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Using Optical Coherence Tomography to Screen for Cognitive Impairment and Dementia

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Abstract

Background: Screening for Alzheimer's disease and related disorders (ADRD) and mild cognitive impairment (MCI) could increase case identification, enhance clinical trial enrollment, and enable early intervention. MCI and ADRD screening would be most beneficial if detection measures reflect neurodegenerative changes. Optical coherence tomography (OCT) could be a marker of neurodegeneration (part of the amyloid-tau-neurodegeneration (ATN) framework).

Objective: To determine whether OCT measurements can be used as a screening measure to detect individuals with MCI and ADRD.

Methods: A retrospective cross-sectional study was performed on 136 participants with comprehensive clinical, cognitive, functional, and behavioral evaluations including OCT with a subset ($n = 76$) completing volumetric MRI. Pearson correlation coefficients tested strength of association between OCT and outcome measures. Receiver operator characteristic curves assessed the ability of OCT, patient-reported outcomes, and cognitive performance measures to discriminate between individuals with and without cognitive impairment.

Results: After controlling for age, of the 6 OCT measurements collected, granular cell layer-inner plexiform layer (GCL + IPL) thickness best correlated with memory, global cognitive performance, Clinical Dementia Rating, and hippocampal atrophy. GCL + IPL thickness provided good discrimination in cognitive status with a cut-off score of 75 μm. Combining GCL + IPL thickness as aproxy marker for hippocampal atrophy with a brief patient-reported outcome and performance measure correctly classified 87% of MCI and ADRD participants.

Conclusion: Multimodal approaches may improve recognition of MCI and ADRD. OCT has the potential to be a practical, non-invasive biomarker for ADRD providing a screening platform to quickly identify at-risk individuals for further clinical evaluation or research enrollment.

Keywords

Alzheimer's disease; dementia; granular cell layer; internal plexiform layer; mild cognitive impairment; optical coherence tomography

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INTRODUCTION

Alzheimer's disease (AD) [1] and related dementias (ADRD) currently affect over 6.2 million Americans [2] and over 50 million people worldwide [3]. The number of ADRD cases is expected to increase as the number of people over age 65 grows by 62% and the number over age 85 is expected to grow by 84% [2, 4]. More than one in eight adults over age 65 has dementia, and current projections indicate a three-fold increase by 2050. Primary care providers are often responsible for the detection, diagnosis, and treatment of ADRD as the number of dementia specialists (neurologists, psychiatrists, and geriatricians) and specialty centers is not sufficient to meet the growing demands [5]. Screening for mild cognitive impairment (MCI) [6] and ADRD could increase case identification, permit advanced care planning, offer opportunities for individuals to participate in clinical trials, and enable early intervention with currently available symptomatic medications and future disease-modifying medications. MCI and ADRD screening would be most beneficial at the earliest detectable signs of disease, particularly if the detection measures reflect pathology and biomarker changes associated with the earliest stages of ADRD [7].

The National Institute on Aging-Alzheimer Association ATN framework [8, 9] emphasizes the incorporation of biomarker measures of amyloid (A), tau (T), and neurodegeneration/neuronal injury (N). Guidelines for the implementation of the ATN system represent an active area of research, providing an opportunity to classify individuals across the AD spectrum. Amyloid and tau can be measured by in cerebrospinal fluid (CSF) or via positron emission tomography (PET), with recent advances to develop plasma biomarkers [10-13]. Neurodegeneration and neuronal injury are currently captured by magnetic resonance imaging (MRI), fluorodeoxyglucose PET, or measuring CSF total tau. Compared with older clinical-pathological definitions, biological definitions of disease can provide clarity and serve as reliable proxies for neuropathology [8,9]. While clinical and cognitive decline occurs over a long period of time, biomarker changes likely precede any methods of clinical detection, in particularly identifying individuals in the "preclinical stage" of disease [14]. A major obstacle in utilizing biomarker for ADRD screening and early detection in clinical samples is the availability, cost, acceptability, and invasiveness of current biomarker approaches.

An emerging technology in ADRD research is optical coherence tomography (OCT) [14-17], a medical imaging technique using near-infrared light to capture 3-D micrometer-resolution, three-dimensional imaging of cornea, lens, anterior chamber, retinal tissue, and retinal vasculature. Embryologically, the eye is derived from the neuroepithelium (retina, ciliary body, iris, optic nerve), surface ectoderm (lens, corneal epithelium, eyelid), and the extracellular mesenchyme (sclera, cornea, blood vessels, muscles, and vitreous). Since cerebral cortex and retina are both of neuroepithelial origin, pathological changes seen in cortical gray matter in ADRD may also be present in the retina [18]. Retinal thickness can be measured non-invasively with OCT and may offer compelling potential as a biomarker for ADRD [19, 20]. Retinal thinning is hypothesized to be a result of retrograde atrophy and/or parallel neurodegenerative processes [21]. Therefore, the use of OCT may allow capture of the "N" component of the ATN framework in a brief, cost-efficient fashion. This

is advantageous because while the “A” and “T” component of the ATN framework are associated with AD, the “N” component is relevant for nearly all forms of neurodegenerative cognitive disorders [8, 9].

We previously developed a variety of novel ADRD screening methods [7] including caregiver [22] and patient-reported [23] surveys, brief measures of executive function [24], and capture of resilience factors [25, 26] including physical activity [27], cognitive activity [28], and mindfulness [29]. While these measures provide clinical and cognitive markers of ADRD risk and can discriminate between individuals with and without cognitive impairment, they are unable to directly provide measurements of neuronal injury and neurodegeneration. We hypothesized that OCT 1) can be used to capture a marker of neuronal injury and neurodegeneration, 2) will correlated with MRI measurements of atrophy, and 3) when combined with a patient reported outcome and cognitive test could form the basis for a brief, inexpensive, yet comprehensive screening paradigm for MCI and ADRD.

METHODS

Participants

This retrospective cross-sectional study was performed on 136 consecutive participants attending our center for clinical care or participation in cognitive aging research who also underwent optical coherence tomography examinations. Each participant was accompanied by a study partner (most commonly a spouse or adult child). During the 3-h visit, participants underwent a comprehensive clinical, cognitive, functional, and behavioral evaluation modeled after the Uniform Data Set (UDS) from the National Institute of Aging Alzheimer Disease Research Center Program [30, 31] with additional components including OCT used in this study. In addition, participants and study partners independently completed rating scales and were independently interviewed to generate the Clinical Dementia Rating (CDR) [32]. Protocols in the clinic and research projects are identical. This study included older adults ranging from no dementia to individuals with mild dementia of any etiology. All components of the assessment are part of standard of care at our center [33] and OCT is a standard biometric assessment collected in all clinical patients and research participants with normal cognition, MCI, and mild ADRD. Individuals with moderate-to-severe dementia were excluded as they were unable to follow directions for OCT. A waiver of consent was obtained for the retrospective review of clinic patients, while prospective research participants provided written informed consent. This study was approved by the University of Miami Institutional Review Board.

Participant characteristics

Demographic information including age, sex, education, socioeconomic status, race, ethnicity, medical history, medications, alcohol, tobacco, and substance use history, co-morbidities, and family history were collected. A detailed ophthalmic medical history was collected regarding co-morbid eye disease (cataracts, glaucoma, macular degeneration, injury), use of corrective lenses, year of diagnosis, surgeries, and medications.

Clinical evaluation

Each participant underwent a comprehensive physical, neurological, and neuro-ophthalmologic examination conducted by an experienced board-certified neurologist (JEG). The neuro-ophthalmologic examination included visual acuity testing, pupillary examination, direct ophthalmoscopy, confrontational visual field testing, and eye movement evaluation by videonystagmography. Standardized scales from the UDS were administered to the study partners to provide ratings of cognition, function, and behavior [30, 31]. The CDR and its sum of boxes (CDR-SB) [32] was used to determine the presence or absence of dementia and to stage its severity; a global CDR 0 indicates no dementia; CDR 0.5 represents MCI or very mild dementia; CDR 1, 2, or 3 correspond to mild, moderate, or severe dementia. The CDR-SB was calculated by adding up the individual CDR categories (range: 0–18; higher scores supporting more severe impairment). Only individuals with a global CDR of 0, 0.5, or 1 were included in this study. The Charlson Comorbidity Index [34] and Functional Comorbidity Index (FCI) [35] were used to measure overall health and medical comorbidities. Global physical performance was captured with the mini-Physical Performance Test (mPPT) [36] and frailty was assessed with the Fried Frailty Scale [37]. Vascular contributions to dementia were assessed with the modified Hachinski scale [38].

Study partner ratings of cognition, function, and behavior

The study partner completed the informant version of the Quick Dementia Rating System (QDRS) to provide a global rating of the participant's cognitive status [22] with scores greater than 1.5 signifying cognitive impairment. Activities of daily living were captured with the Functional Activities Questionnaire (FAQ) [39]. Dementia-related behaviors and psychological features were measured with the Neuropsychiatric Inventory (NPI) [40].

Cognitive evaluation

The participants completed the self-reported version of the QDRS [23] as a patient-reported outcome assessing subjective cognitive performance with scores greater than 1.5 suggesting cognitive impairment. Cognitive testing included the Montreal Cognitive Assessment (MoCA) [41] for a global screen, and the UDS psychometric battery supplemented with additional measures: 15-item Multilingual Naming Test (naming) [31]; Animal naming (verbal fluency) [31]; Hopkins Verbal Learning Task (HVLT, episodic memory for word lists – immediate and delayed recall) [42]; Number forward/backward tests (working memory) [31]; Trailmaking A and B (processing and visuospatial abilities) [43]; and the Number-Symbol Coding Test (attention and executive function) [24]. The 9 components of the cognitive test battery were combined to create a composite z-score to depict overall cognitive performance. The Hospital Anxiety and Depression Scale [44] was performed for distinct ratings of depression (HADS-D) and anxiety (HADS-A).

Consensus research diagnoses

Global rating scales (e.g., CDR, FAQ) were combined with cognitive performance, the neurologic examination, and laboratory tests to assign individuals to the following diagnostic categories at consensus: cognitively normal controls, MCI, or dementia. MCI due to AD was defined using National Institute on Aging-Alzheimer Association criteria [6].

AD was diagnosed using the National Institute on Aging-Alzheimer Association criteria [1]. Non-AD dementias were determined using standardized published criteria for dementia with Lewy bodies (DLB) [45], vascular contributions to cognitive impairment and dementia (VCID) [46], and frontotemporal degeneration (FTD) [47].

OCT evaluation

OCT was performed using the Zeiss Cirrus HD-OCT which provides continuous scale measurements of macular, ganglion cell and retinal nerve fiber layer thickness, and characteristics of the optic nerve head that can be tracked longitudinally. Images were captured in a standardized fashion [20] during three 10-s sessions in each eye and averaged to measure macular, ganglion cell layer, retinal nerve fiber layer, and optic nerve head parameters. OCT exams were conducted in non-dilated pupils. A total of 6 indices from the Zeiss OCT using standardized boundaries were included in this study: 3 macula measures (Central Subfield Thickness, Macula Volume, and Macula Thickness); 2 measures of the granular cell layer and internal plexiform layer (GCL + IPL) (Average GCL + IPL Thickness and Minimum GCL + IPL Thickness); and 1 measure of optic nerve head (Retinal Nerve Fiber Layer (RNFL) Thickness). A total of 149 individuals had OCT evaluations. To assess the potential effects of ocular disease influencing the results of OCT, we conducted an analysis using pairwise *t*-tests and found a significant confounding effect of co-morbid eye disease (glaucoma, cataracts, macular degeneration). Upon further investigation, we localized this effect to the 13 subjects (10.2% of total) with macular degeneration (Table 1), particularly when comparing the mean RNFL, GCL + IPL, and minimum GCL + IPL thickness. To maintain the integrity of our statistical models, these subjects were removed from further analysis, giving a final sample size of 136 individuals.

Apolipoprotein E genotyping

Apolipoprotein E (*APOE*) genotyping was performed by True Health Diagnostics LLC (Richmond, VA). Six possible allelic combinations were obtained. As there was only one individual who was homozygous for the $\varepsilon 4$ allele, participants were dichotomized as being *APOE* 4 carriers or non-carriers.

Volumetric MRI

A subset of individuals ($n = 76$) underwent volumetric MRI with NeuroQuant software (CorTechs Labs, San Diego, CA), an FDA-approved automated quantitative analysis of brain MRI images with normative reference data adjusted for age, sex, and intracranial volume with high correlation to FreeSurfer [48] and visual assessment [49]. Hippocampal volumes were used as a measure of brain health and a biomarker of neurodegeneration [50]. While hippocampal volume is often used as a predictor of conversion of MCI to AD, hippocampal occupancy measures the degree of hippocampal atrophy accounting for volume loss and compensatory inferior lateral ventricle expansion. It is calculated as a ratio of hippocampal volume to the sum of the hippocampal and inferior lateral ventricle volumes in each hemisphere separately, which are then averaged and normalized for age and sex [50]. This measure may aid in differentiation of individuals with congenitally small hippocampi from those with small hippocampi due to a degenerative disorder [50].

Statistical analysis

Analyses were conducted with IBM SPSS Statistics v26 (Armonk, NY). Descriptive statistics were used to examine demographic characteristics of patients, informant and patient rating scales, dementia staging and neuropsychological testing. One-way analysis of variance (ANOVA) with LSD *post-hoc* tests were used for continuous data and Chi-square tests were used for categorical data. Known-group validity was assessed by examining the OCT measures by patient characteristics, *APOE* status, frailty ratings, CDR, and dementia etiology [22-24]. To account for confounding factors, partial correlation controlling for age were used to test strength of association between OCT findings and outcome measures. Correlations between OCT measures, hippocampal volume and hippocampal occupancy scores were compared for the entire cohort. Because hippocampal pathology is more prominent in individuals with AD pathology compared with DLB and VCID, we repeated the analyses considering only healthy controls, AD, and MCI due to AD. Correction for multiple comparisons was performed using Bonferroni corrections. Receiver operator characteristic (ROC) curves were used to assess the ability of OCT measurements to discriminate between individuals with and without cognitive impairment using a potential dementia screening paradigm (a) OCT alone, a patient-reported outcome (QDRS) [23] alone, a patient performance measure (Number Symbol Coding Task) [24] alone, and finally (d) combining QDRS, NSCT, and OCT scores to create a quick, cost-efficient dementia screening paradigm. ROC curves were generated using multivariate logistic regressions with repeated stratified 10-fold 10-repeat cross-validation, implemented using scikit-learn 0.24.2 in Python 3.9 [51]. Regressions used the large-scale bound-constrained optimization technique, as described in [52]. The confounding variable age was accounted for through its inclusion as a covariate in the regression analyses [53]. Results are reported as area under the curve (AUC) with 95% confidence intervals (CIs). Although designed as an observational study with all individuals eligible to participate having OCT, we conducted a power calculation using G*Power (Heinrich-Heine-Universitat Dusseldorf). Based on two published studies examining GCL + IPL thickness as a biomarker [54, 55], the minimum effect size that can be detected based on 80% power and Type I error 5% are 0.508 [54] and 0.792 [55]. With these studies as a framework, a minimum sample size of 50 was required to detect significant differences in GCL + IPL. The minimum effect size that can be detected by our total sample size of 136 (27 controls, 109 cases) was 0.607. We observed an effect size of 0.788 where cases (cognitively impaired individuals) had a mean GCL + IPL thickness of 69.7 ± 12.2 and controls (healthy controls) had a mean GCL + IPL thickness of 78.6 ± 5.3. This provided an observed power of 0.953 to detect significant differences in GCL + IPL thickness.

RESULTS

Sample characteristics

Sample characteristics (n = 136) are shown in Table 2. The participants had a mean age of 71.8 ± 9.8 years (range 38–91 years) with a mean education of 15.9 ± 2.6 years (range 6–20 years). The sample was 50.7% female, 39.8% *APOE* ε4 carriers, 95.6% White with 5.1% of the sample reporting Hispanic ethnicity. The distribution of the CDR staging was 19.9% CDR 0, 62.5% CDR 0.5, and 17.6% CDR 1. The participants had a mean CDR-SB of 2.1

± 1.9 (range 0–7) and a mean MoCA score of 21.9 ± 4.5 (range 5–30). Consensus clinical diagnoses included 27 cognitively normal controls, 66 MCI, and 43 individuals living with dementia (17 AD, 16 DLB, 6 VCID, and 4 FTD). Group-wise comparisons by diagnosis (controls, MCI, dementia) are shown in Table 2. After correction for multiple comparisons, cognitively normal controls were younger than MCI and dementia participants. There was no difference in sex or *APOE* carrier status. As expected, MCI and dementia participants performed worse than controls in all outcome measures.

OCT measures by participant characteristics

We compared the six acquired OCT measurements by age strata, sex, and *APOE* status (Table 3). For both GCL + IPL measurements, participants less than 70 years had greater thickness than individuals over age 70. For macular volumes and RNFL thickness, participants over age 80 were different from other age groups. There was no difference in any OCT measurement between men and women or between *APOE4* carriers versus non-carriers.

OCT measures by diagnostic groups and staging

We compared the six OCT measurements across controls, MCI, and dementia cases and by CDR stages (Table 4). After correction for multiple comparisons, central subfield thickness, macula volume, and RNFL thickness measurements were not different between diagnostic groups. Macula thickness ($p = 0.003$), GCL + IPL thickness ($p < 0.001$), and minimum GCL + IPL thickness ($p < 0.001$) decreased across diagnostic groups on *post-hoc* comparisons. We repeated the analyses to explore whether OCT differences existed by dementia etiology with the caveat of small numbers in each etiologic category. After correction for multiple comparisons, macular volume ($p = 0.007$), macular thickness ($p = 0.002$), GCL + IPL thickness ($p < 0.001$), and minimum GCL + IPL thickness ($p < 0.001$) were different between etiologies. FTD cases showed less OCT changes compared with MCI, AD, DLB, and VCID cases, although this should be interpreted with caution given the small number of FTD cases. We then examined the 6 OCT measurements by CDR staging. After correction for multiple comparisons, GCL + IPL ($p < 0.001$) and minimum GCL + IPL ($p < 0.001$) discriminated across CDR stages.

Strength of association between OCT measurements, cognitive performance, and MRI

We then examined strength of association between the 6 OCT measurements, cognitive performance and hippocampal measurements of volume and occupancy using partial correlation coefficients controlling for age (Table 5). Central subfield, macular thickness, and volume, and RNFL measures were not associated with cognitive performance. Macular volume and thickness were associated with hippocampal volume but not hippocampal occupancy scores. RNFL thickness was weakly correlated with hippocampal volume. GCL + IPL and minimum GCL + IPL thickness measurements showed the strongest pattern of correlation across multiple cognitive domains, cognitive z-scores, and CDR-SB. Both were correlated with hippocampal volume but only GCL + IPL was also correlated with hippocampal occupancy scores. We repeated the analyses considering only individuals who were healthy controls, MCI due to AD and AD and found that GCL + IPL, minimum GCL +

IPL and RNFL thickness measurements were strongly correlated with hippocampal volumes but only GCL + IPL was correlated with hippocampal occupancy scores.

Discriminability of OCT measurements

Based on these results, GCL + IPL provides the most descriptive information regarding brain health status. A cut-off of 75μm provides the best combination of sensitivity (85%) and specificity (61%) in this sample. We then compared individuals with high and low GCL + IPL thickness by performance on cognitive tests and CDR-SB in Table 6. After correction for multiple comparisons, individuals with GCL + IPL thickness <75 μm have lower MoCA scores, lower immediate and delayed recall on HVLT, longer times to complete Trailmaking B, worse scores on Number Symbol Coding, a lower z-score, and higher CDR-SB.

Incorporating optical coherence tomography into a dementia screening program

We then tested the ability of the GCL + IPL thickness and minimum thickness OCT measurements to discriminate between individuals with and without cognitive impairment using logistic regression analyses to provide area under the ROC curve (AUC) (Table 7). GCL + IPL thickness provided the best discrimination (AUC: 0.821; 95% CI: 0.760–0.822) followed by minimum GCL + IPL thickness (AUC: 0.812; 95% CI: 0.736–0.888). Finally, we examined whether incorporating OCT into a brief dementia screening program would (a) improve classification, (b) provide insight into brain health and a proxy imaging measure of neuronal injury and/or neurodegeneration, and (c) inform the need for referral for more extensive evaluation. The selection of instruments was guided by choosing instruments that could be completed without the need for a physician. For primary screening purposes, a brief (3 min) self-report (patient-version of QDRS) and a brief (90 s) performance measure (Number Symbol Coding Task) were selected to determine the presence of cognitive impairment. This was complemented with the best OCT measurement (GCL + IPL thickness) to determine the likelihood of a neurodegenerative process being the cause of cognitive impairment. A series of logistic regressions were computed to predict binary impairment status using each individual measure and then for the three measures combined. Each individual measure provided good to very good discrimination. ROC curves revealed the three measures together improved upon the single measures with an AUC = 0.868 (95% CI: 0.807–0.930) (Table 7).

DISCUSSION

We found that of the 6 OCT measurements evaluated, GCL + IPL thickness provided the most useful information regarding cognitive status. OCT measurements were associated with age but not sex or *APOE* status. GCL + IPL thickness decreased by cognitive status and CDR staging and after controlling for age, correlated with performance on individual cognitive tests of memory (HVLT immediate and delayed recall), global cognitive performance (MoCA, cognitive z-scores), and staging (CDR-SB), as well hippocampal atrophy. The relationship of GCL + IPL to MRI was even stronger when considering only AD-related cases (AD and MCI due to AD). GCL + IPL thickness provided good discrimination between individuals with and without cognitive impairment, and a cut-off score of 75 μm demonstrated differences in cognitive performance in this sample. Although

participants were included as part of an observational study, we were well powered to detect significant differences in GCL + IPL thickness between individuals with and without cognitive impairment with an effect size of 0.788. Combining GCL + IPL thickness as a proxy marker for hippocampal atrophy with a brief patient-reported outcome (QDRS) and performance measure (NSCT) provided evidence of a screening platform for quickly identifying at-risk individuals for further clinical evaluation or enrollment into research projects. While the QDRS and NCST provide a rapid screen for cognitive impairment, the addition of OCT provides evidence of neuronal injury/neurodegeneration (i.e., the "N" of the ATN framework) suggesting that cognitive impairment is due to a neurodegenerative process rather than non-degenerative conditions. This could help facilitate more extensive (and expensive) evaluations in individuals with likely ADRD.

Collectively, our findings indicate the potential utility of OCT for broader medical practice and research beyond its current scope in ophthalmology. If OCT measurements of GCL + IPL thickness could serve a proxy marker for hippocampal atrophy, there are clear advantages to using OCT as a screening test rather than MRI (Table 8). Further, as plasma biomarkers are developed and validated for measuring amyloid and tau proteins [10-13], a relatively low cost, noninvasive way of testing the amyloid-tau-neurodegeneration (ATN) framework [8, 9] can be envisioned.

In recent years, a number of research reports have investigated the potential use of OCT for characterizing AD and MCI, with most studies reporting differences between MCI or AD and healthy controls. In recent meta-analyses in MCI [15], the pooled effect size for four OTC measurements (GCL + IPL, RNFL, macular thickness, and macular volume) revealed that GCL + IPL showed a 50% reduction, RNFL showed a 59% reduction, and macular volume showed a 62% reduction compared with controls. While not all studies have demonstrated differences in macular thickness and volume, most studies reporting positive findings in AD or MCI have found significant differences in RNFL [17, 18, 56-61] or GCL + IPL [16, 17, 54, 55, 58, 60, 62-65] thickness. In a few studies, other OCT measurements such as retinal pigmented epithelial volume [66, 67] or superficial capillary plexus [68] discriminated AD from controls. However, not all studies reported differences [21, 55, 69]. These differences could be due to a number of factors including case ascertainment and populations studied, controlling for co-morbid eye disease (which is very common in older adults), extent of cognitive evaluation (brief screening tests versus neuropsychological battery) and type of OCT device employed [11,20]. However, it is also possible that OCT measurements in isolation are not sufficient to adequately discriminate between cognitively impaired individuals and healthy controls but instead could be used as a supportive biomarker for evaluation. In the present study, the addition of GCL + IPL thickness to a brief patient-reported outcome and brief neuropsychological test improved performance of a logistic regression model using these features by 4.5% compared with OCT measurements alone (Table 6). Further, we found that controlling for age eliminated the significances between either the RNFL and Macula thickness and cognitive measures, suggesting the need to include age as a cofactor when examining OCT as a biomarker for ADRD. This is particularly important as age is a risk factor for eye disease and ADRD and influences OCT measurements.

Besides use in AD, OCT may have value in other forms of neurodegenerative disease. Here we report that provided discrimination in VCID and DLB but not in FTD. Other investigators have reported utility of OCT measurements in FTD [70, 71], normal pressure hydrocephalus [72], Parkinson's disease [66], cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [73], and Huntington's disease [74]. Given the diversity of findings across different neurodegenerative disorders with OCT, there is a need to provide standardization of measurements so that findings from different studies can be compared. A recent meta-analysis [20] proposed steps to standardize future OCT studies including standardizing terminology, optimizing study design, controlling for important covariates such as age and sex, defining anatomical boundaries, using the ATN framework to stratify analyses across the Alzheimer disease continuum, standardizing imaging protocols for use across different OCT devices, and standardizing algorithms for calculating vessel density.

There are several limitations in this study. As this is a cross-sectional study, the longitudinal changes in OCT measurements on transition from cognitively normal controls to MCI and conversion of MCI to ADRD still need to be further elucidated. The majority of dementia cases had either AD or DLB with fewer cases of VCID or FTD. Thus, specific conclusions about VCID or FTD should be made with caution. As the dementia cases were of equal severity, we conducted the analysis grouping AD, DLB, VCID, and FTD together. Future studies could investigate individual diagnoses in greater detail and include ADRD biomarkers. Participants were seen in the context of an academic center where the prevalence of MCI and dementia are high, and patients tend to be better educated and predominantly white. Validation of our findings in other settings where dementia prevalence is lower (i.e., community samples) or where the sample is more diverse is needed. Macular degeneration is a common age-associated eye disease that interferes with OCT measurements. These individuals were eliminated from further consideration in our study, and in many of the referenced studies on OCT. However, exclusion of these individuals may diminish the potential impact of using OCT as a screening tool. We provide an optimal cut-off of GCL + IPL thickness of 75 μm in our sample. This will have to be further evaluation in independent samples. We only considered OCT measurements which were fully automated, however a number of investigations are now examining specific quadrants of OCT parameters to look for regional differences. Another emerging field is OCT angiography [20, 75]. OCT angiography provides high resolution imaging of the retinal microvascular and choroid and because of its non-invasive nature could provide an efficient method for screening for preclinical or clinical dementia. A better understanding of the cause of retina degeneration and longitudinal, standardized studies are needed to determine if OCT can be used as a biomarker for MCI and ADRD.

There are also a number of strengths of our study. Participants were deeply phenotyped and well-characterized with clinical-cognitive-functional-behavioral assessments with a number of Gold Standard measurements (e.g., CDR, UDS neuropsychologic test battery) and OCT was collected at the same time as the assessment. There were sufficient numbers of participants to study age and sex effects on OCT measurements. All participants had *APOE* genotyping, and a subset had volumetric MRI. OCT measurements were collected across different dementia etiologies, and although groups were small, we were able to

compare cognitively normal controls, MCI, AD, DLB, VCID, and FTD across all six OCT measurements replicating findings from other studies.

Our results support that a multimodal approach for detection of at-risk individuals may improve recognition of persons with MCI and ADRD that can be referred for further evaluation. Given the ease of performing visual tests, the accessibility of the eye, and advances in ocular technology, OCT has the potential to be an effective, practical, and non-invasive biomarker for ADRD [20, 76]. Automated OCT segmentation software generates valid measurements of retinal layer volume and thickness, avoiding the need to perform manual correction [77]. Identifying potential screening tests for future cognitive decline is a priority for developing treatments for and the prevention of dementia [59, 78]. Our study supports that OCT measurement of GCL + IPL thickness in combination with other measures can provide sufficient discrimination to consider for low-cost dementia screening paradigms.

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Table 1

Frequency of Co-Morbid Eye Disease

	Overall	Control	MCI	Dementia	χ^2	*p*
Any condition, %	50.4	29.6	54.4	59.5	6.24	0.044
Glaucoma, %	8.7	3.6	8.3	12.8	1.78	0.411
Cataracts, %	25.2	10.7	35.0	20.5	6.63	0.036
Macular degeneration, %	10.2	7.1	10.0	12.8	0.58	0.749
Other, %	4.7	7.1	5.0	2.6	0.78	0.678
Wears Glasses, %	70.6	64.0	72.2	73.3	0.70	0.704

MCI, mild cognitive impairment.

Table 2

Sample Characteristics ($n = 136$)

	Overall Sample		Group-Wise Comparisons			
Variable	**Mean (SD)**	**Range**	**Control**	**MCI**	**Dementia**	***p***
Age, y	71.8 (9.8)	38–91	63.6 (10.4)	71.9 (8.7)	76.9 (7.6)	< **0.001**
Sex, %F	50.7		74.1	50.0	37.2	0.011
Education, y	15.9 (2.6)	6–20	16.6(2.1)	15.8 (2.6)	15.9 (2.6)	0.299
Race/Ethnicity						
% Non-Hispanic White	95.6		96.2	95.5	96.2	0.986
% Hispanic	5.1		7.4	4.5	4.7	0.838
APOE4 carrier, %	39.8		26.1	36.2	38.9	0.583
FAQ	4.2 (5.9)	0–24	0.1 (0.3)	2.7 (3.8)	8.9 (7.3)	< **0.001**
NPI	4.8 (4.9)	0–27	1.4 (2.1)	4.3 (3.9)	7.8 (5.9)	< **0.001**
Charlson	2.2 (1.7)	0–8	0.7 (0.1)	2.4 (1.5)	2.8 (0.3)	< **0.001**
Hachinski	0.9 (1.3)	0–8	0.4 (0.6)	0.9 (1.5)	1.0 (1.4)	0.180
Fried Frailty	1.9 (1.3)	0–5	0.8 (0.9)	1.9 (1.3)	2.5 (1.3)	< **0.001**
MoCA	21.9 (4.5)	5–30	26.3 (2.6)	22.9 (2.9)	17.6(3.8)	< **0.001**
CDR-SB	2.1 (1.9)	0–7	0.2 (0.2)	1.4 (0.8)	4.2 (1.8)	< **0.001**

Mean (SD) or %. **Bold** signifies significance after Bonferroni correction (corrected $p = 0.0038$). FAQ, Functional Activities Questionnaire; NPI, Neuropsychiatric Inventory; MoCA, Montreal Cognitive Assessment; CDR-SB, Clinical Dementia Rating Sum of Boxes; MCI, mild cognitive impairment.

Table 3

OCT Measurements by Age, Sex, and *APOE* Carrier Status

	Age				
	< 60 y	**60–69 y**	**70–79 y**	**80+ y**	***p***
Central Subfield Thickness (μm)	268.4 (19.9)	268.9 (23.4)	260.5 (33.2)	249.9 (39.3)	0.091
Macula Volume (mm^3)	9.7 (0.6)	9.8 (0.7)	9.7 (0.7)	9.2 (1.4)	0.039[a]
Average Macula Thickness (μm)	270.9 (19.1)	272.2 (18.9)	270.2 (18.5)	258.4 (33.6)	0.074
GCL + IPL Thickness (μm)	76.6 (10.6)	76.9 (6.3)	69.9 (11.9)	65.9 (13.5)	**< 0.001** [b]
Minimal GCL + IPL Thickness (μm)	69.0 (18.6)	71.1 (9.3)	63.0 (17.1)	57.5 (17.3)	**0.005** [b]
RNFL Thickness (μm)	85.6 (7.0)	85.9 (10.9)	83.9 (12.1)	74.3 (17.6)	**0.003** [a]
	Sex			***APOE* Status**	
	Men	**Women**	***p***	**Non-carrier**	**Carrier**	***p***
Central Subfield Thickness (μm)	264.3 (35.8)	257.9 (27.7)	0.258	258.8 (33.9)	269.3 (30.0)	0.107
Macula Volume (mm^3)	9.7 (0.8)	9.5 (1.0)	0.255	9.5 (1.1)	9.7 (0.7)	0.330
Average Macula Thickness (μm)	268.9 (23.7)	267.2 (23.3)	0.702	267.2 (26.4)	269.7 (18.5)	0.593
GCL + IPL Thickness (μm)	69.6 (12.7)	73.3 (10.5)	0.064	71.7 (11.7)	71.1 (12.3)	0.799
Minimal GCL + IPL Thickness (μm)	62.9 (18.2)	65.9 (14.2)	0.305	65.3 (15.7)	64.1 (17.8)	0.736
RNFL Thickness (μm)	80.5 (15.5)	84.1 (11.4)	0.139	82.9 (13.6)	81.8 (11.5)	0.688

Mean (SD). **Bold** signifies significance after Bonferroni correction (corrected *p*-value = 0.0083). GCL, ganglion cell layer; IPL, internal plexiform layer; RNFL, retinal nerve fiber layer; *APOE,* Apolipoprotein E; CDR, Clinical Dementia Rating. *Post-hoc* for age: [a]80 + different from other groups; [b] < 60 and 60–69 not different from each other and 70–79 and 80 + not different from each other.

Table 4

OCT Measurements by Diagnostic Group, Dementia Etiology, and CDR Stage

	Control	MCI	Dementia	*p*	CDR 0	CDR 0.5	CDR 1	*p*
Central Subfield Thickness (μm)	272.0 (30.0)	262.0 (27.5)	252.1 (37.7)	0.040	272.3 (29.9)	258.5 (28.2)	257.2 (44.3)	0.133
Macula Volume (mm^3)	10.0 (0.7)	9.6 (0.9)	9.3 (1.2)	0.011	9.9 (0.7)	9.5 (0.9)	9.3 (1.2)	0.030 *c*
Average Macula Thickness (μm)	278.8 (18.4)	269.2 (17.8)	259.3 (30.4)	**0.003** *a*	278.7 (18.4)	266.4 (21.5)	261.3 (31.7)	0.021 *c*
GCL + IPL Thickness (μm)	78.6 (5.3)	73.3 (10.0)	64.2 (13.4)	< **0.001** *a*	78.6 (5.3)	71.3 (11.4)	64.1 (13.6)	< **0.001** *d*
Minimal GCL + IPL Thickness (μm)	74.5 (7.4)	66.1 (14.7)	55.1 (18.3)	< **0.001** *b*	74.5 (7.4)	63.9 (15.7)	54.7 (19.7)	< **0.001** *d*
RNFL Thickness (μm)	87.9 (9.7)	82.3 (12.6)	78.9 (16.2)	0.032	87.9 (9.7)	80.8 (14.6)	81.6 (12.5)	0.066
	Control	**MCI**	**AD**	**DLB**	**FTD**	**VCID**	***p***	
Central Subfield Thickness (μm)	272.0 (30.0)	262.0 (27.5)	249.3 (29.8)	267.0 (36.1)	250.8 (22.0)	225.8 (57.3)	0.015	
Macula Volume (mm^3)	10.0 (0.7)	9.6 (0.9)	9.6 (0.6)	9.1 (1.3)	9.6 (0.4)	8.6 (1.8)	**0.007** *e*	
Average Macula Thickness (μm)	278.8 (18.4)	269.2 (17.8)	267.6 (17.4)	257.3 (34.1)	265.4 (11.6)	238.0 (48.6)	**0.002** *f*	
GCL + IPL Thickness (μm)	78.6 (5.3)	73.3 (10.0)	67.5 (10.3)	60.1 (14.4)	71.6 (8.1)	60.7 (18.9)	< **0.001** *g*	
Minimal GCL + IPL Thickness (μm)	74.5 (7.4)	66.1 (14.7)	55.8 (17.6)	52.7 (20.7)	70.9 (5.9)	48.2 (17.0)	< **0.001** *g*	
RNFL Thickness (μm)	87.9 (9.7)	82.3 (12.6)	83.3 (20.1)	75.6 (13.1)	75.5 (14.5)	77.8 (14.0)	0.087	

Mean (SD). **Bold** signifies significance after correction for multiple comparisons (corrected $p < 0.0083$). MCI, mild cognitive impairment; GCL, ganglion cell layer; IPL, internal plexiform layer; RNFL, retinal nerve fiber layer. [a] *Post-hoc* comparisons: Controls and MCI are different from Dementia, but not each other. [b] *Post-hoc* comparisons: Controls are different from MCI and Dementia; MCI is different from Dementia. [c] *Post-hoc* comparisons: CDR 0 different from CDR 0.5 and 1; CDR 0.5 not different from CDR 1. [d] *Post-hoc* comparisons: All CDR groups different from each other. [e] *Post-hoc* comparisons: Controls are different from VCID and DLB. [f] *Post-hoc* comparisons: Controls are different from VCID, and DLB; MCI is different from VCID. [g] *Post-hoc* comparisons: Controls are different from MCI, AD, VCID, and DLB; MCI is different from AD, DLB, and VCID.

Table 5

Strength of Association Between OCT Measures and Cognitive Tests, Global Ratings, and MRI

	Central Subfield	Macula Volume	Macula Thickness	GCL + IPL Thickness	Minimum GCL + IPL	RNFL Thickness
Cognitive Tests and Ratings						
MoCA	0.122 (0.165)	0.143 (0.106)	0.218 (0.013)	**0.357 (< 0.001)**	**0.363 (< 0.001)**	−0.053 (0.556)
HVLT – Immediate Recall	0.104 (0.236)	0.077 (0.384)	0.192 (0.029)	**0.292 (< 0.001)**	**0.301 (< 0.001)**	0.053 (0.553)
HVLT – Delayed Recall	0.077 (0.380)	0.112 (0.207)	0.215 (0.014)	**0.250 (0.004)**	**0.316 (< 0.001)**	0.099 (0.270)
Trail making A	0.022 (0.807)	0.034 (0.702)	0.030 (0.735)	−0.143 (0.099)	−0.150 (0.089)	−0.047 (0.600)
Trail making B	−0.032 (0.723)	0.001 (0.993)	0.018 (0.839)	−0.133 (0.134)	−0.168 (0.061)	−0.069 (0.453)
Verbal Fluency (Animals)	0.160 (0.067)	0.037 (0.674)	0.035 (0.694)	0.239 (0.005)	**0.316 (< 0.001)**	0.176 (0.048)
MINT	0.026 (0.772)	−0.058 (0.508)	−0.040 (0.647)	−0.102 (0.236)	−0.117 (0.183)	−0.036 (0.687)
Numbers – Forwards	0.105 (0.234)	0.075 (0.396)	0.058 (0.514)	0.211 (0.014)	0.152 (0.083)	0.096 (0.287)
Numbers – Backwards	0.117 (0.186)	−0.010 (0.911)	−0.019 (0.833)	0.175 (0.043)	0.131 (0.136)	−0.025 (0.784)
Number-Symbol Coding Task	0.108 (0.228)	0.018 (0.872)	0.026 (0.776)	0.167 (0.057)	0.218 (0.014)	0.128 (0.161)
Composite z-score	0.140 (0.127)	0.103 (0.267)	0.144 (0.119)	**0.295 (0.001)**	**0.368 (< 0.001)**	0.208 (0.025)
CDR-SB	−0.095 (0.278)	−0.137 (0.118)	−0.177 (0.043)	**−0.376 (< 0.001)**	**−0.339 (< 0.001)**	−0.053 (0.556)
MRI (all groups)						
Hippocampal Volume (mm^3)	0.260 (0.100)	**0.478 (0.002)**	**0.460 (0.003)**	**0.589 (< 0.001)**	**0.514 (< 0.001)**	**0.554 (< 0.001)**
Hippocampal Occupancy Scores	0.108 (0.497)	0.048 (0.770)	0.094 (0.566)	**0.443 (0.003)**	0.372 (0.015)	0.288 (0.071)
MRI (Controls, MCI due to AD, AD only)						
Hippocampal Volume (mm^3)	0.383 (0.044)	0.477 (0.012)	0.445 (0.020)	**0.644 (< 0.001)**	**0.531 (0.004)**	**0.621 (< 0.001)**
Hippocampal Occupancy Scores	0.232 (0.235)	0.002 (0.991)	0.037 (0.856)	**0.510 (0.005)**	0.373 (0.051)	0.315 (0.103)

Partial correlation, controlling for age (p-value) for cognitive measures; Bivariate correlation (p-value) for MRI measures. **Bold** signifies significance after correction for multiple comparisons (adjusted p = 0.0042 for cognitive measures and adjusted p = 0.0125 for MRI measures). GCL, ganglion cell layer; IPL, internal plexiform layer; RNFL, retinal nerve fiber layer; MoCA, Montreal Cognitive Assessment; HVLT, Hopkins Verbal Learning Task; MINT, Multilingual Naming Test; CDR-SB, Clinical Dementia Rating Sum of Boxes.

Table 6

Comparison of Cognitive Performance by GCL + IPL Thickness Cut-off

Variable	GCL + IPL < 75 μm (*n* = 64)	CGL + IPL ≥75 μm (*n* = 72)	*p*
MoCA	20.3 (3.9)	23.7 (4.3)	< **0.001**
Numbers Forward	6.4 (1.4)	7.1 (1.3)	0.006
Numbers Backward	4.5 (1.2)	4.9 (1.5)	0.053
HVLT-Immediate	15.7 (5.3)	18.9 (6.2)	**0.001**
HVLT-Delay	4.1 (3.3)	6.3 (3.5)	< **0.001**
Trail making A, s	44.6 (19.9)	36.4 (22.6)	0.028
Trail making B, s	118.8 (48.2)	92.6 (44.3)	**0.002**
Number Symbol Coding	31.8 (11.2)	40.6 (11.8)	< **0.001**
Animal Naming	15.4 (5.6)	17.9 (5.6)	0.011
MINT	14.4 (0.9)	14.2 (2.1)	0.377
Z-Score	−0.05 (0.8)	0.57 (0.7)	< **0.001**
CDR-SB	2.7 (1.9)	1.3 (1.6)	< **0.001**

Mean (SD). **Bold** signifies significance after correction for multiple comparisons (corrected $p < 0.0042$). GCL, ganglion cell layer; IPL, internal plexiform layer; MoCA, Montreal Cognitive Assessment; HVLT, Hopkins Verbal Learning Test; MINT, Multilingual Naming Test; CDR-SB, Clinical Dementia Rating Sum of Boxes.

Table 7

Discriminability and Utility of OCT

Measure	Control versus Impaired	
	AUC	95% CI
GCL + IPL Thickness (mm)	0.821	0.760–0.882
Minimal GCL + IPL Thickness (mm)	0.812	0.736–0.888
Patient QDRS	0.842	0.768–0.915
Number Symbol Coding Task	0.865	0.797–0.932
OCT + QDRS + NSCT	0.868	0.807–0.930

OCT, optical coherence tomography; AUC, area under the curve; CI, confidence interval; GCL, ganglion cell layer; IPL, internal plexiform layer; QDRS, Quick Dementia Rating System; NSCT, Number Symbol Coding Task.

Table 8

Challenges and Opportunities Comparing Imaging Techniques

Challenges	MRI	OCT
Time to complete	~45 min	~1 min
Cost of equipment	~$3,000,000	~$100,000
Cost of scan	~$1500	~$100
Concerns about metal	Yes	No
Pacemaker/implanted device concerns	Yes	No
Radioactivity	No	No
Claustrophobia	Yes	No

OCT, optical coherence tomography; MRI, magnetic resonance imaging.