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How hyperspectral imaging and artificial intelligence transform Alzheimer's diagnosis

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In a recent multidisciplinary study involving 39 patients, the potential of retinal imaging techniques for the diagnosis of Alzheimer's disease was investigated. An easy-to-use hyperspectral snapshot camera—16 spectral bands between 460 nm and 620 nm with 10 nm bandwidth—was used to quantify amyloid accumulation, while optical coherence tomography allowed the thickness of the retinal nerve fibre layer to be assessed. Dedicated image preprocessing and machine learning were instrumental in discriminating between Alzheimer patients and healthy subjects. The best results were obtained when the hyperspectral and OCT data were combined.

Alzheimer's Disease and its biomarkers

Today, Alzheimer's disease (AD) is diagnosed based on (the combination of) three biomarkers: amyloid-beta (Aβ) and tau protein accumulation and neurodegeneration parameters.[1] Data are assembled by performing positron emission tomography scans or analysing cerebrospinal fluid; both are costly and/or invasive procedures. An affordable and non-invasive diagnostic test for these biomarkers is desirable.

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The eye is closely related to the brain and spinal cord. Therefore, it provides a unique window into the central nervous system. One research route towards non-invasive AD diagnosis focuses on retinal examinations. In transgenic mouse models of AD, Aβ accumulation and plaques were observed in the retina before being present in the brain.[2] There is accumulating evidence in AD patients for the presence of AD disease hallmarks in the retina.[3] Different imaging techniques are being studied to detect retinal changes related to Aβ presence, *in vivo*. One of these techniques is hyperspectral retinal imaging, with wavelengths between 460 nm and 570 nm being the most interesting to use.[4,5] Post-mortem studies in both animal and human retinas, and *in vivo* studies in rodents, have shown that hyperspectral retinal imaging can detect spectral changes that could be caused by the presence of retinal Aβ aggregates.[4,6] Hyperspectral retinal imaging, however, does not directly visualise retinal Aβ deposition, but records a spectral shift at wavelengths between 460 nm and 570 nm that could be explained by the presence of retinal protein deposits in certain stages of aggregation, given the relationship between particle size and different types of light scattering.

An important neurodegeneration biomarker, in the eye, is the thinning of the retinal nerve fibre layer. This can be studied by optical coherence tomography (OCT). This non-invasive and high-resolution tool produces cross-sections of the retina.[7]

From June to September 2019, a study with 39 patients was performed at the Ophthalmology Department of the University Hospital UZ Leuven in Belgium (Figures 1 and 2). Seventeen patients were recruited from the Memory Clinic of UZ Leuven, 10 with clinically-probable AD

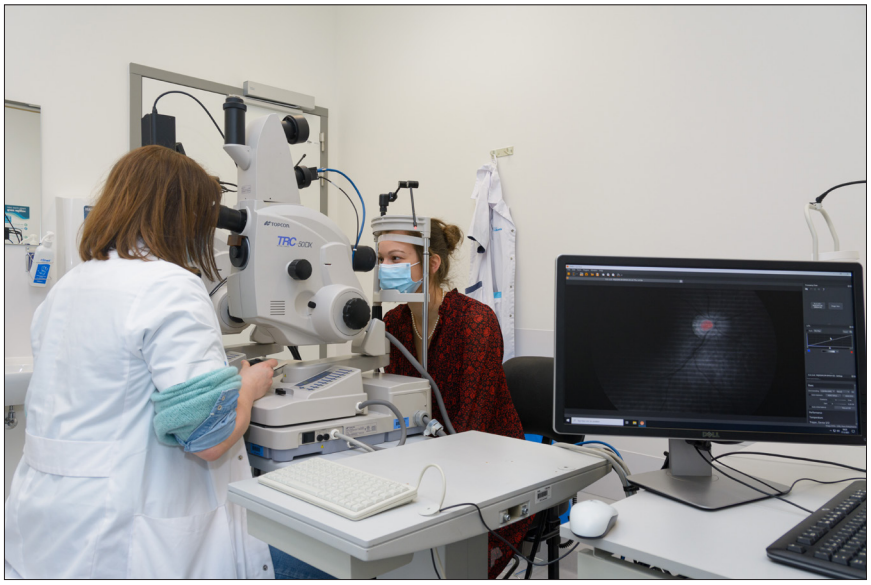

Figure 1. Patient being examined using retinal hyperspectral imaging and optical coherence tomography.

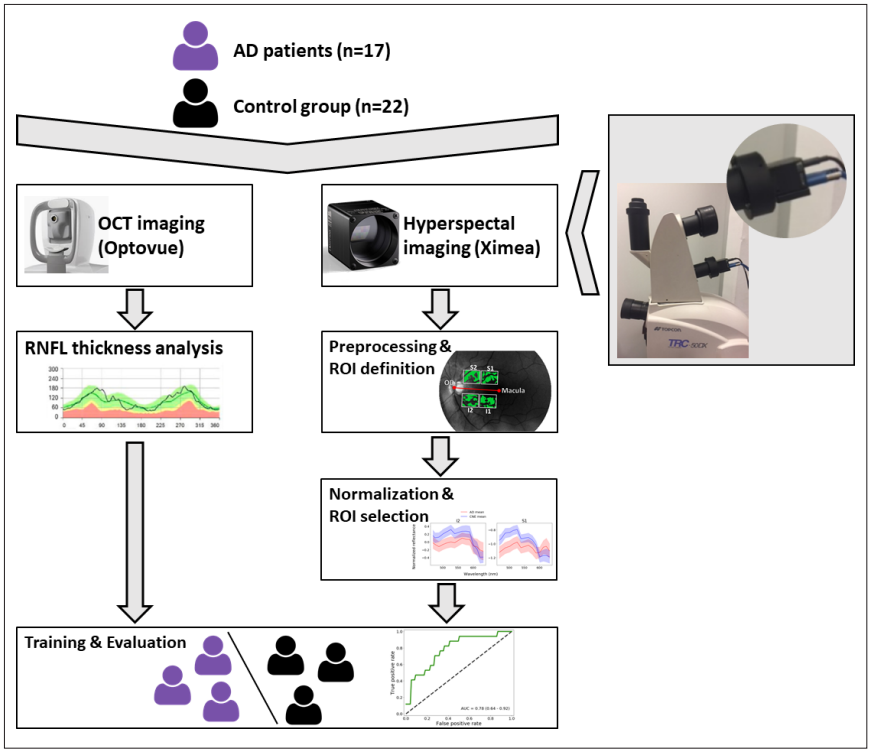

Figure 2. Study set-up.

and 7 with biomarker-proven AD. Also, 22 controls were included in the study.

Hyperspectral imaging of the retina for amyloid quantification

The hyperspectral retinal imaging was performed with a snapshot camera from XIMEA (SNm4x4 VIS), connected to a C-mount to a TL-230T relay lens from Topcon on a Topcon TRC-50DX fundus camera.

At the heart of the XIMEA camera is a hyperspectral sensor from imec. The sensor has a standard CMOS 1088 × 2048 pixel image sensor as a base with mosaic patterned hyperspectral filters post-processed on top of it. This dedicated design allows spatial and spectral data to be acquired in one capture without the need for scanning.[8] 4 × 4 imaging pixels are combined into hyperspectral pixels with 16 spectral bands of 10 nm bandwidth between 460 nm and 620 nm.

An exposure time of 0.2 ms, a 50° field of view and no background illumination were used to acquire the images. Patients were subjected to one short flash of low to moderate intensity while focusing on an external fixation light.

Relative reflectance was computed for each hyperspectral image. Further, blood vessels were removed from the hyperspectral images by applying a difference of Gaussians filter to the entire greyscale image. Finally, four regions of interest (ROIs) were defined for standardisation purposes, based on the centre of the optic disc (Figure 3). This strategy is a compromise between considering the entire retina, with the risk to dilute a possibly weak Aβ signal, and considering a large number of regions, with the risk of detecting random effects.

Optical coherence tomography to visualise the retinal nerve fibre layer thickness

An RT-vue XR Avanti from Optovue was used to perform the OCT analysis and calculate the retinal nerve fibre thickness. This was done both over 360° and per quadrant.

Machine learning, using HSI and OCT data

Classification models were developed based on linear discriminant analysis (LDA). Models were trained using scikit-learn library (version 0.21.3) in a Python programming language environment.

For each region of interest, two input configurations for the classifier were evaluated: one that consisted of normalised hyperspectral data and one that combined normalised hyperspectral data and optical coherence tomography features.

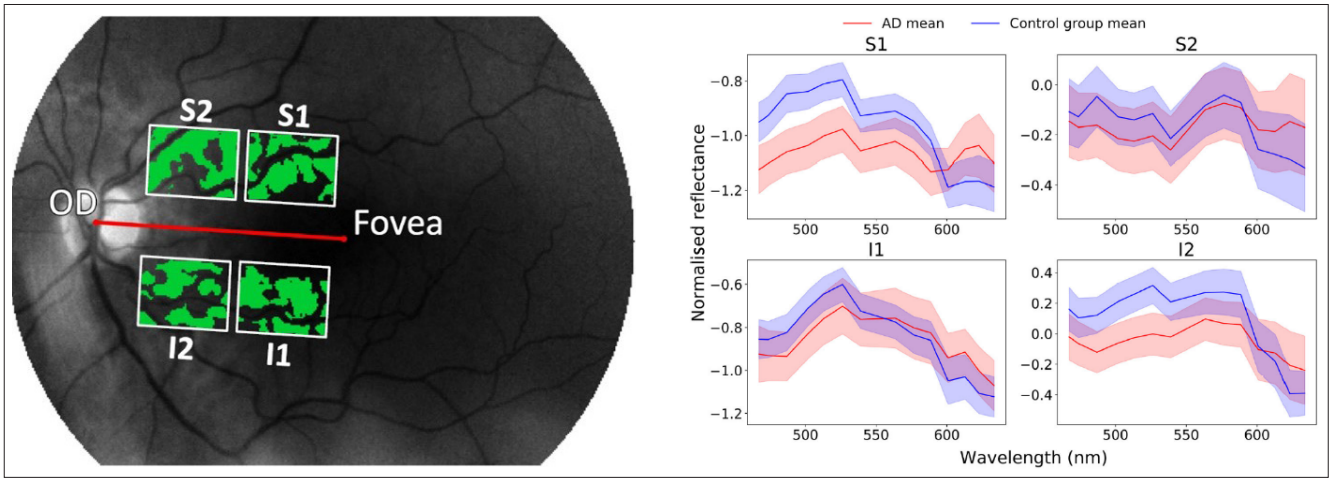

Figure 3. Left: Four regions of interest were defined: superior 1 (S1), superior 2 (S2), inferior 1 (I1) and inferior 2 (I2). The green parts in the image are the ones used for the analysis, with the retinal blood vessels substracted from the image. Right: Mean spectra in the four regions of interest. Shaded areas indicate the mean ± the standard error of the mean.

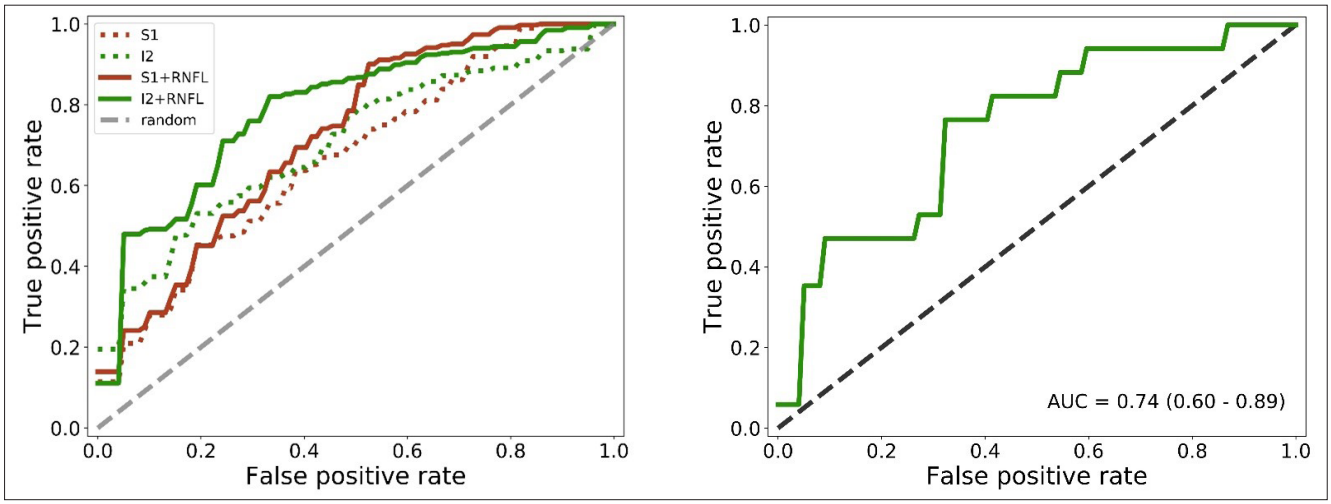

Figure 4. Left: average receiving operating characteristic (ROC) curves over all inner loop cross-validation runs for all configurations. Right: average ROC curve over all outer loop cross-validation runs for the I2+RNFL configuration, which showed the best performance in the inner loop.

Results

The resulting models could discriminate between AD subjects and controls with an accuracy of approximately 75% in a nested leave-one-out cross-validation. Out of the four configurations depicted in the image below, the best one (I2+RNFL), was trained and evaluated, resulting in an area under the curve of 0.74 (95% CI [0.60, 0.89]) (Figure 4). The hyperspectral information present in the images was the main driver for this classification result. The classification accuracy improved by including OCT data.[9]

Conclusion

The bi-modal imaging approach using hyperspectral and OCT data resulted in a successful proof-of-concept to detect amyloid-beta changes in the retina of Alzheimer patients. The data were used to train a model which could discriminate AD patients from controls with 80% accuracy. The accuracy of the model improved when adding the OCT data, a measure of retinal nerve fibre layer thickness.

This study shows the potential of using retinal imaging techniques, based on hyperspectral imaging, for a non-invasive, faster and low-cost diagnostic test for AD than is available today. The snapshot camera used in this study is especially interesting because the spatial and spectral information can be obtained in one take, enabling real-time data acquisition. This is essential to deal with the eye movements, and a key enabler for this application.

Future studies are needed with more patients to confirm the results of this pilot study.

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