

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: <https://orca.cardiff.ac.uk/id/eprint/171626/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Hawken, Jonathan and Robertson, Neil 2024. The role of optical coherence tomography in neurodegenerative disease. *Journal of Neurology* 271 (8) , 5696–5698. 10.1007/s00415-024-12547-2

Publishers page: <http://dx.doi.org/10.1007/s00415-024-12547-2>

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See <http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



The role of Optical Coherence Tomography in Neurodegenerative Disease

Jonathan Hawken, Neil Robertson

Department of Neurology, Division of Psychological Medicine and Clinical Neuroscience, Cardiff University, University Hospital of Wales, Heath Park, Cardiff, CF14 4XN, UK.
robertsonnp@cardiff.ac.uk.

Optical Coherence Tomography (OCT) provides high resolution cross-sectional imaging of the retina and optic nerve. This modality is increasingly offered in routine eye assessments, and can identify a number of conditions at an early stage of disease. This can provide a window of opportunity to offer early or preventative treatment, for example in Glaucoma. However, the value of OCT extends beyond disease limited to the eye. Retinal signatures of systemic disease, termed 'oculomics', offer a non-invasive method of identifying and monitoring a range of diseases. Diabetic retinopathy management already benefits considerably from this detailed assessment. Local and systemic treatments, lifestyle adjustments, and further screening may be initiated by the findings of this test.

Neurodegenerative disorders may also benefit from this modality. Neuronal loss in the retina has previously been confirmed in post-mortem studies of patients with Alzheimer's Disease (AD), Parkinson's Disease (PD), and Motor Neurone Disease (MND). Identifying these changes in life may impact the management of the disease or offer opportunities for preventative measures for those at risk of these conditions.

In this month's journal club, we review OCT findings associated with Parkinson's Disease, assess whether the modality may be used to differentiate atypical Parkinsonism cases, and consider the value of OCT combined with polygenic risk scores in predicting cognitive decline. These studies benefit from use of two primary large volume datasets. The UK Biobank (UKBB) includes de-identified genetic, lifestyle and health information, and biological samples from more than half a million participants recruited between 2006-2010. The AlzEye study combines retinal imaging with clinical data, aiming to identify retinal signatures of systemic disease. Over a ten-year period (2008-2018), more than 1.5 million OCT images were obtained from individuals attending a tertiary ophthalmic institution in the UK.

Retinal OCT features associated with incident and prevalent Parkinson Disease.

Wagner et al. evaluated OCT in patients with established Parkinson's Disease (PD) to identify retinal markers associated with the disease. Data was obtained from the AlzEye study. From this cohort of 154,830 there were 700 individuals (0.45%) with prevalent PD. Retinal nerve fibre layer (RNFL), Ganglion cell-inner plexiform layer (GCIPL), and inner nuclear layer (INL) thickness were assessed.

Significantly thinner GCIPL and INL were seen across all parafoveal locations in patients with PD as compared with controls. RNFL thickness was also reduced, but not in all regions. Diabetes Mellitus was noted to have an impact on results. The exclusion of patients with Diabetes reduced the effect size for GCIPL and INL, following which the RNFL comparison was no longer statistically significant.

These findings were applied to the UK Biobank cohort to determine the predictive value of this retinal signature for incident PD. 50,405 individuals in the Biobank had imaging of sufficient quality for inclusion and no prior record of PD. Reduced GCIPL thickness showed the strongest association with the development of PD. INL and RNFL thinning in one region (inner inferior) were significant, with other INL and RNFL areas being inconclusive. Of note, these results persisted even when those who developed PD in the first 24 months after having had retinal imaging were excluded.

Comment: The primary aim of the study was achieved and confirmed reduced GCIPL thickness and a novel finding of reduced INL thickness in patients with established PD. However, the authors recognise important limitations from the study. Prevalent PD cases did not have detailed clinical information including date of diagnosis or treatment history. The impact of disease duration and treatment modification also requires further investigation. The secondary aim, exploring the potential of OCT findings as a predictive marker for PD, may have considerable clinical significance. These results show promise with significant abnormalities being identified two years prior to diagnosis providing potential for earlier multi-modal assessment, diagnosis and intervention.

Wagner et al. (2023) Neurology 101: 1581-1593.

Retinal morphological differences in atypical Parkinsonism: A cross-sectional analysis of the AlzEye cohort.

This study aimed to investigate differences in retinal morphology in individuals with Atypical Parkinsonian Syndrome (APS). The authors highlight that this patient group has received less focus due to lower prevalence than PD. In addition to OCT, colour fundus photography data to compare patients with APS (n=51) versus controls (n=97,119).

Data was obtained from the AlzEye study in which hospital admission records attributed the label of APS. Within this group 16/51 had Secondary Parkinsonism as defined by ICD-10, and this may include cases of neuroleptic malignant syndrome, post-encephalitic Parkinsonism, vascular Parkinsonism, and other causes. The remainder of the cohort is undefined due to small numbers and data privacy. A further limitation of this study was incomplete demographic data as there is known to be variation in OCT metrics for healthy individuals in different population groups. In this study, ethnicity was unknown for 37.3% of APS patients and 35.8% of controls.

Individuals with APS had a significantly thinner GCIPL but no difference in RNFL or INL. These findings remained significant when adjusting for age, sex, and comorbidity (hypertension and diabetes). No significant difference was identified by colour fundus photography in cup-disc ratio or retinovascular indices.

Comment: The utility of this study is limited by low patient numbers, heterogeneity of the APS cohort, and incomplete demographic data. It is suggested that thinning of the GCIPL, without INL or RNFL involvement, may distinguish APS. However, conflicting INL results have previously been seen in underpowered studies, and the evidence here does not appear sufficient to consider this a reliable signature of APS.

Patel et al. (2024) Biomarkers in Neuropsychiatry 10: 100096.

Association of retinal optical coherence tomography metrics and polygenic risk scores with cognitive function and future cognitive decline.

Sekimitsu et al. aimed to evaluate the potential of combining retinal OCT measurements with polygenic risk scores in order to identify individuals at risk of cognitive impairment. The UK Biobank provided the dataset including cognitive test results and OCT images. Polygenic risk scores obtained from genome-wide association studies were applied to this dataset. The overall cohort of 462,332 participants included 1749 PD cases and 832 AD cases.

The first analysis compared polygenic risk scores with retinal layers, adjusted for age, sex, and relevant co-morbidity. 50,342 participants with at least one high-quality OCT scan were included in the analysis. Significant results in a variety of retinal layers were identified for each 1 unit increase in polygenic risk for both AD and PD.

The second analysis compared retinal layer thickness, baseline cognitive function, and future cognitive decline. 50,242 participants had baseline cognitive assessment, and follow-up assessment was undertaken in 7,684 at a median time of 4.4 years. Lower baseline and follow-up cognitive performance were both associated with significant retinal layer findings. In a logistic regression model, the prediction of cognitive decline was improved by including retinal layer thicknesses and polygenic risk scores for AD and PD.

Comment: This study shows novel associations between OCT metrics, polygenic risk scores, and cognitive performance. The authors highlight the limitations of polygenic risk scores, which are better defined for AD than PD, and the UK Biobank cognitive assessment follow-up strategy which may have reduced the effect of these results. Overall, whilst the addition of genetic data to OCT measurements improves prediction of cognitive decline, clinical utility at scale remains to be proven.

Sekimitsu et al. (2024) British Journal of Ophthalmology 108: 599-606.

Conclusion

Identifying reliable retinal signatures of neurodegenerative disease has important clinical potential. These studies suggest that OCT may help to detect neurodegenerative diseases at an earlier stage. The addition of polygenic risk scores is shown to improve case prediction, and the combination of these modalities offers hope for improvement in this field. This could improve access to and efficacy of disease-modifying and neuroprotective therapies. However, the ability of OCT to differentiate cases will rely on accurate study phenotyping and improved understanding of the pathological mechanisms in the retina.