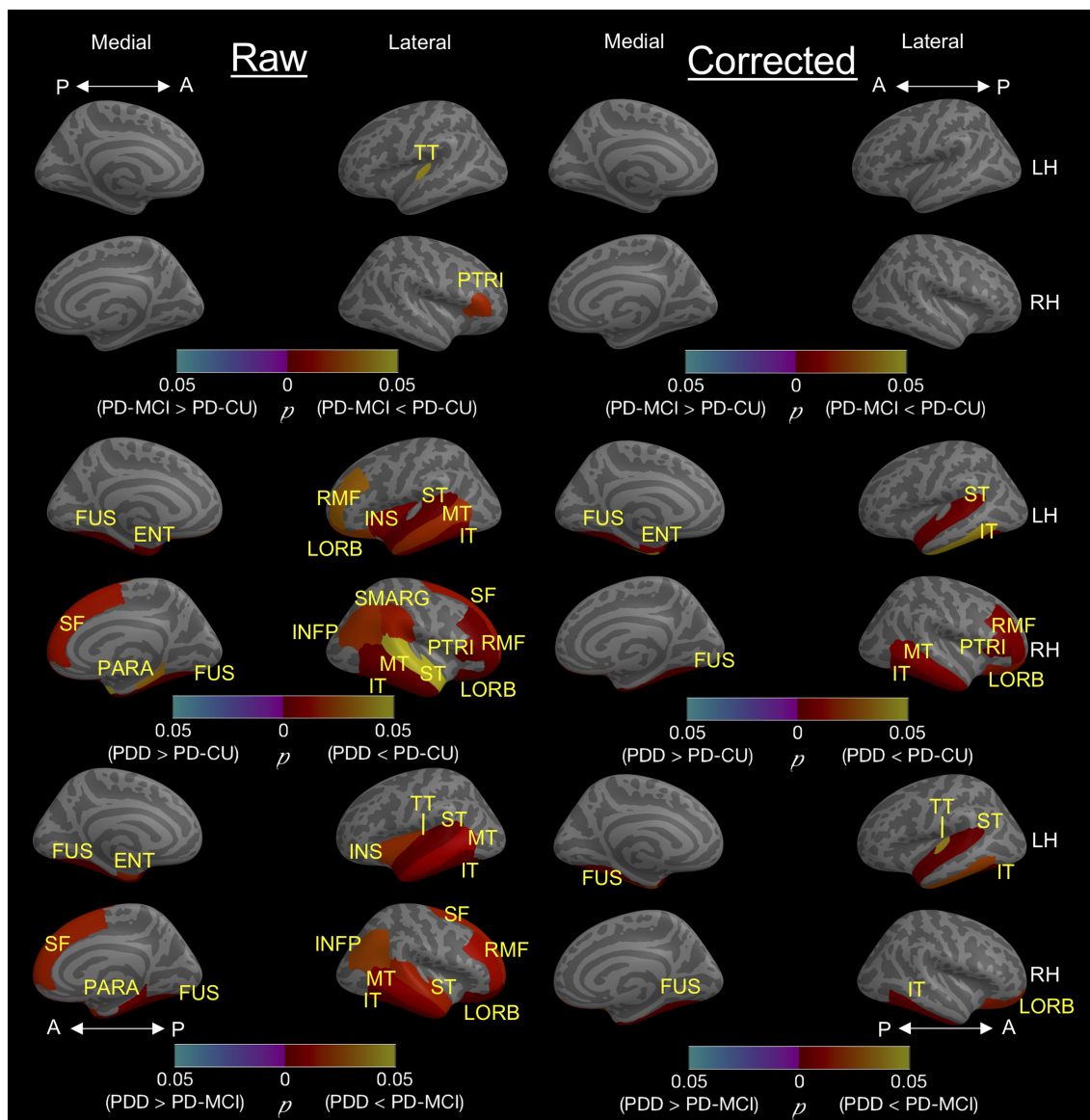


FIGURE 5 Group differences in cortical thickness, Parkinson's disease (PD) groups. Areas of the cortex where the thickness is reduced in one group compared with the other. Raw p values are presented in the left column, with Bonferroni corrected p values presented on the right. Abbreviations: ENT, entorhinal cortex; FUS, fusiform gyrus; IT, inferior temporal cortex; INFP, inferior parietal cortex; INS, insula cortex; LORB, lateral orbitofrontal cortex; MT, middle temporal cortex; PARA, parahippocampal gyrus; PTRI, pars triangularis; RMF, rostral middle frontal cortex; SF, superior frontal; SMARG, supramarginal cortex; ST, superior temporal cortex; TT, transverse temporal cortex

that their finding is likely due to significant changes in the PD participants diagnosed with dementia, and the results of the current study support this finding. PDD participants in our study demonstrated reduced callosal thickness compared with PD-CU and PD-MCI, predominantly around central callosal regions. Our research found a reduction in thickness of the callosum towards the middle part of the structure, an area interconnecting pre- and supplementary motor areas (Hofer & Frahm, 2006). This finding may represent anatomical substrates of the motor programming deficits that are common in the disorder and at their most advanced in

PD patients with dementia (Szeto et al., 2020). Our finding of a lack of significant differences between cognitively normal PD and MCI subjects aligns with the work of Goldman et al. (2017), who also found no differences in callosal volumes in a PD-MCI cohort compared to cognitively unimpaired PD participants, as well as a control group. In this context, our study builds on previous research findings and indicates that the morphology of the corpus callosum is impacted in advanced PD stages and that PD patients with mild or no cognitive impairment have no observable structural alterations to the callosum. Considering possible pathophysiological

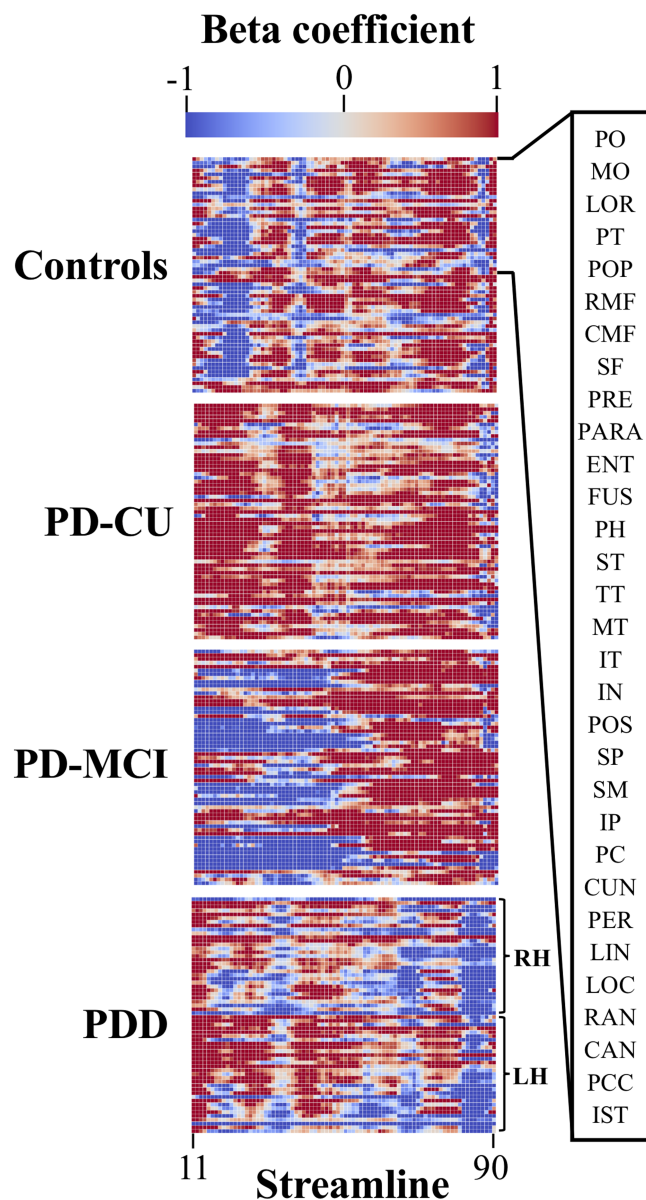


FIGURE 6 Correlation between callosal thickness and cortical thickness. Beta correlation coefficients show the directionality of the relationship between callosal and cortical thicknesses.

Associated corrected p values are presented in Figure S1.

Abbreviations: PO, pars orbitalis; MO, medial orbitofrontal cortex; LOR, lateral orbitofrontal cortex; PT, pars triangularis; POP, pars opercularis; RMF, rostral middle frontal cortex; CMF, caudal middle frontal cortex; SF, superior frontal cortex; PRE, precentral cortex; PARA, paracentral cortex; ENT, entorhinal cortex; FUS, fusiform gyrus; PH, parahippocampal gyrus; ST, superior temporal cortex; TT, transverse temporal cortex; MT, medial temporal cortex; IT, inferior temporal cortex; IN, insula; POS, postcentral cortex; SP, superior parietal cortex; SM, supramarginal cortex; IP, inferior parietal cortex; PC, precuneus; CUN, cuneus; PER, pericalcarine cortex; LIN, lingual cortex; LOC, lateral occipital cortex; RAN, rostral anterior cingulate; CAN, caudal anterior cingulate cortex; PCC, posterior cingulate cortex; IST, isthmus cingulate cortex

mechanisms that may be responsible for structural changes observed in the callosum in PD dementia, it has been suggested that changes may be due to 'Wallerian degeneration' whereby atrophy of connected cortical regions is passed down neuronal axons causing a loss of synapses and subsequent neurodegeneration of the structure (Coleman & Freeman, 2010). A second pathophysiological mechanism that may contribute to thinning of the corpus callosum in PD related dementia relates to the effects of primary white matter pathology. This has been hypothesised to drive atrophic callosal changes in Alzheimer disease (di Paola et al., 2010), and diffusion-weighted imaging research has demonstrated that microstructural white matter integrity is reduced in PD and that these changes are exacerbated in people with greater cognitive dysfunction (Agosta et al., 2014; Bledsoe et al., 2018; Melzer et al., 2013).

To investigate whether changes in the thickness of the corpus callosum are reflective of changes to connected cortical regions, this study investigated associations between these two metrics. Such an investigation was performed due evidence suggesting partially overlapping genetic loci are involved in the thickness of both structures (Gozzo et al., 1979), while in people with corpus callosum agenesis, there are fewer cortical neurons in areas that are expected to receive input from the callosum (Abreu-Villaça et al., 2002). While we found a relationship between left medial orbitofrontal cortical thickness and streamlines in the anterior corpus callosum in PD-MCI participants, most correlational analyses between thickness of the callosum and thickness of the cortex showed no significant relationships. While these results are valid, it should be noted that we used the Bonferroni correction to address the multiple-testing problem. Correcting across multiple tests using metrics derived along the thickness of the corpus callosum is challenging given the existing, but invariably unknown, dependency between the data. While still a valid statistical method, using the Bonferroni approach for brain imaging data in this way can be overly conservative, given that dependence (Zugman et al., 2020). Nonetheless, due to this lack of a clear relationship between callosal and cortical thickness, callosal thickness does not show much efficacy as a proxy measure for changes to the cerebral cortex associated with PD.

Cortical thickness changes in PD were not the primary focus of this study and have been documented extensively both cross-sectionally (Laansma et al., 2021; Mak et al., 2015; Melzer et al., 2012; Pereira et al., 2014; Segura et al., 2014; Wilson et al., 2019; Zarei et al., 2013) and longitudinally (Ibarretxe-Bilbao et al., 2012; Mak

et al., 2015); however, they are worth mentioning at this stage as they can shed light on other results in this study. The present work found no significant differences in cortical thickness between PD-CU and Controls groups, which is consistent with several previous studies (Ibarretxe-Bilbao et al., 2012; Melzer et al., 2012; Zarei et al., 2013). However, other works have demonstrated reduced cortical thickness in cognitively unimpaired groups compared with control subjects (Pereira et al., 2014; Segura et al., 2014; Tinaz et al., 2011; Wilson et al., 2019). Changes in PD cohorts with MCI are common (Mak et al., 2015; Melzer et al., 2012), and our demonstration of reductions in cortical thickness in frontal and temporal cortices in PDD broadly supports findings in the literature of increased grey matter changes in advanced disease stages, with changes commonly found in frontal, temporal and also parietal cortices (Burton et al., 2004; Laansma et al., 2021; Zarei et al., 2013). While there are a few similarities between the present work and previous studies, both in terms of changes to the corpus callosum and the cortex, there are also inconsistencies. Factors that may account for these discordant findings include variable disease staging and symptom profiles of PD cohorts, as well as variable methods used to assess structural brain changes and the statistical methods used to analyse the results.

Morphological analysis of brain structures can be performed with several shape descriptors, with thickness being just one way to approach the problem. The current work models thickness of the callosum with the use of nominally parallel non-overlapping thickness streamlines, which are evenly placed along the midline of the structure, connecting orthogonally with the superior and inferior callosal edges. This method was developed to better model thickness of the structure without having to use a volumetric approach, which can be a difficult concept to reconcile, as the lateral boundaries of the structure are hard to model in three-dimensions due to a lack of clear anatomical boundaries (Walterfang et al., 2014). While our chosen method models thickness at very fine-grained level of detail, the approach may miss morphological alterations to the callosum that take place at other points along the sagittal plane. A second possible limitation involves the incompatibility of our chosen method for analysing the genu and splenium of the callosum. As shown in Figure 1b, streamlines generated in these regions run in a curvilinear fashion, to maintain orthogonal connecting points with the superior and inferior boundaries of the structure. This makes the interpretation of their lengths difficult, which is important for the current work when we consider the callosal genu, as fibres from this region give rise to the white matter tract of the forceps minor that

connects frontal cortices and is crucial to prefrontal cortical functioning (Goldstein et al., 2017). Other minor limitations in this work include the role that disease duration likely plays in contributing to the morphological changes associated with PD subjects with dementia, as well as the cross-sectional nature of the work. Future work should investigate callosal morphology longitudinally to reduce the impact of this and other confounding variables on the analyses. Clinical implications of this study are that changes to the structure of the corpus callosum are difficult to discern on structural T_1 -weighted MRI, limiting their usefulness as potential clinical biomarkers of cognitive impairment in the disorder.

Overall, this study demonstrates thinning of the callosum in PD participants with dementia compared with cognitively unimpaired PD participants and those with MCI. PD participants with dementia also demonstrated significant thinning of the cortex, primarily across the frontal and temporal lobes. Thickness of the corpus callosum was only correlated with thickness of the cortex in one very small region, whereas callosal thickness was also not significantly correlated with measures of clinical function, limiting the applicability of this metric as a proxy for changes in these domains. The findings of this study suggest that the mid-sagittal thickness technique can detect the expected structural changes to the callosum in the advanced disease stage of PDD, however, requires more investigation if it is to be used when investigating PD participants with mild or no cognitive impairment.

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CONFLICT OF INTEREST

The authors report no competing interests.

AUTHOR CONTRIBUTIONS

COW contributed to study design and performed statistical analyses and was primary contributor to manuscript development. CA contributed to study design, developed and then ran corpus callosum segmentation software and contributed to manuscript drafts. MW contributed to study design and manuscript drafts. SH, DvW and OH performed crucial clinical and imaging data collection and contributed to manuscript drafts. MS and JCLL contributed to study design and contributed to manuscript drafts.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Due to European General Data Protection Regulation Research, raw data are not able to be shared.

ORCID

Conor Owens-Walton  <https://orcid.org/0000-0003-0589-638X>

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SUPPORTING INFORMATION

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