

RESEARCH ARTICLE

Optical coherence tomography as a potential biomarker for the logopenic variant of primary progressive aphasia: A cross-sectional prospective study

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Abstract

BACKGROUND: Optical coherence tomography (OCT) and OCT angiography (OCT-A) have been studied as biomarkers for Alzheimer's disease (AD), with promising results. Nevertheless, their potential in the logopenic variant of primary progressive aphasia (lvPPA), which shares the same amyloid pathology, has not yet been explored. This work aimed to characterize retinal changes in lvPPA compared to healthy controls.

METHODS: Ten participants with lvPPA and eleven controls underwent OCT and OCT-A imaging. Amyloid pathology in lvPPA was confirmed by lumbar puncture. Retinal parameters included retinal nerve fiber layer (RNFL) thickness and foveal avascular zone (FAZ).

RESULTS: Compared to controls, lvPPA participants exhibited reduced RNFL thickness in the temporal sector ($p = 0.013$) and significantly decreased FAZ circularity ($p = 0.002$).

DISCUSSION: RNFL thinning may reflect trans-synaptic degeneration from cortical atrophy, while reduced FAZ circularity suggests early microvascular changes related to amyloid burden. Our findings support OCT and OCT-A as potential biomarkers for lvPPA.

KEYWORDS

Alzheimer's disease, amyloid, foveal avascular zone, logopenic variant of primary progressive aphasia, neurodegeneration, optical coherence tomography, optical coherence tomography angiography, primary progressive aphasia, retinal biomarker, retinal degeneration, retinal nerve fiber layer, retrograde degeneration

Highlights

- For the first time, OCT and OCT-A are studied as potential biomarkers for lvPPA.
- Compared to healthy controls, retinal nerve thickness is decreased in lvPPA patients.
- Retinal vasculature exhibits structural alterations in lvPPA patients.

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1 | BACKGROUND

The retina is considered an extension of the central nervous system (CNS) as both structures embryonically emerge from the diencephalon.¹ There is abundant literature suggesting that physiopathological mechanisms causing CNS degeneration can affect retinal structures in a homologous way.^{2,3} In the last two decades, an increasing number of papers have therefore been published on the potential of retinal imaging as a non-invasive biomarker of neurodegenerative diseases,⁴ especially with the advent of optical coherence tomography (OCT).

Developed by Huang et al. in 1991,⁵ OCT is nowadays part of the routine ophthalmic exam. This technique uses retroreflected light and yields a cross-sectional view of retinal layers with micrometric resolution. Optical coherence tomography angiography (OCT-A) is a more recent non-invasive dye-free angiography technique coupled to the OCT system, allowing for micron-level characterization of retinal vasculature without requiring any contrast injection. Due to their non-invasive nature and high resolution, OCT and OCT-A have rapidly become ideal imaging modalities for the development of retinal biomarkers for various neurocognitive disorders, particularly Alzheimer's disease (AD).^{6,7} In this disease, the most prevalent OCT findings are a decrease in retinal nerve fiber layer (RNFL) thickness, macular thickness, and ganglion cell inner plexiform layer (GC-IPL) thickness.⁶ As for OCT-A, the most reported findings in AD are a decrease in retinal vessel density (VD) and perfusion density (PD) of the macular region, enlargement of the foveal avascular zone (FAZ), as well as structural alterations in the retinal vasculature such as vessel caliber and tortuosity changes.^{2,8,9} The two major mechanisms proposed to explain these findings are brain-to-retina retrograde degeneration and amyloid beta (A β)-induced atrophy of retinal neurons.¹⁰ Altogether, a combination of structural and vascular alterations of the neuroretina are both thought to reflect neurodegenerative processes in the brain.

This rapidly growing literature is mostly focused on the amnesic variant of AD.¹¹ Only a few studies have examined the retinal changes in atypical AD variants, namely visual, behavioral, and language variants. Studies in the visual variant AD (also named posterior cortical atrophy or PCA) found either no significant differences in RNFL thickness between AD, PCA, and controls^{12,13} or thinner RNFL and GC-IPL layers as well as vascular alterations.^{12,13} No studies have yet explored the use of OCT in the behavioral variant of AD. The language variant of AD (also named logopenic variant of primary progressive aphasia or lvPPA), is a rare neurodegenerative disorder, which predominantly affects language functions.^{14,15} Clinically, its cardinal symptoms are anomia and impaired repetition, especially of the latter part of long sentences¹⁶. Disease progression brings a global cognitive decline with increasing difficulties in visuospatial and executive abilities, memory, and possibly visual apperceptive agnosia.¹⁷⁻¹⁹ From the neuroimaging perspective, lvPPA is characterized by a temporoparietal atrophy of the dominant hemisphere.²⁰ In 2018, a large international study by Bergeron et al. showed that, in 86% of lvPPA cases, the underlying neuropathology is amyloidopathy similar to AD.²¹

RESEARCH IN CONTEXT

1. **Systematic review:** Numerous studies investigated OCT and OCT-A as biomarkers for AD. In 2018, Bergeron et al. reported that up to 86% of patients with lvPPA had underlying amyloid pathology similar to AD. As of March 23rd, 2025, the authors conducted a literature search in PubMed and found no OCT or OCT-A data in lvPPA.
2. **Interpretation:** Compared to healthy controls, lvPPA patients exhibited significant retinal nerve thinning, as well as notably altered retinal vasculature. Altogether, these findings suggest that OCT and OCT-A could serve as valuable biomarkers for the diagnosis of lvPPA.
3. **Future directions:** Based on our data, future studies should aim to generate longitudinal data which could provide insights into the dynamic progression of retinal degeneration in lvPPA. OCT-A parameters would also benefit from a more standardized framework for its analysis and interpretation.

To this date, no research group has studied OCT/OCT-A as a biomarker of lvPPA. Given existing literature on retinal findings in AD and the common pathogenesis underlying lvPPA and AD, our goal was to explore possible differences in OCT/OCT-A between lvPPA and healthy controls (HCs).

2 | METHODS

2.1 | Study participants

We conducted a cross-sectional prospective study including patients with lvPPA followed at our memory clinic (CHU de Québec – Université Laval, Québec, Canada) and HCs matched for age and sex. Participants with lvPPA were diagnosed by a behavioral neurologist specialized in cognitive neurology based on the criteria established by Gorno-Tempini et al.¹⁶ HCs were volunteers with no history of cognitive impairment. Exclusion criteria were: presence of a neurological disorder that could significantly alter cognitive functions (e.g., active substance use disorder, history of stroke or traumatic brain injury, depressive or bipolar disorders), an ophthalmic condition that may impair the integrity of the retina and/or optic nerve (e.g., glaucoma, age-related macular degeneration, optic neuritis), a systemic disease that could affect the retina (diabetes mellitus, uncontrolled high blood pressure, cancer, long-term corticosteroids use, renal failure, and cardiovascular diseases), an ophthalmic condition that may interfere with OCT/OCT-A imaging (dense cataract as defined by Lens Opacities Classification System III,²² nystagmus, strabismus, or visual field defects), or a contraindication to a lumbar puncture (LP; this criteria was applied to the lvPPA group only).

For participants with lvPPA, a first appointment took place at the ophthalmology department of CHU de Québec – Université Laval, and consisted of an extensive ophthalmic examination to rule out the abovementioned conditions, followed by OCT/OCT-A imaging. A second appointment took place at the Clinique Interdisciplinaire de Mémoire (CHU de Québec – Université Laval) and comprised a cognitive assessment as well as an LP. HCs were only required to attend the first appointment. This project received approval from the CHU de Québec Ethics Board according to the Declaration of Helsinki.

2.2 | Ophthalmic examination

Best corrected visual acuity (BCVA) was assessed with a metric Snellen chart and the pinhole test, and was noted in LogMAR units. Visual field perimetry was tested with the Swedish Interactive Testing Algorithm (SITA) Fast 24-2 threshold testing, performed on a Humphrey field analyzer (Carl Zeiss Meditec). An ophthalmologist (A.D.) specialized in retinal diseases then assessed eye alignment and extraocular movements. The anterior segment was assessed using slit lamp biomicroscopy, gonioscopy, and tonometry to confirm there was no contraindication for pupillary dilation. Dilation was performed using tropicamide (1%) and phenylephrine (2.5%) in both eyes. Thirty minutes after dilation, fundus photography, fundus autofluorescence, and OCT/OCT-A imaging protocol were performed. Finally, the retina specialist performed fundoscopic examination to confirm absence of posterior segment pathology that could influence OCT/OCT-A measurements.

2.3 | OCT/OCT-A protocol and parameters

OCT/OCT-A imaging was performed using the Cirrus 6000 HD-OCT System (Carl Zeiss Meditec) and all measurements were directly derived from the automated segmentation software of the system. Both eyes were imaged for all research subjects. RNFL thickness in four quadrants (superior, temporal, inferior, and nasal, Figure 1A) were measured with an Optic Disc Cube of 200 scans $\times$ 200 scans. RNFL represents a layer of axons of retinal ganglion cells that coalesce to form the optic nerve, which projects visual information to the brain.²³ The macular region of the retina is responsible for high-acuity central vision. Macular thickness was centered on the fovea and sectorized according to the Early Treatment Diabetic Retinopathy Study (ETDRS) grid (Figure 1B) in nine sectors (fovea, inner superior, inner temporal, inner inferior, inner nasal, outer superior, outer temporal, outer inferior, and outer nasal). The four inner sectors formed the inner ring, while the four outer sectors formed the outer ring. Macular cube volume was obtained with a Macular Cube of 512 scans $\times$ 128 scans. The GC-IPL layer contains cell bodies of retinal neurons whose axons represent the RNFL. The GC-IPL thickness was measured in six sectors (superior, superior temporal, inferior temporal, inferior, inferior nasal, and superior nasal, Figure 1C). The vascular parameters were acquired with the Cirrus AngioPlex OCT Angiography. High-definition

scans measuring 6 mm $\times$ 6 mm, centered on the fovea and segmented according to the ETDRS grid as detailed previously, were performed (Figure 1D). VD, PD, FAZ area, perimeter, and circularity were derived from the superficial retinal vascular plexus of the macular region. FAZ is the capillary-free area located at the center of the macula and reflects the foveal perfusion status, with an enlarged FAZ usually thought to indicate poorer retinal perfusion.²⁴ The circularity index measures quantitatively how a given FAZ shape is similar to a perfect circle, for which a value of 1.0 means that FAZ has perfectly circular shape.²⁵ No data of the deep plexus were provided by the automated segmentation. Given the exploratory nature of this study and the lack of consensus on the manual delineation and interpretation of OCT-A data, no manual segmentation was undertaken.

2.4 | Cognitive assessment

For lvPPA participants, the Clinical Dementia Rating (CDR) was used to assess severity of the neurocognitive disorder to ensure their comparability. The CDR scale evaluates six functional domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care.^{26,27} For each domain, the impairment can be scored as: 0 (no impairment), 0.5 (questionable impairment), 1 (mild impairment), 2 (moderate impairment), and 3 (severe impairment). A global score, ranging from 0 to 3, is then derived from a computed algorithm²⁸. A global CDR score of 0, 0.5, 1, 2, and 3 represents, respectively, no dementia, very mild (earliest symptomatic stage), mild, moderate, and severe dementia.²⁹ The cognitive assessment was performed by a certified CDR examiner (F.W.) and the scoring was validated by a behavioral neurologist (R.L.) specialized in cognitive neurology and a speech–language pathologist (M.L.) specialized in primary progressive aphasia.

2.5 | Lumbar puncture

An experienced behavioral neurologist (R.L.) performed all LPs in lvPPA participants.

2.6 | Statistical analysis

The Fisher exact test and pooled two-sample *t* test were used to compare the mean sex and age between lvPPA and HC groups, respectively. Visual acuity and intraocular pressure (IOP) means were compared among groups using a two-tailed Mann–Whitney *U* test. To compare OCT/OCT-A parameters between groups, estimated mean values were yielded by a linear mixed model. Unlike raw measurements, this model takes into consideration that both eyes from the same participant are mutually associated. The significance threshold (*p*-value) was set to 0.05. Because of the exploratory nature of this study, no additional adjustments for covariates were performed.

3 | RESULTS

3.1 | Demographic and clinical data

Ten participants with lvPPA and eleven HCs were enrolled in this study. Demographic and clinical data are presented in Table 1. No statistically significant differences were found between groups for sex, age, BCVA, and IOP (all $p > 0.05$). One lvPPA patient refused LP after inclusion due to concerns about side effects. In this particular case, AD pathophysiology was supported by characteristic left parieto-temporal hypometabolism on fluorodeoxyglucose positron emission tomography. All nine other patients had underlying amyloid pathology confirmed by cerebrospinal fluid (CSF) analysis (see Table 1). For lvPPA patients, mean disease duration was ≈ 3 years at assessment and the mean CDR global score was 0.55 ± 0.16 points, which corresponds to very mild dementia. One participant with lvPPA failed to complete all procedures, resulting in missing OCT-A data for that individual. After assessment by an ophthalmologist, one HC and one lvPPA patient had their right eye OCT-A data excluded post hoc due to artifacts. In consequence, for OCT measurements (RNFL, macular thickness, GC-IPL), 22 HC eyes and 20 lvPPA eyes were included for analysis. For OCT-

A measurements (VD, PD, FAZ), 21 HC eyes and 17 lvPPA eyes were included.

3.2 | OCT parameters

Measurements of RNFL thickness for HC and lvPPA participants are presented in Table 2. The estimated mean temporal region RNFL thickness was significantly lower in the lvPPA group compared to HCs ($p = 0.013$; Figure 2A). No statistically significant differences in RNFL were observed in the three other quadrants (all $p > 0.05$) and the average RNFL did not differ among groups ($p = 0.769$). Measurements of macular thickness are presented in Table 3. Estimated mean macular thickness was not significantly different between groups in any specific ETDRS region (all $p > 0.05$). Nevertheless, the estimated average macular thickness was significantly greater in the lvPPA group compared to the HC participants ($p = 0.022$; Figure 2B). The macular cube volume was also significantly higher in the lvPPA group compared to HCs ($p = 0.022$; Table 3). Finally, Table S1 in supporting information presents measurements of GC-IPL in HC and lvPPA participants. Results showed no statistically significant differences between the two groups (all $p > 0.05$).

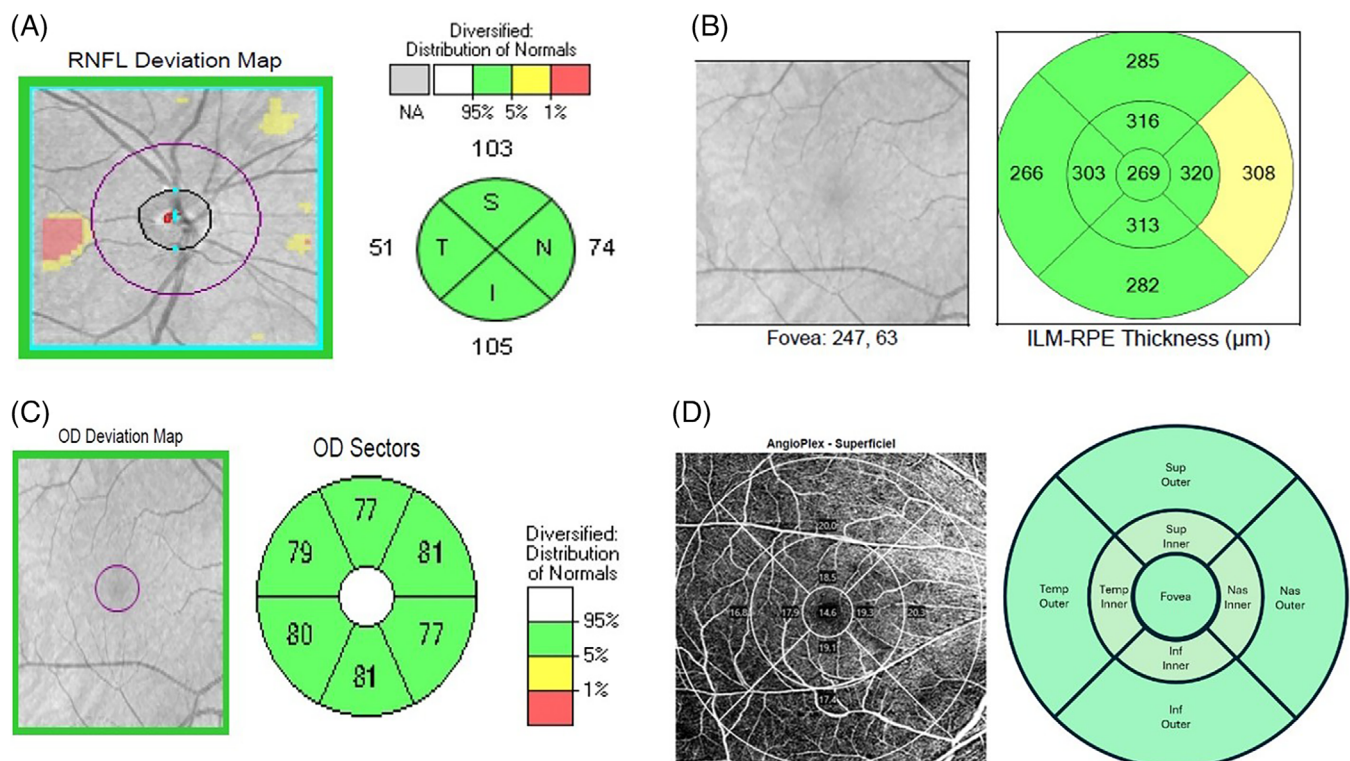


FIGURE 1 Illustrations of OCT/OCT-A imaging. A, RNFL localization and thickness quantification in the four quadrants (S, superior; T, temporal; I, inferior; N, nasal). B, Macular region segmented according to the ETDRS grid and centered on the fovea. Macular thickness quantification in all ETDRS regions. C, GC-IPL localization and thickness quantification in the six regions (superior, superior temporal, inferior temporal, inferior, inferior nasal, and superior nasal). D, Superficial plexus VD measurements in all ETDRS regions, centered on the fovea of the macula. An illustration of the ETDRS grid on the right side. The FAZ is located in the foveal region. Note that PD quantification and segmentation followed the same protocol as VD.

TABLE 1 Participants' demographics.

	HC (n = 11)	lvPPA (n = 10)	p-value
Sex			
Male/female	6/5	6/4	1.000
Age (years)			
Mean (SD)	60.91 (7.18)	60.60 (7.53)	0.924
BCVA (LogMAR)			
Mean (SD)	0.03 (0.06)	0.03 (0.08)	0.516
IOP (mmHg)			
Mean (SD)	14.86 (2.64)	14.35 (1.93)	0.841
CDR global score			
Mean (SD)		0.55 (0.16)	
Disease duration (years)			
Mean (SD)		2.80 (0.79)	
Aβ42 (pg/mL)*			
Mean (SD)		545.67 (102.03)	
T-tau (pg/mL)*			
Mean (SD)		445.00 (148.57)	
P-tau (pg/mL)*			
Mean (SD)		45.78 (16.99)	

Abbreviations: A β , amyloid beta; BCVA, best corrected visual acuity (i.e. with the most recent prescription of corrective lens), a smaller numeric value indicates a better vision; CDR, Clinical Dementia Rating; HC, healthy control; IOP, intraocular pressure; logMAR, logarithm of the minimum angle of resolution; lvPPA, logopenic variant primary progressive aphasia; p-tau, phosphorylated tau protein; SD, standard deviation; p-tau, total tau protein. *Cerebrospinal fluid analysis performed for nine of ten lvPPA patients (one lvPPA patient refused the lumbar puncture, yet his Alzheimer's disease pathophysiology was supported by fluorodeoxyglucose positron emission tomography).

3.3 | OCT-A parameters

Table 4 presents FAZ measurements for HC and lvPPA participants. The FAZ circularity was significantly lower in the lvPPA group compared to HCs ($p = 0.002$; Figure 2C). No statistically significant differences in estimated mean FAZ area and perimeter were found between the two groups ($p = 0.904$ and $p = 0.55$, respectively). VD measurements are presented in Table S2 in supporting information for both groups. The estimated average VD of the inner ring was significantly lower in the lvPPA group compared to the HCs ($p = 0.045$). For specific ETDRS sectors, results showed that estimated mean inner superior VD ($p = 0.004$), inner nasal VD ($p = 0.040$), outer superior VD ($p = 0.017$), and outer nasal VD ($p = 0.029$) were significantly lower in the lvPPA group compared to the HCs. No significant differences in VD were observed in any other specific ETDRS region (all $p > 0.05$). Finally, Table S3 in supporting information presents estimated PD measurements. The estimated mean outer superior PD ($p = 0.020$) and outer nasal PD ($p = 0.047$) were significantly lower in the lvPPA group compared to HC. No other significant differences in PD were observed between the two groups (all $p > 0.05$).

TABLE 2 Estimated RNFL thickness measurements.

Group HC: <i>n</i> = 11; lvPPA: <i>n</i> = 10	Estimated mean thickness (μm)	SEM (μm)	95% CI (μm)	<i>p</i> -value
Superior RNFL				
HC	108.9	2.75	103.2; 114.7	0.589
lvPPA	111.1	2.88	105.1; 117.1	
Temporal RNFL				
HC	75.6	3.16	68.98; 82.20	0.013*
lvPPA	63.1	3.31	56.17; 70.03	
Inferior RNFL				
HC	109.7	4.65	99.95; 119.4	0.282
lvPPA	117.2	4.88	106.9; 127.4	
Nasal RNFL				
HC	64.0	2.32	59.14; 68.86	0.071
lvPPA	70.5	2.44	65.35; 75.55	
Average RNFL				
HC	89.5	2.21	84.92; 94.17	0.769
lvPPA	90.5	2.32	85.65; 95.35	

Abbreviations: CI, confidence interval; HC, healthy control; lvPPA, logopenic variant primary progressive aphasia;

RNFL, retinal nerve fiber layer; SEM, standard error of the mean.

*Statistically significant ($p < 0.05$).

4 | DISCUSSION

We conducted a cross-sectional study to describe the retinal changes in patients with lvPPA compared to HCs. The main findings were decreased RNFL thickness in the temporal sector, increased average macular thickness, as well as significantly decreased FAZ circularity. Over the entire retinal region imaged, average VD and PD values did not differ between lvPPA and controls. Nevertheless, we found that the average VD was weakly, yet significantly, decreased in the inner ring sector ($p = 0.045$). Secondary results include significantly decreased VD in four retinal sectors (inner superior, inner nasal, outer superior, and outer nasal), and significantly decreased PD in two sectors (outer superior, outer nasal). Our findings closely mirror prior data in AD. Specifically, RNFL thinning—consistently reported as the most common OCT finding in AD⁶—was also evident in our lvPPA cohort. Similarly, reductions in VD and PD, well established in AD,⁹ were observed. These parallels remain align closely with our rationale of a shared neurodegenerative mechanism between AD and lvPPA.

In AD, two main mechanisms have been put forward to explain the RNFL thinning, which are the retrograde hypothesis and the A β hypothesis. The retrograde hypothesis advances that when disease-induced brain atrophy occurs in regions through which the optic pathways (optic nerve, optic tract, lateral geniculate nucleus, and visual cortex) pass, the retinal neurons suffer degeneration secondarily due to their loss of postsynaptic target³⁰ and trophic support.³¹ Pathological evidence corroborates this theory. Indeed, Leuba et al. studied post

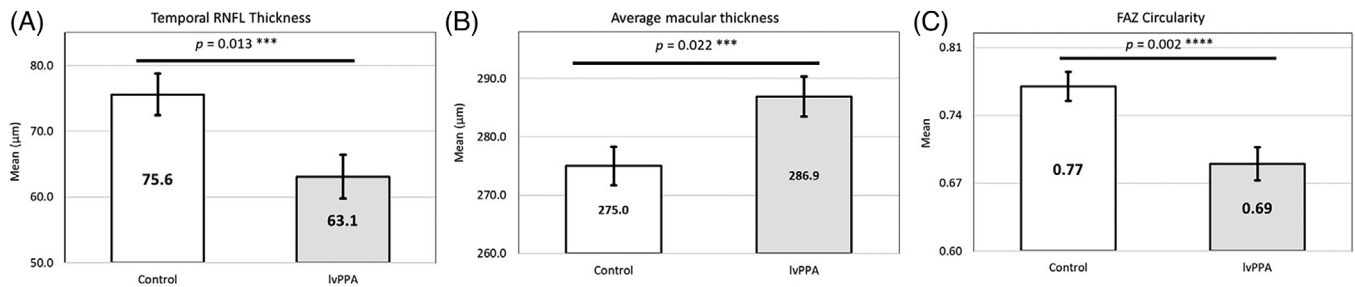


FIGURE 2 Bar graphs showing differences in OCT/OCT-A parameters among groups. A, Estimated mean temporal RNFL thickness among groups. B, Estimated mean average macular thickness among groups. C, Estimated mean FAZ circularity among groups. In this linear mixed model, left and right eyes from the same participant are considered mutually associated. ***Statistically significant ($p < 0.05$). **** $p < 0.005$. FAZ, foveal avascular zone; OCT, optical coherence tomography; OCT-A, optical coherence tomography angiography; RNFL, retinal nerve fiber layer.

mortem AD brains and found senile plaques in both the magnocellular and parvocellular cell layers of the lateral geniculate nucleus, the lateral inferior pulvinar nucleus, the superior colliculus, and the primary visual cortex.³² Sadun et al. studied the optic nerve from AD patients and found an overall decrease in optic nerve axon density and diameter compared to age-matched controls. They also observed nuclear pyknosis and disintegration, considered signs of apoptosis,³³ in retinal ganglion cells from AD retinas.³⁴ The $A\beta$ hypothesis states that abnormal retinal accumulation of $A\beta$ could induce both neuronal and vascular degeneration of the retina. Numerous studies have confirmed the presence of $A\beta$ in AD retinas.³⁵ Immunopathological evidence showed that retinal layers where these proteinaceous deposits were found matched the regions where cell loss was observed.³⁶ From the vascular standpoint, several $A\beta$ -induced mechanisms of degeneration have been proposed to explain the decrease in VD and PD. In retinas from AD patients, Shi et al. reported immunofluorescent evidence of $A\beta$ plaque accumulation in the lumen of retinal vessels adjacent to endothelial cells, inside pericytes, and in perivascular space. These changes occurred in conjunction with pericyte loss,³⁷ contributing to the vascular degeneration of the retina. The $A\beta$ accumulation is also thought to exert compressive forces to retinal vessels,³⁸ thus inducing tissular hypoxia.

In our study, the region specificity of RNFL thinning was, however, different from previous studies conducted in AD. Indeed, we showed significant RNFL thinning in the temporal quadrant in our lvPPA cohort. In contrast, studies applying OCT to AD showed RNFL atrophy to be most pronounced in the superior quadrant, followed by the inferior quadrant, while nasal and temporal quadrants usually exhibited less RNFL thinning.^{6,39} A possible explanation is that superior and inferior quadrants are the thickest regions of RNFL, thus containing more neurons and being more susceptible to degeneration.^{39,40} Because our study is the first to explore OCT in lvPPA, we hypothesize that lvPPA may exhibit a distinct retinal degeneration pattern from that of AD. If this finding is confirmed by further studies, OCT would have an even greater value in describing the pathological signature of lvPPA compared to AD.

A major yet unexpected finding of our study is the significantly altered FAZ circularity in lvPPA participants, with preservation of the FAZ area. In the existing literature, enlarged FAZ was far more

extensively reported in AD than the alteration of FAZ circularity. The main mechanisms to explain this loss of vascularization include those detailed above, as well as that of reduced angiogenesis. Vascular endothelial growth factor responsible for angiogenesis is thought to be blocked by and confined in the $A\beta$ plaques.⁴¹ Nevertheless, as pointed out by Linderman et al., the FAZ area exhibits substantial variation even among normal individuals,⁴² while FAZ circularity changes are more sensitive to minor changes because early FAZ morphology changes could significantly alter FAZ circularity while maintaining a similar FAZ area. Evidence also suggested that the circularity index is less affected by normal variance, thus yielding better repeatability and reproducibility.⁴³ It is worth highlighting that, as shown by their mean CDR score, our lvPPA patients were at a very mild stage of dementia. Consequently, our results most probably captured an early stage of vascular alterations in lvPPA, with altered FAZ shape measurements yet preserved FAZ area.

Another interesting finding is the significantly increased macular thickness and macular cube volume in our lvPPA cohort. Although the majority of studies have showed decreased macular volume and thickness in AD, these results are less consistent than those regarding RNFL thinning.⁶ Nevertheless, thickening of the macula has been reported in different stages of AD. For example, Lad et al. found significant thickening of specific retinal areas coexisting with areas of retinal thinning in AD and mild cognitive impairment (MCI) retinas compared to the controls. However, their average macula thickness did not significantly differ between AD, MCI, and controls.⁴⁴ Ascaso et al. found significantly increased macular thickness in MCI patients, contrasting to significantly decreased macular thickness in AD patients.⁴⁵ Although these heterogeneous results may be attributed to variations in methods or subject characteristics, it is worth highlighting that one model of progressive degeneration has recently gained increasing recognition in explaining these dynamic changes in retinal thickness. This model advances that in early stages of AD, the transient retinal thickening could be the result of inflammatory processes such as gliosis, before the eventual death of retinal neurons in more advanced disease stages.^{44,45} This inflammatory hypertrophy, or swelling, of astrocytes and neurons could be secondary to ischemia or $A\beta$ -induced cytotoxicity, the mechanisms of which have been detailed above. Because lvPPA patients in this study were at a fairly early stage of dementia

TABLE 3 Estimated macular measurements.

Group HC: n = 11; lvPPA: n = 10	Estimated mean thickness (μm)	SEM (μm)	95% CI (μm)	p-value
Foveal MT				
HC	271.1	6.26	258.0; 284.2	0.394
lvPPA	278.9	6.40	265.5; 292.3	
Inner superior MT				
HC	322.4	4.13	313.8; 331.1	0.384
lvPPA	327.8	4.33	318.7; 336.8	
Inner temporal MT				
HC	311.2	4.22	302.4; 320.1	0.234
lvPPA	318.8	4.42	309.5; 328.0	
Inner inferior MT				
HC	320.1	4.67	310.4; 329.9	0.421
lvPPA	325.7	4.90	315.5; 335.9	
Inner nasal MT				
HC	326.6	4.55	317.0; 336.1	0.347
lvPPA	332.9	4.77	322.9; 342.9	
Average inner ring MT				
HC	320.1	4.25	311.2; 329.0	0.327
lvPPA	326.3	4.46	316.9; 335.6	
Outer superior MT				
HC	274.8	3.58	267.3; 282.3	0.255
lvPPA	280.9	3.75	273.0; 288.8	
Outer temporal MT				
HC	258.4	3.67	250.7; 266.0	0.086
lvPPA	268.0	3.85	260.0; 276.0	
Outer inferior MT				
HC	265.2	4.51	255.7; 274.6	0.144
lvPPA	275.2	4.74	265.2; 285.1	
Outer nasal MT				
HC	294.3	4.62	284.6; 303.9	0.259
lvPPA	302.0	4.72	292.1; 311.8	
Average outer ring MT				
HC	273.2	3.81	265.2; 281.1	0.148
lvPPA	281.5	4.00	273.1; 289.9	
Average MT				
HC	275.0	3.30	268.0; 281.9	0.022*
lvPPA	286.9	3.46	279.6; 294.1	
Group HC: n = 11; lvPPA: n = 10	Estimated mean volume (mm ³)	SEM (mm ³)	95% CI (mm ³)	p-value
Macular cube volume				
HC	9.90	0.118	9.65; 10.15	0.022*
lvPPA	10.33	0.123	10.07; 10.58	

Abbreviations: CI, confidence interval; HC, healthy control; lvPPA, logopenic variant primary progressive aphasia; MT, macular thickness; SEM, standard error of the mean.

*Statistically significant ($p < 0.05$).

TABLE 4 Estimated FAZ measurements.

FAZ area	Estimated mean area (mm ²)	SEM (mm ²)	95% CI (mm ²)	p-value
HC (n = 11)	0.20	0.029	0.14; 0.26	0.904
lvPPA (n = 10)	0.21	0.038	0.13; 0.29	
HC (n = 11)	1.76	0.129	1.49; 2.03	0.55
lvPPA (n = 10)	1.89	0.174	1.53; 2.26	
HC (n = 11)	0.77	0.015	0.74; 0.80	0.002**
lvPPA (n = 10)	0.69	0.017	0.65; 0.72	

Abbreviations: CI, confidence interval; FAZ, foveal avascular zone; HC, healthy control; lvPPA, logopenic variant primary progressive aphasia; SEM, standard error of the mean.

**Statistically significant ($p < 0.005$).

progression, our results could be due to this transient, inflammatory macular thickening preceding the eventual thinning of the retina.

We identified three main limitations in our study. Careful selection of patients with no comorbid and confounding eye diseases, as well as pathophysiological proof of underlying amyloid pathology yielded a small group of only 10 lvPPA patients. One must consider that this is a relatively rare disease of much lower prevalence than typical amnesic AD. Researchers in the field typically publish data on similar sample sizes although multicenter projects should be undertaken in the future to increase statistical power. Second, due to the exploratory nature of this study, our OCT-A results were solely based on the automated analysis of Cirrus 6000, limiting the extent of our interpretation. Third, like most studies in this field,⁶ our study was cross-sectional, thus the hypotheses and models inferred could not be validated. Again, future studies should favor multi-institutional collaborations. Use of multiple FAZ parameters, such as the acircularity index and the axial ratio⁴² could generate a more reliable picture of retinal perfusion state. Additionally, based on our exploratory data, future studies should formulate more targeted hypotheses to avoid multiple comparisons fallacy. Finally, with long-term follow-up of test subjects, longitudinal data would provide insights to the dynamic progression of retinal degeneration in rare neurodegenerative conditions like lvPPA.

Our study used a rigorous methodology, an extensive analysis of mechanisms, and a creative study design. With our stringent selection criteria and thorough ophthalmic examination, we were able to exclude most confounders. The CSF analysis prevented non-amyloidopathy cases of lvPPA from confounding the conclusions. As shown by our demographic data, our groups exhibit high comparability. Furthermore, in addition to a descriptive overview of retinal manifestations, we provided a detailed discussion on possible contributing mechanisms and models of progressive degeneration.

To the best of our knowledge, this study is the first to characterize the retinal changes in lvPPA. Our work provides preliminary data to this previously understudied field of the literature. This study could serve as a promising foundation for future research aimed to characterizing retinal features in atypical dementias, eventually contributing to the development of effective and non-invasive retinal biomarkers to better diagnose such cognitive conditions.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the [supporting information](#).

CONSENT STATEMENT

All human subjects provided informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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