Is retinal thickness associated with cognitive impairment in Parkinson's and Alzheimer's disease?

Student No.: 170617068

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Newcastle University

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Abstract

Reduced retinal thickness has recently been indicated as a feature of mild cognitive impairment (PD-MCI) and dementia associated with Parkinson's disease (PDD), as well as Alzheimer's disease (AD). The present study aimed to identify retinal thickness differences in people with PDD, PD-MCI and AD, as well as to explore relationships between total mean retinal thickness and global cognition. This was a cross-sectional study, recruiting 81 participants across four clinical groups: PD (n = 25); PDD/PD-MCI (n = 17); early AD/amnestic cognitive impairment (AD-MCI; n = 14); healthy, age-matched controls (n = 25). Total mean retinal thickness was measured using the Spectralis® Multicolour spectra domain optical coherence tomography (SD-OCT) system (Heidelberg Engineering, Inc., Heidelberg, Germany). Retinal images were taken from the macular areas of the retina. An 8x8 volumetric grid of the retina was produced, leading to an investigation of 64 individual retinal areas. PDD and PD-MCI participants were found to have significantly reduced retinal thickness in the temporal and inferotemporal retinal quadrants compared to PD and control groups. No other significant total mean retinal thickness differences were observed. Retinal thickness in 10 areas of the retina was found to correlate with global cognition in PD, PDD and PD-MCI participants. Furthermore, retinal thickness in two superior-temporal retinal areas significantly predicted global cognitive functioning in PD, PDD and PD-MCI participants. However, only one temporal retinal area correlated significantly with global cognition in AD participants. It was concluded that retinal thickness is associated with cognitive impairment in PD, but not in AD.

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Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder distinguished by a diverse range of both motor and non-motor symptoms (London, Benhar & Schwartz, 2013). There are four key features of motor dysfunction associated with PD: bradykinesia, defined by slow movement, muscular rigidity, resting tremor and postural instability (Jankovic, 2008). Other, non-motor features include sleep disorders, depression, severe fatigue, and cognitive impairment (Chaudhuri, Healy & Schapira, 2006). Previous research indicates that mild cognitive impairment, defined as cognitive impairment not severe enough to impair activities of daily living (Goldman & Litvan, 2011), is detected in around 43% of newly diagnosed PD patients (Yarnall et al., 2014). Mild cognitive impairment in PD (PD-MCI) at baseline assessment has also been recognised as a risk factor for developing dementia associated with PD (PDD; Pedersen, Larsen, Tysnes & Alves, 2013), which has been demonstrated to be present in up to 80% of PD patients (Hely, Reid, Adena, Halliday & Morris, 2008). People with PDD were found to experience poorer quality of life (Lawson et al., 2016) and increased caregiver burden (Lawson et al., 2017) when compared to patients with PD alone and patients with PD-MCI. Currently, however, there are no established biomarkers – measurable indicators – for PDD or PD-MCI that could demonstrate high enough accuracy, specificity and sensitivity for routine use in clinical settings (Delgado-Alvarado, Gago, Navalpotro-Gomez, Jiménez-Urbieta & Rodriguez-Oroz, 2016).

The pathological process in PD begins with the deterioration of dopaminergic cells, predominantly in the basal ganglia (Yu et al., 2014). Other key pathogenic factors, which are more prominent in patients with PDD, include deposition of proteins alpha-synuclein (α-syn) and amyloid-beta (Aβ) within the brain (Compta et al., 2011). Research suggests that aggregation and

spread of these proteins throughout the brain of PDD patients act synergistically and exert detrimental effects upon neurones (Irwin, Lee & Trojanowski, 2013). Aβ accumulation in the brain is also associated with dementia (Villemagne et al., 2013) and neural tissue atrophy (Archer et al., 2006) in Alzheimer's disease (AD). AD is a progressive neurodegenerative disorder and is the most common cause of dementia worldwide (Anand, Gill & Mahdi, 2014).

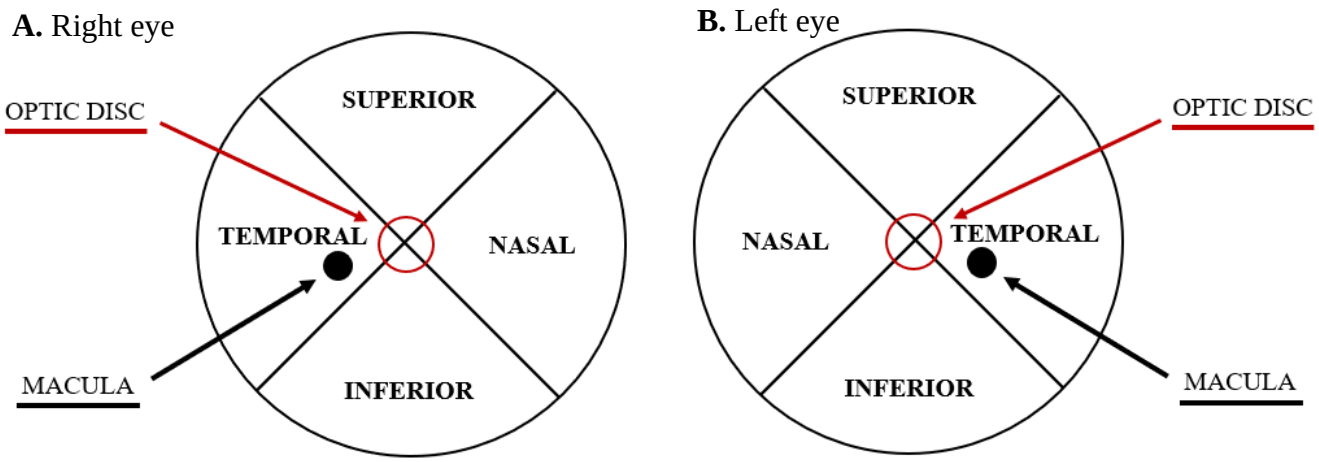
In addition to the brain, aggregation of Aβ has also been identified in the retina of patients with AD. A study by Koronyo et al. (2017) has found that AD patients have a heavier retinal Aβ burden as well as increased neuronal loss in the retina compared to controls. Furthermore, Koronyo et al. (2017) has also shown that retinal Aβ plaques mirrored Aβ brain pathology in both controls and AD patients, suggesting that Aβ burden in the brain and retina are interconnected. Such findings are consistent with the discovery of retinal thinning in patients with AD, including degeneration of retinal nerve fibre layer (RNFL; Berisha, Feke, Trempe, McMeel & Schepens, 2007) as well as reduction in thickness of macular ganglion cell complex (Bayhan, Bayhan, Celikbilek, Tanık, & Gürdal, 2015). Furthermore, reduced RNFL and macular thickness have been associated with lower scores on global cognition assessments after controlling for age (Kim & Kang, 2019), suggesting a relationship between retinal structural differences and dementia in AD that is independent of ageing. Nonetheless, whether retinal thickness is associated with AD remains a controversial topic, with several studies not being able to replicate the mentioned findings (Pillai et al., 2016; Uchida et al., 2018).

Similarly, PD has also been associated with pathologies in the retina, namely degeneration of RNFL as well as macular thickness (Ma et al., 2018). In addition, some studies have found evidence for reduction of RNFL thickness in patients with PDD when compared to controls (Moreno-Ramos, Benito-León, Villarejo, & Bermejo-Pareja, 2013). However, although

both PD and AD patients show reduced thickness of RNFL, they exhibit different patterns of thinning: while people with AD demonstrate a more pronounced neuronal loss in the superior quadrant of the retina (Coppola et al., 2015), PD patients show a more accentuated degeneration of neurones in the inferior and temporal retinal regions (La Morgia et al., 2013; Yu et al., 2014; see Figure 1). Research suggests that such abnormalities in the PD retina may be due to the aggregation of retinal α-syn, which has been found to resemble α-syn accumulation in the brain as well as correlate with motor symptom severity in patients with PD (Ortuño-Lizarán et al., 2018). Nonetheless, a review of the literature concerning the association between retinal thickness and PD yielded mixed results, with some studies finding no link between the two (Pillai et al., 2016; Uchida et al., 2018).

It is worth noting that many of the studies which found no associations between retinal thickness and PD as well as AD (Pillai et al., 2016; Uchida et al., 2018) used the Cirrus optical coherence tomography (OCT) system for obtaining eye scans. Although reliable, this OCT system fails to correct for optical aberrations and differences, such as refractive error or ocular size, which could interfere with meaningfully comparing the results between subjects and between eyes (Bueno-Gimeno, España-Gregori, Gene-Sampedro, Ondategui-Parra & Zapata-Rodriguez, 2018). Therefore, the present study will employ the Spectralis® Multicolour spectral-domain optical coherence tomography (SD-OCT) system (Heidelberg Engineering, Inc., Heidelberg, Germany). This OCT system is able to correct for these optical differences if axial length and refraction data are entered into the device prior to scan acquisition (Wang et al., 2017).

Figure 1. *Four Retinal Quadrants of the Right and Left Eyes, Seen from the Front.*



Nonetheless, although a consensus about retinal structural differences in PD has not yet been reached, reduced retinal thickness has been found to be related to several clinical features associated with PD, providing further evidence for its relationship with the disease. Together with retinal thickness, these features, such as old age, motor symptom severity, and decline of global cognition, have also been shown to correlate with cognitive impairment that has been observed in PD cases. For example, Yarnall et al. (2014) have demonstrated that among PD patients, those meeting the criteria for PD-MCI are markedly older, have spent fewer years in education, exhibit more severe motor symptoms, and score lower on assessments of global cognition. In line with such evidence, various longitudinal studies have demonstrated that the rate of retinal degeneration in patients with PD as they get older is several times greater than that observed in controls (Ma et al., 2018; Murueta-Goyena et al., 2021). A similar pattern of findings has also been established for motor symptom severity. For example, Satue et al. (2014) found that in PD patients, macular thickness decreases as the severity of motor symptoms increases.

Global cognition in people with PD has also been shown to vary significantly between different levels of retinal thickness. For example, a longitudinal study by Zhang et al. (2021)

discovered that, in a sample of PD patients, participants with thinnest RNFL also had significantly lower cognitive assessment scores when compared to those with thickest RNFL. Furthermore, Zhang et al. (2021) discovered that global cognition decline rates over time were greatest for those with the thinnest RNFL and differed significantly from decline rates of participants with thickest RNFL, even when age, disease duration and years of education were controlled for. Therefore, to conclude, retinal thickness differences have been linked to cognitive impairment and global cognition decline in both PD and AD. Therefore, it could perhaps act as a biomarker for detecting cognitive impairment early in the progression of these diseases.

It must be noted that the study by Zhang et al. (2021) calculated mean retinal thickness by averaging thickness values obtained from the four retinal quadrants and calculating mean retinal thickness for the eye as a whole. Employing such a method may lead to overlooking some key retinal thickness differences that are more localised (La Morgia, Ross-Cisneros, Sadun & Carelli, 2017), which could be avoided by measuring mean retinal thickness across multiple areas in the retina. Thus, the present study aims to improve upon the precision of measurement by analysing mean retinal thickness differences across 64 individual retinal areas.

However, screening for early signs of cognitive impairment or dementia in PD and AD remains difficult due to the lack of accessibly measurable indicators of these diseases (Delgado-Alverado et al., 2016). Many of the proposed biomarkers, such as cerebral fluid components or brain structure differences, are difficult to assess in population-wide screenings due to their high cost, invasiveness and complexity of technology used to detect them (Cheung, Chan, Mok, Chen & Wong, 2019). Nonetheless, recent advancements in retinal imaging technology, like the development of spectral-domain optical coherence tomography (SD-OCT), allow for non-invasive, cost-effective, and repeated screening of the eye (Cheung, Ikram, Chen & Wong,

2017). If retinal structural differences were to be established as a biomarker for dementia, it would become possible to have a more suitable biomarker for routine screenings and detection of cognitive impairment early on. In addition, such biomarker could potentially allow for more cost-effective treatment interventions to be designed, which would target those more at risk of developing dementia or cognitive impairment associated with PD or AD.

Therefore, considering the evidence presented, the current study has two aims. Firstly, the study aims to identify retinal thickness differences in patients with mild cognitive impairment and dementia associated with PD and AD as well as healthy controls, using spectral-domain optical coherence tomography (SD-OCT). Secondly, the study aims to explore associations between retinal thickness and global cognition in all participants. The present study has 3 hypotheses. The main hypothesis is that patients with mild cognitive impairment or dementia in PD and AD differ in mean retinal thickness compared to healthy controls, which predicts that PDD, PD-MCI and AD patients will exhibit reduced retinal thickness in contrast to controls. The second hypothesis is that the pattern of retinal thinning is different in patients with PD compared to patients with AD. The prediction is that PD patients will exhibit more prominent retinal thinning in the inferior and temporal quadrants of the retina, while patients with AD will show more substantial retinal thinning in the superior quadrant of the retina. Lastly, the third hypothesis states that retinal thickness is associated with global cognition in PD and AD, which predicts that as global cognition decreases, retinal thickness decreases as well. In addition, it is predicted that retinal thickness will predict global cognition score in PD and AD patients.

Methods

Participants

The present project will use data from a study which was carried out previously by a research team in Newcastle University and Newcastle upon Tyne Hospital (NUTH) NHS Foundation Trust (Structural Retinal Changes: A biomarker for dementia in Parkinson's disease?; REC Ref: 16/ES/0018)

The study recruited 81 participants of both sexes in total throughout four groups: people with PD (n = 25); people with PDD/PD-MCI (n = 17); people with early AD/amnestic cognitive impairment (AD-MCI; n = 14); healthy, age-matched controls (n = 25). Two participants were excluded at baseline assessments due to ocular pathology. Participants were recruited through NHS clinics in Newcastle, through Voice North or word of mouth. Inclusion criteria comprised having the capacity to consent and being diagnosed by a specialist according to relevant criteria (Table 1). Participants' capacity to consent was evaluated by a trained professional in accordance with Mental Capacity Act 2005. After it was confirmed, written consent was obtained, allowing examination to proceed. Participants were excluded from the study if they were not able to consent, had poor sitting stability rendering the examinations difficult for the patients, other active physical or psychiatric illnesses which could interfere with assessments, or past and present ocular problems, which could hinder accurate interpretations of the results obtained.

Table 1. *Diagnostic Criteria of Each Clinical Group.*

PD	PDD/PD-MCI	AD/AD-MCI	Controls
Diagnosis of PD made by a movement disorder specialist according to the UK Brain Bank criteria (Gibb & Lees, 1988). Normal cognition (ACE-R score > 88; Mioshi, Dawson, Mitchell, Arnold & Hodges, 2006).	Diagnosis of PDD made by a movement disorder specialist in accordance to the Movement Disorder Society Task Force Criteria for PDD (Emre et al., 2007). PD-MCI diagnosed by a clinician or by neurpsychological testing: MoCA score < 24 (Nasreddine et al., 2005), MMSE score < 24 (Folstein, Folstein & McHugh, 1975). Subjective decline of cognition must also be present.	Diagnosis of AD dementia made according to McKhann et al. (2011) diagnostic criteria. Possible AD or AD-MCI diagnosed by a clinician or by neurpsychological testing: MoCA score < 24 (Nasreddine et al., 2005), MMSE score < 24 (Folstein, Folstein & McHugh, 1975). Subjective decline of cognition must also be present.	No clinical features of parkinsonism. Normal cognition (ACE-R score > 88; Mioshi, Dawson, Mitchell, Arnold & Hodges, 2006)

Note. Abbreviations: PD = Parkinson's disease; PDD = dementia associated with Parkinson's disease; PD-MCI = mild cognitive impairment associated with Parkinson's disease; AD = Alzheimer's disease; AD-MCI = amnestic cognitive impairment; ACE-R = Addenbrooke's Cognitive Examination Revised; MoCA = Montreal Cognitive Assessment; MMSE = Mini Mental State Examination.

Design

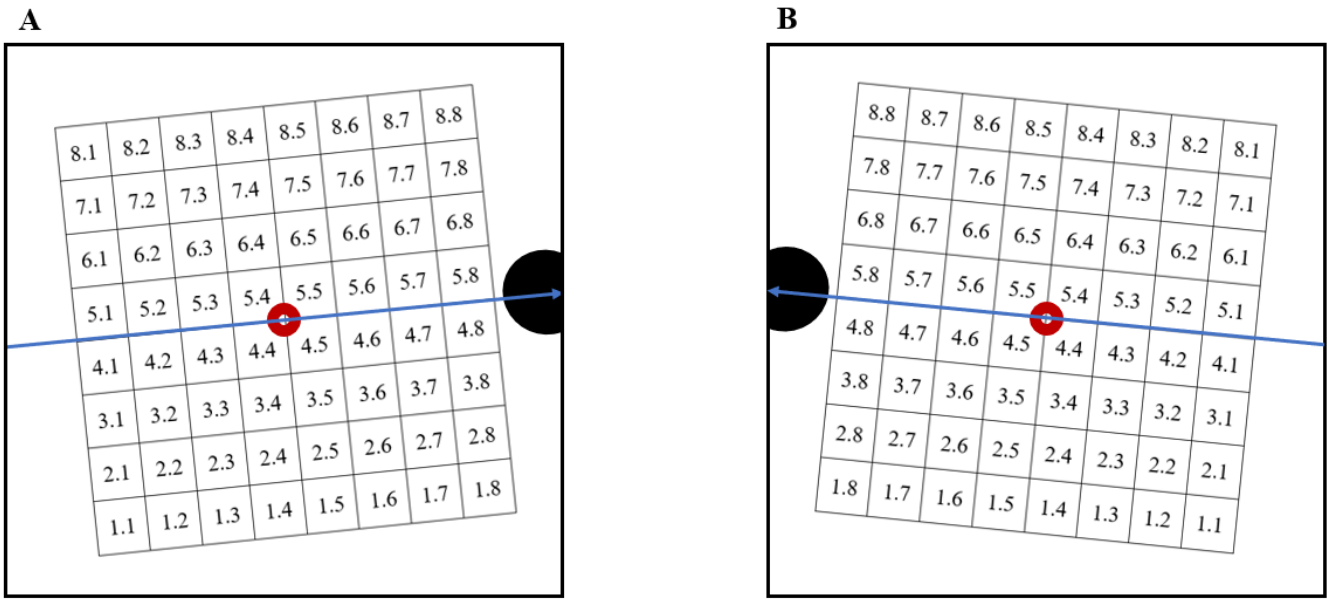
This is a cross-sectional, between-subjects design study – retinal images obtained using Spectralis® Multicolour SD-OTC system during a single visit were compared between the four groups of participants. The variables analysed in this study include retinal thickness, global cognition, disease duration, motor symptom severity, Hoehn and Yahr stage, and demographic information, namely gender, age and years of education.

Apparatus

To obtain ocular axial length and refractor measurements, Zeiss IOL-Master® system (Carl Zeiss AG, Oberkochen, Germany) and a standard autorefractor were used, respectively. Retinal images of the posterior pole of the retina were obtained using the Spectralis® Multicolour SD-OCT system. The system uses rapidly scanning lasers for obtaining cross-sectional images of the retina, producing an 8×8 volumetric grid with 64 individual mean retinal thickness data points (see Figure 1). The grid is positioned symmetrically to the fovea-optic disc axis. Both the Zeiss IOL-Master® and the Spectralis® Multicolour SD-OCT systems were equipped with adjustable chin and forehead rests for comfort.

Figure 2.

8×8 Volumetric Grid With 64 Individual Data Points for Mean Retinal Thickness, Centred Around the Fovea.



Note. The grids are seen from the front of the eye. The black semi-circle denotes the optic disc. The red circle indicates the macula, and the white area in the centre of the red circle represents the fovea. The blue arrow indicates the fovea-optic disc axis. (A) The right eye. (B) The left eye.

Materials

Participants completed demographic information, such as age, sex and years of education, in addition to their clinical history, including date of diagnosis, known co-morbidities and any medications that were being administered at the time of the study. Global cognition was assessed in all participants by employing Addenbrooke's Cognitive Examination Revised (ACE-R; Mioshi, Dawson, Mitchell, Arnold & Hodges, 2006). The test measures 5 different cognitive domains: memory, visuospatial abilities, verbal fluency, language and attention/orientation. It is scored out of 100, with higher scores indicating higher cognitive ability. The test has two cut-off

scores for possible cognitive impairment: a score of <88 to screen for MCI and a score of <83 to screen for dementia. ACE-R has been established as having excellent reliability (Cronbach's alpha of 0.8), as well as relatively good concurrent validity, showing significant correlations (r = -.321, p < .001) with the Clinical Dementia Scale (Mioshi et al., 2006).

The Movement Disorder Society – Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS III; Goetz et al., 2008) was used to assess participants for motor symptoms associated with PD. MDS-UPDRS III contains 18 items that produce 33 scores, measured on a 5-point scale ranging from 0 = normal to 4 = severe, with a minimum score of 0 and a maximum score of 165. Higher scores indicate more severe motor symptoms. MDS-UPDRS III has been found to exhibit excellent reliability (Cronbach's alpha of 0.93) in addition to very high concurrent validity, demonstrating significant correlations (r = .960, p < .001) with the Unified Parkinson's Disease Rating Scale (Goetz et al., 2008).

Procedure

The research session took place at the ophthalmic research and imaging suite in Newcastle Eye Centre, Royal Victoria Infirmary. Following the obtainment of participants' written consent to take part in the study, demographic and clinical information was collected. Cognitive state and motor symptom severity were assessed by the ACE-R and MDS-UPDRS III, respectively.

Afterwards, an ophthalmic clinical examination was completed by a consultant ophthalmologist. It included autorefraction of both eyes, to identify person's refractive error, followed by a visual acuity assessment. Finally, measurements of overall retinal thickness were acquired using the Spectralis® SD-OCT system, with images taken from macular areas. In order

to obtain images that have been corrected for ocular length and refraction error, axial length and refraction data were input into the OCT device prior to imaging. Imaging took up to 20 seconds for each eye. Procedures listed above were completed for both eyes.

Data analysis

Statistical analysis was performed using SPSS (Version 24.0.0.1). Normality testing comprised histograms, boxplots and Q-Q plots, where symmetry and linearity of the plots was examined, and the Shapiro-Wilk test. Means and standard deviations were used to represent descriptive statistics for normally distributed data; medians and interquartile range were employed to represent descriptive statistics for data that were not normally distributed. In order to analyse data across the four groups of participants, one-way ANOVA was used for normally distributed continuous variables or Kruskal-Wallis H test if the normality assumptions were not met. For post-hoc testing, independent t-tests or Mann-Whitney U tests were employed, applying the Bonferroni's correction ($\alpha = .050$/number of comparisons). Chi-squared tests were used for investigating gender differences within the four clinical groups. Associations between individual retinal thickness data points and global cognition were examined by employing Spearman's correlation. To construct predictive models of global cognition, hierarchical regression models were employed. Backwards stepwise multiple linear regression analysis was performed to identify a basic model predicting ACE-R total score. Variables included in the model were age, gender, years in education, and MDS-UPDRS III total score. Retinal thickness variables were then separately entered into the model to establish whether retinal thickness could predict participants' global cognition. In all statistical analyses besides post-hoc testing, $\alpha \leq .050$ was considered to be statistically significant.

Results

Overall, 81 participants were recruited in the present study. One participant was excluded from the study due to poor sitting stability. In total, 80 participants were enrolled in the analysis, including participants with PD (*n* = 25), PDD/PD-MCI (*n* = 16), AD/AD-MCI (*n* = 13), and healthy, age-matched controls (*n* = 26).

Table 2. *Participants' demographic and clinical information, separated by clinical group.*

Demographic & clinical data	PD (*n* = 25)		PDD/PD-MCI (*n* = 16)		AD/AD-MCI (*n* = 13)		Controls (*n* = 26)		*H* (*df*)[c]	*p* value
	Median	IQR	Median	IQR	Median	IQR	Median	IQR		
Age	66.98[f]	11.34	71.05	10.20	81.07[d]	13.87	71.84	7.80	12.6 (3)	.006**
Years in education	15.00	6.50	11.50	4.80	12.00[a]	7.00[a]	11.00[b]	6.00[b]	3.4 (3)	.336
Disease duration (years)	5.17[e, f]	5.62	1.45[d]	4.65	2.71[d]	4.20	-	-	11.9 (2)	.003**
ACE-R total score	87.00[e, f]	9.00	78.50[d, g]	14.00	65.00[d, g]	16.00	94.50[e, f]	7.00	45.6 (3)	< .001***
MDS-UPDRS III total score	43.00[f, g]	15.00	54.50[f, g]	13.00	11.00[d, e]	11.00	8.00[d, e]	9.00	62.4 (3)	< .001***
MDS-UPDRS Hoehn and Yahr stage	2.00[f, g]	1.00	3.00[f, g]	2.00	0.00[d, e]	0.00	0.00[d, e]	0.00	67.0 (3)	< .001***

Note. Abbreviations: PD = Parkinson's disease; PDD = dementia associated with Parkinson's disease; PD-MCI = mild cognitive impairment associated with Parkinson's disease; AD = Alzheimer's disease; AD-MCI = amnestic cognitive impairment; IQR = interquartile range; ACE-R = Addenbrooke's Cognitive Examination Revised; MDS-UPDRS = The Movement Disorder Society – Unified Parkinson's Disease Rating Scale; MDS-UPDRS III = The Movement Disorder Society – Unified Parkinson's Disease Rating Scale Part III. [a] *n* = 11. [b] *n* = 24. [c] Kruskal-Wallis H test. [d] Significantly different from PD

participants. [e] Significantly different from PDD/PD-MCI participants. [f] Significantly different from AD/AD-MCI participants. [g] Significantly different from control participants. * $p \leq .050$. ** $p \leq .010$. *** $p \leq .001$.

The demographics and clinical variables of participants in each group are shown in Table 1. Kruskal Wallis H test revealed that age was significantly different between the groups ($H(3) = 12.6$, $p = .006$). Post-hoc Mann-Whitney U tests showed that AD/AD-MCI participants were significantly older than PD participants ($z = -3.1$, $p < 0.01$), but no other significant group differences were observed ($p > .027$ for all). In addition to age, ACE-R total score was also observed to differ significantly between the four groups ($H(3) = 45.6$, $p < .001$). Mann-Whitney U post hoc analysis found that AD/AD-MCI and PDD/PD-MCI participants had the poorest cognitive scores ($p < .001$ for all). MDS-UPDRS III total score was also significantly different between the groups ($H(3) = 62.4$, $p < .001$), with PD and PDD/PD-MCI participants scoring the highest on the motor symptom scale ($p < .001$ for all). In addition, PDD/PD-MCI group was found to contain significantly more males ($n = 15$, 94%; $\chi^2(1, N = 16) = 12.3$, $p < .001$), while the control group, conversely, was discovered to be composed of significantly more females ($n = 22$, 85%; $\chi^2(1, N = 26) = 12.5$, $p < .001$). Out of all clinical and demographic data collected, years in education was the only variable not found to differ significantly between the four groups, $H(3) = 3.4$, $p = .336$. For all post-hoc Mann-Whitney U test statistics, see Appendix A.

Retinal thickness differences

The data in Table 3 represent descriptive statistics for mean retinal thickness across the 64 OCT retinal grid points, separated by clinical group. For this part of data analysis and onwards, only right eyes were used as they had less missing retinal thickness data than left eyes

(*n* = 6 vs. *n* = 9). Overall, 74 out of a total of 80 right eyes were used for data analysis in the present study across the four groups: PD (*n* = 24), PDD/PD-MCI (*n* = 14), AD/AD-MCI (*n* = 11), and the control group (*n* = 25).

Table 3. *Participants' Mean Retinal Thickness Across the 64 OCT Retinal Grid Point Output Areas.*

Retinal grid point	Clinical group	Retinal grid point							
		1	2	3	4	5	6	7	8
8	PD	227.50 (18.00)	239.50 (20.00)	253.50 (22.00)	267.00 (20.00)	271.50 (23.00)	280.00 (30.00)	293.75 (27.39)[a]	298.08 (27.31)[a]
	PDD/PD-MCI	233.50 (20.00)	244.50 (14.00)	253.50 (21.00)	265.50 (18.00)	275.00 (23.00)	281.50 (23.00)	287.50 (18.82)[a]	298.64 (24.30)[a]
	AD/AD-MCI	232.00 (8.00)	238.00 (16.00)	254.00 (19.00)	266.00 (16.00)	273.00 (14.00)	279.00 (25.00)	297.55 (20.00)[a]	299.73 (17.32)[a]
	Controls	235.00 (19.00)	245.00 (12.00)	259.00 (14.00)	270.00 (16.00)	278.00 (17.00)	287.00 (21.00)	297.52 (23.82)[a]	306.44 (21.06)[a]
7	PD	237.00 (19.00)	253.50 (21.00)	271.00 (19.00)	289.00 (20.00)	296.50 (16.00)	292.50 (18.00)	291.00 (29.00)	309.54 (26.18)[a]
	PDD/PD-MCI	240.00 (15.00)	255.50 (15.00)	276.50 (26.00)	287.00 (22.00)	295.00 (27.00)	292.00 (25.00)	294.00 (23.00)	306.86 (23.21)[a]
	AD/AD-MCI	237.00 (16.00)	247.00 (19.00)	263.00 (18.00)	283.00 (16.00)	288.00 (19.00)	291.00 (17.00)	294.00 (34.00)	317.00 (23.64)[a]
	Controls	240.00 (13.00)	254.00 (18.00)	275.00 (21.00)	293.00 (27.00)	300.00 (25.00)	298.00 (23.00)	299.00 (21.00)	316.96 (23.57)[a]
6	PD	246.50 (18.00)	271.00 (19.00)	302.00 (16.00)	331.00 (19.00)	338.00 (22.00)	319.00 (24.00)	303.00 (17.00)	307.00 (28.00)
	PDD/PD-MCI	251.00 (22.00)	275.00 (26.00)	306.50 (29.00)	324.50 (35.00)	329.00 (36.00)	318.00 (23.00)	298.50 (18.00)	298.00 (40.00)
	AD/AD-MCI	242.00 (24.00)	262.00 (17.00)	294.00 (15.00)	316.00 (25.00)	330.00 (37.00)	313.00 (29.00)	306.00 (27.00)	310.00 (40.00)
	Controls	250.00 (20.00)	272.00 (23.00)	305.00 (24.00)	336.00 (28.00)	340.00 (30.00)	324.00 (26.00)	309.00 (26.00)	310.00 (31.00)
5	PD	252.50 (13.00)	283.00 (13.00)	322.00 (14.00)	316.00 (30.00)	329.50 (35.00)	348.00 (23.00)	314.00 (25.00)	304.88 (21.77)[a]
	PDD/PD-MCI	254.50 (25.00)	288.50 (27.00)	319.50 (45.00)	311.00 (28.00)	324.00 (28.00)	341.50 (27.00)	313.50 (17.00)	292.00 (20.77)[a]

	AD/AD-MCI	249.00 (16.00)	278.00 (12.00)	313.00 (22.00)	311.00 (29.00)	318.00 (37.00)	336.00 (46.00)	315.00 (28.00)	304.27 (23.57)[a]
	Controls	258.00 (26.00)	288.00 (29.00)	329.00 (28.00)	314.00 (22.00)	319.00 (20.00)	347.00 (30.00)	317.00 (36.00)	297.04 (23.93)[a]
4	PD	257.50 (14.00)	287.00 (18.00)	328.00 (18.00)	324.00 (28.00)	329.00 (37.00)	346.00 (21.00)	313.00 (22.00)	301.50 (25.00)
	PDD/PD-MCI	254.00 (14.00)	286.00 (27.00)	322.50 (40.00)	317.00 (16.00)	328.50 (26.00)	346.50 (28.00)	310.50 (24.00)	293.50 (26.00)
	AD/AD-MCI	245.00 (20.00)	279.00 (17.00)	312.00 (23.00)	318.00 (18.00)	322.00 (35.00)	342.00 (48.00)	315.00 (24.00)	297.00 (46.00)
	Controls	262.00 (19.00)	292.00 (29.00)	330.00 (33.00)	322.00 (29.00)	326.00 (21.00)	345.00 (37.00)	313.00 (37.00)	294.00 (36.00)
3	PD	249.00 (18.00)	268.00 (28.00)	301.00 (27.00)	328.00 (22.00)	332.00 (22.00)	319.50 (24.00)	307.00 (21.00)	319.00 (30.00)
	PDD/PD-MCI	249.50 (19.00)	271.00 (24.00)	304.50 (30.00)	328.50 (36.00)	329.00 (37.00)	314.50 (26.00)	295.00 (15.00)	298.50 (29.00)
	AD/AD-MCI	250.00 (22.00)	268.00 (25.00)	292.00 (27.00)	321.00 (31.00)	331.00 (32.00)	318.00 (24.00)	313.00 (22.00)	322.00 (61.00)
	Controls	251.00 (20.00)	273.00 (27.00)	307.00 (29.00)	334.00 (33.00)	335.00 (30.00)	314.00 (33.00)	298.00 (29.00)	314.00 (44.00)
2	PD	237.50 (14.00)	250.50 (24.00)	269.00 (27.00)	281.00 (23.00)	290.00 (21.00)	290.54 (16.33)[a]	300.42 (17.26)[a]	319.13 (19.67)[a]
	PDD/PD-MCI	236.50 (12.00)	251.00 (20.00)	269.00 (22.00)	283.50 (23.00)	287.00 (21.00)	286.57 (13.74)[a]	295.29 (20.92)[a]	318.93 (19.20)[a]
	AD/AD-MCI	243.00 (23.00)	255.00 (16.00)	268.00 (22.00)	278.00 (15.00)	290.00 (14.00)	293.82 (15.28)[a]	307.36 (23.05)[a]	320.18 (26.05)[a]
	Controls	238.00 (16.00)	255.00 (16.00)	268.00 (23.00)	281.00 (24.00)	287.00 (24.00)	285.52 (16.74)[a]	298.73 (22.08)[a]	317.24 (24.03)[a]
1	PD	235.50 (21.00)	245.50 (22.00)	252.00 (20.00)	266.00 (24.00)	277.29 (15.17)[a]	287.88 (18.94)[a]	298.88 (18.17)[a]	291.88 (21.23)[a]
	PDD/PD-MCI	234.50 (20.00)	243.50 (22.00)	252.50 (17.00)	263.50 (14.00)	272.43 (14.69)[a]	184.14 (17.79)[a]	301.93 (13.71)[a]	300.07 (15.21)[a]
	AD/AD-MCI	236.00 (22.00)	241.00 (27.00)	260.00 (30.00)	263.00 (38.00)	274.45 (18.37)[a]	286.82 (22.93)[a]	295.91 (23.61)[a]	287.36 (25.50)[a]
	Controls	238.00 (21.00)	244.00 (13.00)	253.00 (18.00)	265.00 (19.00)	270.72 (19.10)[a]	282.16 (21.90)[a]	293.00 (20.77)[a]	285.72 (23.90)[a]

Note. Values shown in the table are presented as median (interquartile range) unless otherwise stated. The present table represents Figure 2A and is not a matrix table – it should be read from left to right (the first grid point number is the row's number, the second grid point number is the column's number) in order to understand to which exact retinal grid point the value corresponds. Abbreviations: PD = Parkinson's

disease; PDD = dementia associated with Parkinson's disease; PD-MCI = mild cognitive impairment associated with Parkinson's disease; AD = Alzheimer's disease; AD-MCI = amnestic cognitive impairment. [a] Values presented as mean (standard deviation).

No statistically significant differences between the groups in mean retinal thickness across the 64 retinal grid point areas were found ($p > .050$ for all, Table 4). However, post-hoc tests between groups found statistically significant differences between 2 group comparisons: PD and PDD/PD-MCI participants were found to differ significantly in OCT output areas 4.4, (*Mdn* = 324.00 vs. *Mdn* = 317.00, respectively, $U = 93.5$, $z = -2.3$, $p = .024$), 4.8, (*Mdn* = 301.50 vs. *Mdn* = 293.50, respectively, $U = 103.0$, $z = -2.0$, $p = .049$), and 3.8 (*Mdn* = 319.00 vs. *Mdn* = 298.50, respectively, $U = 98.0$, $z = -2.2$, $p = .029$), with PDD participants showing retinal thinning in all of the mentioned areas. Retinal thinning was also observed in PDD/PD-MCI participants compared to the control group in area 1.8 (300.07 ± 15.21 vs. 285.72 ± 23.90, respectively, $t(37) = 2.0$, $p = .050$).

Table 4. *Differences Between Clinical Groups in Mean Retinal Thickness Across the 64 Retinal Grid Point Areas.*

Retinal grid point	Statistics	Retinal grid point							
		1	2	3	4	5	6	7	8
8	Test statistic	2.240[a]	1.185[a]	0.900[a]	2.355[a]	1.746[a]	1.893[a]	0.608[b]	0.628[b]
	p-value	.524	.757	.825	.502	.627	.595	.612	.600
7	Test statistic	0.009[a]	0.580[a]	2.864[a]	2.357[a]	2.074[a]	0.813[a]	0.831[a]	0.769[b]
	p-value	1.000	.901	.413	.502	.557	.846	.842	.515

6	Test statistic	1.043[a]	1.661[a]	2.255[a]	2.983[a]	1.881[a]	1.772[a]	1.067[a]	2.066[a]
	p-value	.791	.646	.521	.394	.597	.621	.785	.559
5	Test statistic	1.565[a]	2.339[a]	2.841[a]	2.751[a]	2.064[a]	1.708[a]	0.259[a]	1.225[b]
	p-value	.667	.505	.417	.432	.559	.635	.968	.307
4	Test statistic	1.744[a]	1.809[a]	2.950[a]	4.520[a]	2.391[a]	1.241[a]	1.518[a]	3.825[a]
	p-value	.627	.613	.399	.210	.495	.743	.678	.281
3	Test statistic	0.297[a]	0.442[a]	1.686[a]	2.952[a]	1.964[a]	1.577[a]	4.986[a]	4.575[a]
	p-value	.961	.931	.640	.399	.580	.665	.173	.206
2	Test statistic	0.879[a]	0.523[a]	0.142[a]	0.356[a]	1.003[a]	0.905[b]	0.746[b]	0.056[b]
	p-value	.831	.914	.986	.949	.801	.443	.528	.983
1	Test statistic	0.372[a]	0.575[a]	0.912[a]	0.977[a]	0.647[b]	0.357[b]	0.753[b]	1.393[b]
	p-value	.946	.902	.822	.807	.588	.784	.524	.252

Note. The present table represents Figure 2A and is not a matrix table – it should be read from left to right (the first grid point number is the row's number, the second grid point number is the column's number) in order to understand to which exact retinal grid point the value corresponds. Abbreviations: PD = Parkinson's disease; PDD = dementia associated with Parkinson's disease; PD-MCI = mild cognitive impairment associated with Parkinson's disease; AD = Alzheimer's disease; AD-MCI = amnestic cognitive impairment. [a] Kruskal-Wallis H test. [b] Analysis of Variance (ANOVA).

Associations between retinal thickness and global cognition

In order to explore relationships between retinal thickness and ACE-R total score, Spearman's correlational analysis was performed. For this part of the analysis and onwards, PD

and PDD/PD-MCI groups were combined to give a single PD group. Correlations were analysed for each clinical group separately as well as for the whole sample (Table 5). For a visual representation of how correlation patterns differed between the PD as well as AD/AD-MCI groups and the whole sample, refer to Figure 3.

Table 5. *Correlation Coefficients of Retinal Thickness Across the 64 OCT Retinal Grid Points and ACE-R Total Score as Well as Their Probability Values.*

Retinal grid point	Clinical group	Retinal grid point							
		1	2	3	4	5	6	7	8
8	Across groups	0.092 (0.436)	0.210 (0.073)	0.204 (0.081)	**0.309 (0.007)****	**0.258 (0.027)***	0.204 (0.082)	0.172 (0.144)	0.201 (0.085)
	PD	0.173 (0.298)	0.251 (0.128)	0.273 (0.097)	**0.322 (0.049)***	0.260 (0.115)	0.256 (0.121)	**0.343 (0.035)***	0.178 (0.286)
	AD/AD-MCI	0.164 (0.629)	0.342 (0.303)	0.325 (0.330)	0.364 (0.271)	0.197 (0.562)	0.118 (0.729)	0.278 (0.408)	0.338 (0.309)
	Controls	-0.171 (0.414)	0.078 (0.711)	0.075 (0.723)	0.108 (0.606)	0.124 (0.555)	0.003 (0.988)	-0.094 (0.655)	0.057 (0.785)
7	Across groups	0.071 (0.547)	0.157 (0.181)	0.212 (0.070)	**0.273 (0.019)***	**0.274 (0.018)***	0.227 (0.052)	0.159 (0.175)	0.143 (0.224)
	PD	0.111 (0.508)	0.194 (0.242)	0.200 (0.228)	**0.329 (0.044)***	**0.399 (0.037)***	**0.365 (0.024)***	0.232 (0.160)	0.239 (0.149)
	AD/AD-MCI	0.542 (0.085)	**0.603 (0.050)***	0.524 (0.098)	0.287 (0.392)	0.214 (0.527)	0.114 (0.738)	0.275 (0.414)	0.384 (0.243)
	Controls	-0.081 (0.702)	-0.090 (0.670)	-0.061 (0.772)	-0.122 (0.561)	-0.089 (0.673)	-0.053 (0.800)	-0.089 (0.673)	-0.146 (0.487)
6	Across groups	0.186 (0.113)	**0.234 (0.045)***	**0.309 (0.007)****	**0.315 (0.006)****	**0.265 (0.022)***	0.218 (0.062)	0.156 (0.186)	0.134 (0.256)
	PD	0.216 (0.194)	0.192 (0.249)	0.313 (0.056)	0.311 (0.057)	0.302 (0.065)	0.270 (0.101)	0.261 (0.113)	**0.336 (0.039)***
	AD/AD-MCI	0.433 (0.184)	0.437 (0.179)	0.261 (0.438)	0.032 (0.926)	0.032 (0.926)	-0.064 (0.852)	0.050 (0.883)	0.173 (0.611)
	Controls	-0.136 (0.518)	-0.004 (0.983)	0.081 (0.702)	0.046 (0.827)	-0.048 (0.819)	-0.061 (0.771)	-0.065 (0.757)	-0.124 (0.556)
5	Across groups	0.176 (0.133)	0.222 (0.057)	**0.240 (0.039)***	0.037 (0.754)	0.022 (0.855)	0.171 (0.145)	0.104 (0.376)	0.040 (0.734)

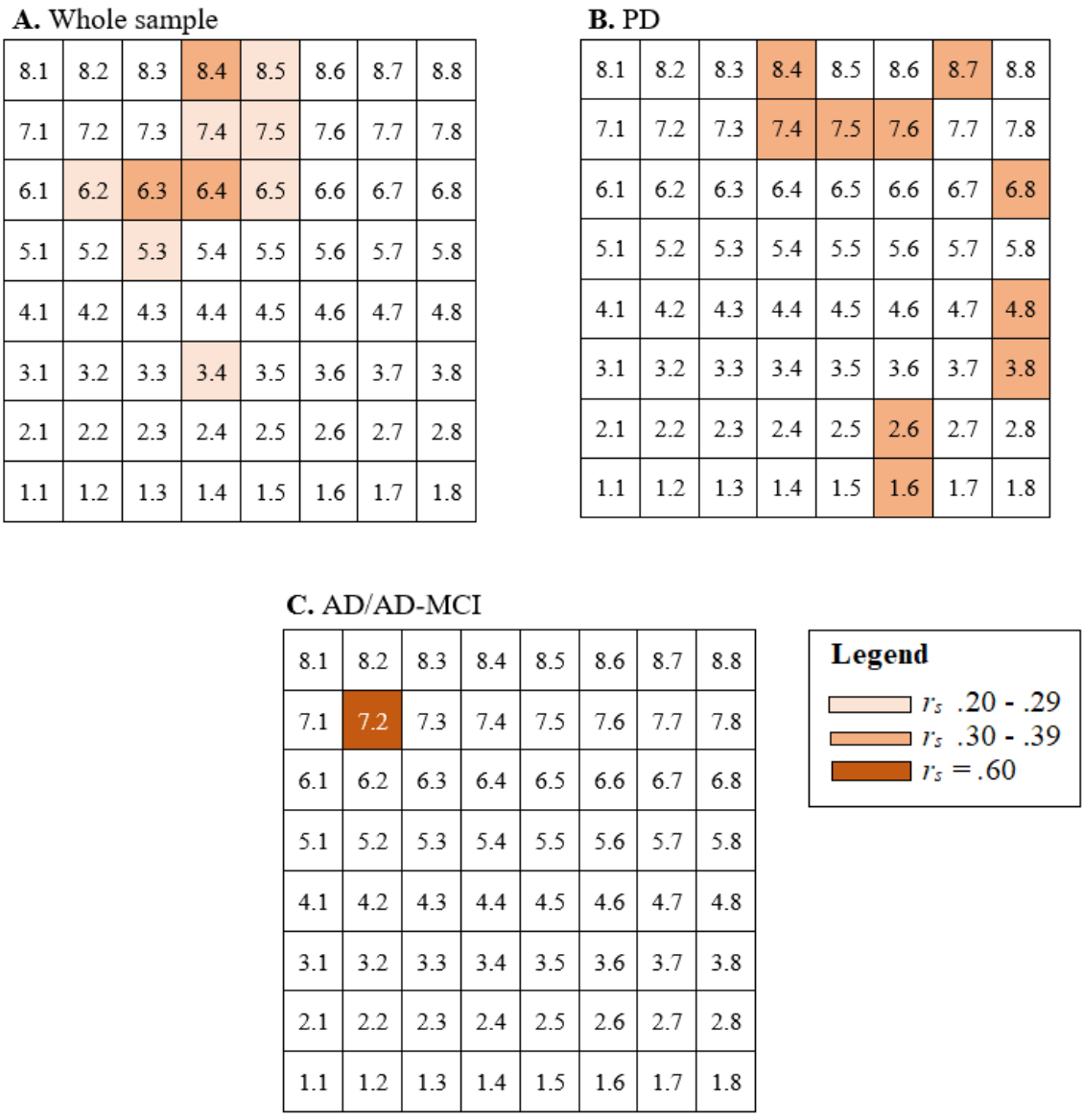
	PD	0.182 (0.273)	0.189 (0.256)	0.208 (0.210)	0.042 (0.800)	0.040 (0.814)	0.197 (0.236)	0.194 (0.243)	0.212 (0.202)
	AD/AD-MCI	0.398 (0.225)	0.396 (0.228)	0.311 (0.352)	0.182 (0.592)	0.169 (0.620)	0.037 (0.915)	0.091 (0.790)	-0.073 (0.831)
	Controls	-0.174 (0.404)	-0.164 (0.434)	-0.076 (0.717)	-0.205 (0.326)	-0.114 (0.589)	-0.135 (0.521)	-0.048 (0.820)	-0.015 (0.943)
4	Across groups	0.186 (0.112)	0.228 (0.051)	0.212 (0.070)	0.011 (0.924)	-0.021 (0.861)	0.064 (0.586)	0.028 (0.812)	0.149 (0.205)
	PD	0.221 (0.183)	0.217 (0.191)	0.201 (0.227)	0.020 (0.903)	-0.067 (0.688)	0.025 (0.882)	0.101 (0.545)	**0.343 (0.035)***
	AD/AD-MCI	0.456 (0.159)	0.374 (0.258)	0.018 (0.957)	0.076 (0.825)	0.128 (0.709)	0.032 (0.926)	0.255 (0.449)	-0.078 (0.819)
	Controls	-0.185 (0.375)	-0.145 (0.488)	-0.162 (0.439)	-0.230 (0.269)	-0.097 (0.643)	-0.120 (0.568)	-0.033 (0.877)	-0.054 (0.799)
3	Across groups	0.177 (0.131)	0.169 (0.151)	0.201 (0.086)	**0.240 (0.039)***	0.163 (0.166)	0.076 (0.522)	0.028 (0.810)	0.100 (0.397)
	PD	0.187 (0.260)	0.188 (0.258)	0.195 (0.240)	0.256 (0.121)	0.180 (0.281)	0.129 (0.440)	0.285 (0.083)	**0.370 (0.022)***
	AD/AD-MCI	0.260 (0.441)	0.442 (0.174)	0.274 (0.415)	-0.114 (0.739)	0.032 (0.926)	0.059 (0.862)	-0.110 (0.748)	-0.048 (0.889)
	Controls	0.058 (0.783)	0.028 (0.895)	-0.097 (0.645)	-0.050 (0.812)	-0.042 (0.842)	0.109 (0.604)	0.034 (0.872)	-0.131 (0.533)
2	Across groups	0.030 (0.800)	0.108 (0.362)	0.130 (0.269)	0.129 (0.273)	0.045 (0.704)	0.012 (0.919)	0.069 (0.557)	0.125 (0.290)
	PD	0.118 (0.482)	0.216 (0.192)	0.218 (0.189)	0.251 (0.128)	0.230 (0.165)	**0.334 (0.041)***	0.302 (0.066)	0.303 (0.064)
	AD/AD-MCI	0.214 (0.527)	0.064 (0.852)	0.263 (0.435)	0.021 (0.952)	-0.064 (0.852)	0.030 (0.931)	0.037 (0.915)	0.428 (0.189)
	Controls	-0.018 (0.930)	0.043 (0.838)	-0.090 (0.670)	-0.110 (0.600)	-0.088 (0.676)	-0.095 (0.653)	-0.179 (0.393)	0.068 (0.748)
1	Across groups	0.098 (0.405)	0.064 (0.587)	0.011 (0.926)	0.038 (0.748)	0.072 (0.540)	0.103 (0.383)	0.071 (0.549)	-0.023 (0.847)
	PD	0.052 (0.759)	0.130 (0.436)	0.137 (0.411)	0.209 (0.207)	0.300 (0.067)	**0.322 (0.049)***	0.165 (0.323)	-0.063 (0.705)
	AD/AD-MCI	0.465 (0.150)	0.314 (0.346)	0.410 (0.210)	0.378 (0.252)	0.398 (0.225)	0.278 (0.408)	0.569 (0.067)	0.525 (0.097)
	Controls	-0.007 (0.975)	-0.107 (0.612)	-0.119 (0.570)	-0.232 (0.264)	-0.197 (0.346)	-0.148 (0.481)	0.209 (0.316)	0.286 (0.165)

Note. The values are presented as Spearman's rho (*p*-value). The present table represents Figure 2A and is not a matrix table – it should be read from left to right (the first grid point number is the row's number, the second grid point number is the column's number) in order to understand to which exact retinal grid

point the value corresponds. Abbreviations: PD = Parkinson's disease; PDD = dementia associated with Parkinson's disease; PD-MCI = mild cognitive impairment associated with Parkinson's disease; AD = Alzheimer's disease; AD-MCI = amnestic cognitive impairment. * $p \leq .050$. ** $p \leq .010$.

In total, 18 OCT output areas were discovered to be significantly associated with ACE-R total score. All of the weak but significant associations were positive – as retinal thickness increased, so did the global cognition scores. Retinal thickness in areas 3.4, 5.3, 6.2, 6.3, 6.4, 6.5, 7.4, 7.5, 8.4, and 8.5 was found to be weakly significantly associated with ACE-R total score when analysed at the level of the whole sample (r_s ranged from .24 to .32, $p < .050$ for all, Figure 3A). Furthermore, areas 1.6, 2.6, 3.8, 4.8, 6.8, 7.4, 7.5, 7.6, 8.4 and 8.7 were found to be weakly significantly associated with ACE-R total score within the PD group (r_s ranged from .32 to .37, $p < .050$ for all, Figure 3B). Lastly, retinal thickness in area 7.2 was strongly significantly associated with ACE-R total score only within the AD/AD-MCI group ($r_s(9) = .60$, $p = .050$, Figure 3C). No significant associations between retinal thickness and global cognition were found within the control group ($p > .165$ for all).

Figure 3. *Patterns of Correlations Between Retinal Thickness Across the 64 OCT Output Areas and ACE-R Total Score, as well as Their Corresponding Strength.*



Note. (A) Correlation strength across the whole sample. (B) Correlation strength within the PD group. (C) Correlation strength within the AD/AD-MCI group. Abbreviations: PD = Parkinson's disease; PDD = dementia associated with Parkinson's disease; PD-MCI = mild cognitive impairment associated with Parkinson's disease; AD = Alzheimer's disease; AD-MCI = amnestic cognitive impairment.

The last step in the analysis was to investigate whether retinal thickness could predict ACE-R total score. To achieve this, hierarchical multiple linear regression analysis was performed, with ACE-R total score as the dependent variable (Table 6). Backwards stepwise multiple linear regression was employed to generate a basic model predicting ACE-R total score. Gender, age, years in education and MDS-UPDRS III total score were all entered into the model. Gender and years in education were the only significant predictors of ACE-R total score, and thus formed the basic model (R^2 *adj* = .151, $F(2, 73) = 7.679$, $p = .001$).

Table 6. *Hierarchical Multiple Linear Regression Model Statistics for the PD Group.*

Model	Test statistics					
	R^2 *adj*.	*F* (df)	*p*-value[a]	β	*t* (df)	*p*-value[b]
Basic model	.151	7.679 (2, 73)	.001**			
Years in education				.231	2.169 (73)	.033*
Gender				.356	3.343 (73)	.001**
PD group						
Basic model† + 8.7	.343	7.439 (3, 34)	.001**	.303	2.269 (34)	.030*
Basic model† + 6.8	.327	7.000 (3, 34)	.001**	.277	2.058 (34)	.047*

Note. Abbreviations: MDS-UPDRS III = The Movement Disorder Society – Unified Parkinson's Disease Rating Scale Part III. [a] Associated with ANOVA. [b] Associated with the independent t-test. * $p \leq .050$. ** $p \leq .010$. † Co-variates included in the model are years of education and gender.

Hierarchical backwards multiple linear regression analysis was used to establish whether retinal thickness was associated with ACE-R total score. It was performed separately for each group. Retinal thickness variables used in this part of the analysis included those retinal grid points which significantly correlated with ACE-R total score. No significant associations were found in controls or AD/AD-MCI participants ($p > .050$ for all). In PD participants, only areas 8.7 ($\beta = .303$, $t(34) = 2.269$, $p = .030$) and 6.8 ($\beta = .277$, $t(34) = 2.058$, $p = .047$) were discovered

to significantly predict ACE-R total score while controlling for gender and years in education (Table 6).

Discussion

The aim of the present investigation was to analyse retinal thickness differences among patients with mild cognitive impairment or dementia associated with PD and AD. In addition, the study aimed to explore associations between retinal thickness and global cognition. As predicted, PDD and PD-MCI participants were discovered to exhibit significantly more pronounced retinal thinning than healthy controls or PD participants. However, no significant retinal thickness differences were observed in AD or PD participants. Therefore, the hypothesis that patients with mild cognitive impairment or dementia associated with PD and AD exhibit reduced retinal thickness compared to controls was only partially supported. As no evidence of retinal thinning in AD patients was found, the hypothesis that retinal thinning patterns differ between PD and AD subjects was not supported. Nonetheless, global cognitive functioning was found to be positively associated with retinal thickness in several different parts of the retina, although more so for PD, PDD and PD-MCI patients than for AD participants. No significant correlations were found in the control group. Furthermore, two areas in the superior-temporal quadrant of the retina were found to predict global cognition scores while controlling for gender and years in education, but only in PD, PDD and PD-MCI subjects. No similar findings were observed for AD or control participants. Nonetheless, the hypothesis that retinal thickness is associated with global cognition in PD and AD was fully supported.

The finding that PDD and PD-MCI patients have reduced retinal thickness compared to healthy controls is consistent across the literature (Moreno-Ramos et al., 2013; Cheung et al.,

2017). The present study identified four areas in the PDD and PD-MCI retina that exhibit thinning. Three of these areas were located in the temporal quadrant of the retina, one near the macula and two near the peripapillary region of the optic disc, while one of the areas was observed in the inferotemporal quadrant of the retina. These results in part mirror the findings of a previous study, which discovered a reduction of the RNFL thickness in the peripapillary region of the PDD retina (Moreno-Ramos, 2013). In addition, reduced retinal thickness in the macular area (Ma et al., 2018), papillomacular bundle (La Morgia et al., 2013) and inferotemporal quadrant (Inzelberg, Ramirez, Nisipeanu & Ophir, 2004) have been reported in people with PD. However, the present study did not find any retinal thickness differences in PD participants. Such findings do not support previous literature (Yu et al., 2014). It could be the case that in PD patients, significant degeneration of retinal thickness is potentially confined within individual layers of the retina, and therefore is not severe enough to be observed when total mean retinal thickness is analysed. Indeed, several studies have found significant reductions in photoreceptor (Roth et al., 2014), ganglion cell as well as inner and outer plexiform layers (Garcia-Martin et al., 2014) in PD patients. Therefore, such findings suggest that measuring distinct retinal layers might potentially yield more accurate representations of how retinal thickness differs in people with PD than measuring total mean retinal thickness. Further research should also consider examining how thickness across individual layers of the retina differs in PDD and PD-MCI patients since similar retinal pathologies in PD have also been implicated in PDD as well as PD-MCI (Cheung et al., 2017).

Contrary to the hypotheses and predictions of the present study, no retinal thickness differences were observed in AD participants. Literature concerning retinal thinning in people with AD is in disagreement, with some studies finding no links between the two (Pillai et al.,

2016; Uchida et al., 2018). However, a meta-analysis by den Haan, Verbraak, Visser, & Bouwman (2017) demonstrated that, across 24 studies, the RNFL as well as macular thickness in AD patients is significantly decreased when compared to healthy controls. Therefore, the finding that people with AD do not differ from healthy controls in their retinal thickness is not consistent with previous literature. No detection of retinal thickness differences in AD participants in the present study could be due to the small AD group size (n = 11). Such a small group size might reduce the study's statistical power, leading to an increased probability of a Type II error – accepting a false null hypothesis (Faber & Fonseca, 2014). Moreover, Ito et al. (2020) demonstrated that people with AD show reduced thickness in the RNFL, ganglion cell-inner plexiform layer and ganglion cell complex. Therefore, similarly to PD participants, the deterioration of individual retinal layer thickness in AD retina might not be substantial enough for a distinguishable reduction in total mean retinal thickness. Thus, further research should consider recruiting more AD participants to allow for meaningful interpretations of results. In addition, further research should also consider measuring individual retinal layer thickness differences in AD patients as the total mean retinal thickness might not be representative of retinal pathologies in AD.

In line with the evidence of retinal thinning in PDD and PD-MCI patients, retinal thickness was found to correlate positively with global cognition. In the PD-combined group, 10 retinal areas were found to be associated with cognitive functioning, ranging from superior-temporal to inferotemporal quadrants of the retina. Similar findings have been observed in previous studies (Zhang et al., 2021). However, all of the correlations in the PD-combined group were weak. Such findings suggest that although there is an association across multiple areas of the retina between retinal thickness in PD, PDD and PD-MCI participants and global cognition,

most of the observed relationships are not robust. Nevertheless, two areas in the superior-temporal quadrant of the retina were found to predict global cognitive functioning in the PD-combined group, with gender and years in education being controlled for. Therefore, these findings demonstrate that retinal thickness in the superior-temporal quadrant of the retina could potentially act as a biomarker for identifying dementia or cognitive impairment associated with PD. Clinical validation of such a biomarker could aid professionals in detecting PDD or PD-MCI early in the progression of the disease as well as in developing accessible, population-wide treatment options (Snyder et al., 2021). However, more sophisticated statistical analysis is needed to assess whether retinal thickness is an effective and accurate indicator of cognitive impairment or dementia in PD. For example, receiver operating curve (ROC) analysis could be employed to evaluate retinal thickness's diagnostic ability as a biomarker (Søreide, 2009).

In contrast, only one area in the temporal retinal quadrant was discovered to correlate with global cognition in AD participants. Nevertheless, the observed correlation was strong, indicating a robust relationship between retinal thickness and cognitive functioning. Such a discrepancy in correlational findings could be due to the difference in group sizes. The AD group (n = 11) was more than three times smaller than the PD-combined group (n = 38). Therefore, due to the reduced statistical power within the AD group, the relationship between retinal thickness in AD participants and global cognition had to be several times greater than that observed for the PD-combined group to be considered significant. Indeed, strength of the correlations in many parts of the AD retina exceeded that seen in the PD-combined group. Therefore, the above-mentioned findings cannot be meaningfully compared between the groups. Further research should consider recruiting clinical groups of similar sizes in order to meaningfully compare results between them. Moreover, due to the small AD group size, some of the potentially

significant correlational analysis results within the AD group may have been masked by a potential Type II error. Thus, although results of the present study indicate that retinal thickness is associated with global cognitive functioning in only one area of the AD retina, no definitive conclusions about relationships between other retinal areas and global cognition in AD could be drawn.

The present study has several advantages over previous studies that were investigating the relationship between retinal thickness and cognitive impairment in PD and AD. Firstly, axial length as well as refraction error were controlled for by entering them into the Spectralis® SD-OCT imaging system prior to obtaining retinal scans. Long axial length has been found to skew OCT imaging results by magnifying retinal thickness measurements (Kang, Hong, Im, Lee & Ahn, 2010). Furthermore, the present study used true eye-tracking technology within the Spectralis® SD-OCT imaging system, which allows for an increased accuracy of measurement (Hafner et al., 2018). Lastly, the present study analysed retinal thickness differences across 64 different retinal areas, which allowed for a detection of more localised differences in the retina.

As with any other study, there are several limitations that must be addressed. Namely, the sample of the present study was small. As discussed earlier, small sample sizes might reduce the study's statistical power, increasing the probability of a Type II error (Faber & Fonseca, 2014). Furthermore, there were inconsistencies in gender proportions within the PDD an PD-MCI and control groups, with the PDD and PD-MCI group being predominantly male and the control group being predominantly female. Such gender discrepancies between the groups might interfere with meaningfully comparing results between them due to sex differences that might affect the data (Gillies, Pienaar, Vohra & Qamhawi, 2014). Further research should consider recruiting group samples with equal gender proportions. Lastly, due to the cross-sectional design,

the study lacks longitudinal data, and thus is unable to establish any cause-and-effect interactions (Wang & Cheng, 2020). Further research is encouraged to follow up on participants in order to investigate whether any changes occur in the relationship between retinal thickness and global cognition over time.

To conclude, the present study has shown that retinal thickness is associated with cognitive impairment in PD, but not in AD. PDD and PD-MCI patients were found to exhibit retinal thinning in the temporal and inferotemporal quadrants of the retina. In addition, PD, PDD and PD-MCI patients demonstrated associations between retinal thickness and global cognition in temporal, inferotemporal and superior-temporal areas of the retina. However, these relationships were weak. Nonetheless, retinal thickness in two areas of the superior-temporal quadrant of the retina was found to predict global cognitive functioning in PD, PDD and PD-MCI patients after controlling for gender and years in education. These findings demonstrate a prospective role of retinal thickness in the superior-temporal retinal quadrant as a biomarker of cognitive impairment in PD. However, more advanced statistical analyses, such as ROC analysis, are needed to confirm the diagnostic ability of retinal thickness. No significant retinal thickness differences were observed in AD patients. Retinal thickness in only one area of the temporal retinal quadrant was found to be associated with global cognitive functioning in AD patients, demonstrating a strong relationship. However, for definitive conclusions about the relationship between retinal thickness and global cognition in AD to be drawn, a bigger pool of AD participants is required. Further longitudinal studies are needed to confirm the relationship between retinal thickness and global cognition in PD and AD.

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Appendix

Appendix A. *Group Comparison Mann-Whitney U Test Statistics.*

Clinical & demographic information	Pair comparison	Mann-Whitney U test statistics		
		U	z	p
Age[a]	AD/AD-MCI vs. PD	62.000	-3.092	.002***
	AD/AD-MCI vs. PDD/PD-MCI	67.000	-1.623	.105
	AD/AD-MCI vs. Controls	95.000	-2.205	.027
	PD vs. PDD/PD-MCI	128.000	-1.924	.054
	PD vs. Controls	214.000	-2.091	.036
	PDD/PD-MCI vs. Controls	196.000	-0.311	.756
Disease duration[b]	AD/AD-MCI vs. PD	83.000	-2.446	.014**
	AD/AD-MCI vs. PDD/PD-MCI	89.000	-0.658	.511
	PD vs. PDD/PD-MCI	83.000	-3.127	.002*
ACE-R total score[a]	AD/AD-MCI vs. PD	11.500	-4.650	> .001***
	AD/AD-MCI vs. PDD/PD-MCI	49.000	-2.413	.016
	AD/AD-MCI vs. Controls	5.500	-4.880	> .001***
	PD vs. PDD/PD-MCI	69.500	-3.492	> .001***
	PD vs. Controls	187.000	-2.606	.009
	PDD/PD-MCI vs. Controls	24.500	-4.760	> .001***
MDS-UPDRS III total score[a]	AD/AD-MCI vs. PD	10.500	-4.680	> .001***
	AD/AD-MCI vs. PDD/PD-MCI	0.000	-4.565	> .001***
	AD/AD-MCI vs. Controls	118.500	-1.508	.131
	PD vs. PDD/PD-MCI	50.500	-3.999	> .001***
	PD vs. Controls	4.000	-6.053	> .001***
	PDD/PD-MCI vs. Controls	0.000	-5.394	> .001***
	AD/AD-MCI vs. PD	9.000	-5.148	> .001***

	AD/AD-MCI vs. PDD/PD-MCI	3.500	-4.632	> .001***
	AD/AD-MCI vs. Controls	168.000	-0.064	.949
MDS-UPDRS Hoehn and Yahr stage[a]	PD vs. PDD/PD-MCI	125.000	-2.291	.022
	PD vs. Controls	0.000	-6.638	> .001***
	PDD/PD-MCI vs. Controls	0.000	-5.994	> .001***

Note. Abbreviations: PD = Parkinson's disease; PDD = dementia associated with Parkinson's disease; PD-MCI = mild cognitive impairment associated with Parkinson's disease; AD = Alzheimer's disease; AD-MCI = amnestic cognitive impairment; IQR = interquartile range; ACE-R = Addenbrooke's Cognitive Examination Revised; MDS-UPDRS = The Movement Disorder Society – Unified Parkinson's Disease Rating Scale; MDS-UPDRS III = The Movement Disorder Society – Unified Parkinson's Disease Rating Scale Part III. [a] Bonferroni's adjusted $\alpha = .008$. [b] Bonferroni's adjusted $\alpha = .017$. ** $p \leq .010$. *** $p \leq .001$.