

## Through the eyes into the brain, using artificial intelligence

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### ABSTRACT

**Introduction:** Detection of neurological conditions is of high importance in the current context of increasingly ageing populations. Imaging of the retina and the optic nerve head represents a unique opportunity to detect brain diseases, but requires specific human expertise. We review the current outcomes of artificial intelligence (AI) methods applied to retinal imaging for the detection of neurological and neuro-ophthalmic conditions.

**Method:** Current and emerging concepts related to the detection of neurological conditions, using AI-based investigations of the retina in patients with brain disease were examined and summarised.

**Results:** Papilloedema due to intracranial hypertension can be accurately identified with deep learning on standard retinal imaging at a human expert level. Emerging studies suggest that patients with Alzheimer's disease can be discriminated from cognitively normal individuals, using AI applied to retinal images.

**Conclusion:** Recent AI-based systems dedicated to scalable retinal imaging have opened new perspectives for the detection of brain conditions directly or indirectly affecting retinal structures. However, further validation and implementation studies are required to better understand their potential value in clinical practice.

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**Keywords:** Alzheimer's disease, deep learning, dementia, optic neuropathy, papilloedema

### INTRODUCTION

Neurological dysfunction is a leading cause of disability, affecting more than 276 million people worldwide.<sup>1</sup> Over the last decades, the prevalence of neurological dysfunction has increased, particularly in the ageing population which is commonly affected by dementia, stroke and brain tumours.<sup>1,2</sup> The increasing number of

patients suffering from neurological disorders raises concerns about the efficiency of screening programmes and early clinical interventions. Cognitive impairment and dementia are major causes of chronic neurological impairment in Singapore—they are also significant individual determinants of emergency department utilisation.<sup>3</sup> Early detection of treatable diseases in

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## CLINICAL IMPACT

### What is New

- Retinal imaging with standard cameras complements clinical ophthalmoscopy for the detection of associated neurological conditions affecting the optic nerves. However, these modalities require high human expertise for interpretation.
- Deep learning (DL) methods have recently enabled automated and accurate interpretation of such retinal images for the diagnosis of papilloedema due to neurological conditions that cause increased intracranial pressure.

### Clinical Implications

- Recent studies suggest that DL applied to retinal images could also identify patients with Alzheimer's disease, but more prospective data are needed to assess clinical applications in real-life situations.

predisposed patients is a key strategy for improving global healthcare; it is applicable for many conditions such as colon cancer, breast cancer, diabetic retinopathy, etc. Unfortunately, few screening strategies have been developed for the detection of neurological diseases due to many factors, including phenotypic variability and disease complexity.<sup>4</sup>

In overcoming these issues, the eye is an excellent candidate to facilitate the detection of neurological disorders, which often also affect the retina or the optic nerve as they both contain neural tissue.<sup>5</sup> Standard imaging of the retina and the optic nerve (e.g. retinal fundus photography and optical coherence tomography [OCT]) are non-invasive and real-time methods to investigate the integrity of the visual system. They also provide an indirect reflection of cerebral health in various neurological conditions, such as multiple sclerosis and intracranial hypertension.<sup>6</sup> However, direct fundoscopy and interpretation of retinal images require high human expertise, which is a barrier for their utilisation by non-ophthalmic healthcare providers.<sup>7</sup> Recently, artificial intelligence (AI) methods such as deep learning (DL) have been applied for automated interpretation of medical data, including retinal images. In brief, by “learning” from a large sample of retinal images with robust reference diagnosis, specific DL algorithms have the potential to automatically identify structural lesions on retinal photographs, leading to the

detection of underlying neurological conditions. The aim of this review is to summarise the current and emerging concepts related to the detection of various neurological conditions via a DL-based analysis of retinal images.

### Retinal imaging modalities

The main retinal imaging modalities used in clinical practice include retinal fundus photography with adapted cameras, OCT and more recently, OCT angiography (OCTA). Colour fundus photography is the most common and affordable method for imaging the retina and optic nerve head (ONH) structures. It can be performed by desktop cameras or by recently developed handheld cameras. Traditionally, retinal fundus photography is performed by mydriatic cameras after pharmacological pupillary dilation to allow optimal visualisation of the periphery of the back of the eye. This method is associated with some inconvenience (e.g. photophobia, loss of accommodation, risk of allergy, etc.). However, non-mydriatic fundus cameras can also achieve excellent imaging performance, which may accelerate a possible transition of their use to non-ophthalmic settings, such as in the emergency departments and diabetes and endocrinology clinics.<sup>7</sup> New, non-mydriatic handheld fundus cameras or smartphones have also been successfully used for the detection of diabetic retinopathy (DR),<sup>8,9</sup> but their use is yet to be evaluated for neuro-ophthalmic purposes.

OCT is a retinal imaging technique that has transformed ophthalmology. Initially used for the evaluation of retinal diseases (e.g. diabetic macular oedema and age-related macular degeneration [AMD]) and glaucoma, OCT has been progressively used to also assess the structure of ONHs in various optic neuropathies. Based on an interferometric technique, OCT generates cross-sectional images of the retina, allowing micron-level spatial resolution. The latest generations of OCT provide greater resolution images, and increased field of view and depth of the study area within a short amount of time.

## METHOD

The authors examined and summarised current and emerging concepts related to the detection of neurological conditions that uses AI-based investigations of the retina in patients with brain disease.

## RESULTS

### Applications of AI to retinal imaging

Retinal image analysis by humans remains a partially subjective operation, with high intra- and intergrader

variability that exposes patients to interpretation bias. Recent technological developments offered by AI—particularly machine learning (ML) and DL methods—have opened new horizons for improved, automated diagnosis on retinal images. To date, DL has been successfully developed and deployed across many different fields in medicine, such as in radiology, dermatology, pathology and ophthalmology.<sup>10,11</sup> In ophthalmology, there are currently 2 algorithms approved by the US Food and Drug Administration for the detection of DR, namely IDx-DR (Digital Diagnostics, Coralville, US) and EyeArt (Eyenuk Inc, Woodland Hills, US).<sup>12</sup> Numerous other DL systems (DLSs) have shown promise for detecting AMD, retinopathy of prematurity, and other retinal pathologies.<sup>13</sup>

The performance of a DLS is evaluated by comparing its predicted results with a reference standard (ground truth), which is typically provided by ophthalmologists and formulated according to expert judgment. Sensitivity, specificity, precision and accuracy are the most used indices to quantify the diagnostic effectiveness of a DLS. The area under the receiver-operator-characteristic curve (AUROC) is also a commonly used performance parameter. The performance of a model is conventionally assessed through 2 operational steps: firstly, through internal validation (cross-validation), followed by testing on an independent external dataset. Notably, the independent datasets should ideally include ethnically and demographically diverse patients, with data collected from different clinical settings to secure the generalisability of DLS.<sup>14</sup>

### Detection of papilloedema and other optic neuropathies

The diagnosis of optic neuropathies in everyday practice is based on the identification of structural or functional abnormalities of the optic nerves. Diagnosing an optic neuropathy is based on a constellation of clinical signs and ancillary investigations (including evaluation of colour vision, visual fields, measurement of the optic nerve morphometric parameters with OCT, and sometimes electrophysiology). Ophthalmoscopically, an optic neuropathy can be associated with a normal appearance (if the lesion is very posterior within the orbit), or can cause swelling of the optic disc (if the anterior part of the nerve is affected). With time, swelling of the optic disc can either regress if appropriately treated, or can evolve into optic atrophy. Papilloedema is defined as ONH swelling due to raised intracranial pressure. It can be either idiopathic or secondary (the latter due to brain tumours, haematomas, venous sinus thrombosis, etc.). Papilloedema is not necessarily associated with visual dysfunction, which

explains why patients may not complain of visual loss, especially in the early stages. Patients may present with headache or other systemic signs of raised intracranial pressure. However, detection of papilloedema at the back of the eye—whether visually symptomatic or not—is of critical importance, as delayed recognition may result in permanent visual loss, neurological deficits and even death. Papilloedema is traditionally identified by direct ophthalmoscopy, and it requires skill to differentiate the condition from other causes of optic disc swelling (e.g. ischaemic optic neuropathy and optic neuritis). More rarely, other optic disc anomalies (known as pseudo-papilloedema) such as optic disc drusen and myelinated intraocular nerve fibres can mimic papilloedema. Their appropriate detection is essential in clinical practice to avoid unnecessary, expensive and potentially harmful investigations. On the other hand, patients with intracranial hypertension usually present with headache, tinnitus and variable visual loss. They require evaluation of the optic discs, which is difficult in everyday practice without the direct assistance of ophthalmologists or neuro-ophthalmologists. As an alternative, it has been suggested that imaging of the retina and the ONH may improve the detection of various ONH abnormalities by non-ophthalmic healthcare providers.<sup>7</sup>

Computer-aided diagnostic systems could help improve the detection of papilloedema and other ONH abnormalities.<sup>15</sup> In an early study, Akbar et al.<sup>16</sup> developed a classification model aimed at automatically differentiating between papilloedema and normal ONHs on retinal images, based on structural features of the ONH (disc margin obscuration, disc colour and continuity of disc vessels) using support vector machine (SVM) for classification purposes. In the limited sample, the authors achieved good performance for differentiating papilloedema from normal ONH with an accuracy, sensitivity and specificity of 92.9%, 90.0%, and 96.4%, respectively.

To address the more complex reality of everyday clinical practice, a recent DLS has been developed for the detection of papilloedema and other ONH abnormalities on conventional retinal photographs. Milea and an international neuro-ophthalmology consortium called Brain and Optic Nerve Study with Artificial Intelligence (BONSAI) have developed, trained and tested a DLS<sup>17</sup> in a large, retrospective and multiethnic dataset. The team used multiple fundus digital cameras from 24 neuro-ophthalmology sites in 15 countries, aimed to discriminate papilloedema from normal ONHs and other ONH anomalies. The model was trained and validated on 14,341 photographs of normal and

abnormal ONHs, and the external testing dataset consisted of 1,505 photographs from 5 different countries. Papilloedema detection in the external testing dataset was achieved with high AUROC (0.96) and sensitivity (96.4%) indices, and good specificity (84.7%). Altogether, although obtained in a retrospective study, these results suggest that a DLS could accurately identify papilloedema and other abnormal optic discs on standard retinal images.

Despite the excellent classification performance of the BONSAI DLS, this retrospective study did not ascertain the model's performance in comparison with expert neuro-ophthalmologists. An additional study subsequently compared the performance of 2 expert neuro-ophthalmologists against the BONSAI DLS, using 800 fundus photographs (400 normal ONH, 201 papilloedema and 199 other ONH abnormalities photographs).<sup>18</sup> The performance of the BONSAI DLS for detecting papilloedema (AUROC 0.96, accuracy 91.5%, sensitivity 83.1% and specificity 94.3%) and overall correct classification (84.7%) was comparable with the performance of neuro-ophthalmology experts, but significantly better than the performance of non-expert first-line clinicians (neurologists, internists, emergency room doctors, ophthalmologists and optometrists).<sup>19</sup>

Determining papilloedema severity in clinical practice is important for treatment decisions and disease prognosis. Papilloedema severity is typically assessed using the 5-grade modified Frisen classification system, which is difficult to apply, not very practical, and thus results in a low interobserver agreement that can be as low as 36%.<sup>20</sup> For this reason, BONSAI has adopted a new, simplified classification: mild to moderate papilloedema (including Frisen grades 1 to 3); and severe papilloedema (including Frisen grades 4 and 5).<sup>21</sup> In order to automatically determine papilloedema severity, a specific DLS was trained on 2,103 fundus photographs of confirmed papilloedema from multiple centres. Two expert neuro-ophthalmologists then graded the papilloedema severity according to the above-mentioned simplified binary grading scale, for algorithm training. The DLS performance on the external testing dataset achieved a high diagnostic performance (AUROC 0.93), being also comparable to the majority agreement among 3 neuro-ophthalmologists (agreement score between DLS and neuro-ophthalmologists of 0.62), which was interestingly higher compared to the agreement score of 0.54 among the 3 neuro-ophthalmologists themselves.

In addition to the structural identification of papilloedema at the back of the eye, it is also essential

to evaluate its functional visual consequences. Visual field (VF) testing is a critical method of measuring the optic nerve function, and it poses multiple technical and interpretation challenges in assessing the consequences of papilloedema. Recently, ML methods were applied to VF testing in patients with papilloedema due to idiopathic intracranial hypertension (IIH). For this purpose, archetypal analysis (AA) was developed based on data collected in the IIH Treatment Trial (IIHTT)—the first large randomised study that analysed baseline and laboratory characteristics of untreated patients with IIH—as an additional tool to conventional VF indices (i.e. mean deviation and pattern standard deviation). AA is an unsupervised ML technique that identifies representative patterns (archetypes) within a dataset of VFs, thereby analysing a given VF as the weighted sum of its archetypes.<sup>22,23</sup> As a start, Doshi et al.<sup>22,23</sup> identified 14 archetype patterns in the IIHTT dataset, which were comparable to expert categorisations. A subsequent follow-up study showed that archetypal weight changes were identifiable over a 6-month period and were dependent on IIH treatments. Although it is too early to generalise these initial results to various IIH severities, they are promising for the clinical management of IIH, because they provide a more standardised evaluation of IIH than the current practice, wherein individual clinical interpretation is inevitably qualitative and variable with current conventional VF indices.

Papilloedema can regress under treatment. However, if not adequately treated, it can cause optic atrophy that represents the late, non-specific stage of any optic neuropathy, irrespective of its cause (e.g. compression, ischaemia, inflammation, trauma, hereditary, etc.).<sup>24</sup> Identification of optic atrophy, which can be subtle, is important in clinical practice, because it can be caused by treatable causes (e.g. compression by a meningioma). However, optic atrophy may be difficult to discriminate from the similar-looking glaucomatous optic neuropathy (GON). Yet, it is critical to clearly differentiate both conditions as each requires a different work-up and specific management. In a recent study, Yang et al.<sup>25</sup> developed a DLS aimed to discriminate non-glaucomatous optic neuropathies (NGON) from GON, based on the evaluation of standard colour fundus photographs. A total of 3,815 fundus photographs (486 GON, 446 NGON and 2,883 normal) were retrospectively collected and used for training and testing. The training dataset included a wide range of causes of NGON (including compression, hereditary diseases, ischaemia, inflammation, trauma and toxic causes). On an internal testing set of 2,675 photographs (106 GON, 66 NGON and 2,503 normal ONH), the DLS (based on the ResNet-50 classification model)

yielded an area under the precision-recall curve of 0.874, sensitivity of 93.4% and specificity of 81.8%.

More recently, modern DL methods have been applied to more sophisticated OCT retinal imaging for neurological patients, to discriminate true papilloedema (requiring prompt intervention) from pseudo-papilloedema. Clinically, it is sometimes very difficult to distinguish papilloedema (due to life-threatening conditions) from benign pseudo-papilloedema (e.g. caused by optic disc drusen), given that they may have similar visual appearance. Modern DL methods have been used to distinguish papilloedema from benign pseudo-papilloedema, in order to avoid expensive, invasive and often unnecessary investigations. In a first pilot study, DL applied to OCT raster scans of the ONH could accurately identify various ONH structures, leading to high performance for the detection of optic disc drusen (AUROC  $0.99 \pm 0.001$ ), papilloedema (AUROC  $0.99 \pm 0.005$ ) or normal discs (AUROC  $0.98 \pm 0.01$ ).<sup>26</sup>

In summary, recent advances of new DLSs may transform the way we detect ONH abnormalities on retinal images acquired in neurological patients. Based on a survey among general practitioners in Singapore, the application of teleophthalmology (with specialist consultation or using AI-integrated systems) will increase the performance of interpreting fundus findings.<sup>27</sup> However, even in this context, AI cannot replace a physician's experience or rational judgment, and it remains a complementary and assistive tool.<sup>28</sup> There is a high need to validate these initial results in future prospective or real-life studies. It is possible that the performance of these systems will be further improved with the incorporation of additional clinical data (visual performance, presence of headache, nausea, tinnitus, etc.).

### Alzheimer's disease and dementia

Based on the population estimates in 2021, 6.2 million Americans aged 65 years or older are living with Alzheimer's disease (AD) dementia,<sup>29</sup> and this number is expected to increase to 131.5 million by 2050.<sup>30</sup> AD dementia is the most common form of dementia, but its pathophysiology is still poorly understood. The definition and diagnosis of both AD dementia and mild cognitive impairment (MCI) have evolved over recent years, moving from purely clinical evaluations to assessment of various biomarkers, with the hope of early detection. Brain amyloid- $\beta$  (A $\beta$ ) deposition, identified with dedicated positron emission tomography (PET) brain scans, low A $\beta$ 42 in the cerebrospinal fluid (CSF) or elevated CSF tau protein can be detected

years before the symptomatic development of AD dementia.<sup>31,32</sup> However, these investigations are invasive, costly, not easily accessible and difficult to perform in large-scale screening interventions. There is therefore a need to develop simple, accessible and reliable screening tools for the detection of AD dementia and other neurodegenerative diseases.<sup>33</sup>

For a long time, the retina has been considered a potential candidate for detecting neurodegenerative conditions, due to its high similarity and connections to the brain.<sup>34,35</sup> Similar to the brain, the retina is affected by ageing and neurodegenerative processes. However, a crucial question would be whether the pathological ageing of the retina reflects the nature and amount of associated brain lesions, especially in patients with dementia. Thus, a few studies have suggested that patients with AMD have a higher risk of developing AD dementia.<sup>36</sup> Similarly, A $\beta$  protein deposits are present in both AMD and AD dementia, even at early AD dementia stages.

The ageing retina is characterised by neuronal loss resulting in retinal thinning, which can be easily quantified by OCT devices.<sup>37,38</sup> Interestingly, age-related brain atrophy is also associated with retinal thinning on OCT; ageing also affects the retinal nerve fibre layer (RNFL), retinal ganglion cell complex layer and outer nuclear layer,<sup>39</sup> most likely due to axonal and neuronal death.<sup>42-44</sup> Additional longitudinal studies are required to better delineate the dynamics of these findings.<sup>43-47</sup> Several studies have reported the association between the deposits of A $\beta$  and phosphorylated tau proteins, with alterations in cerebral microvessels, including vascular dysfunction, changes in collagen content and increased cellular apoptosis.<sup>40-42</sup> It has been hypothesised that similar vascular changes could be detected in the retina using OCTA. Several such studies have suggested retinal capillary dropout, enlargement of the foveal avascular zone and decrease in density of the capillary plexus in pre-clinical and symptomatic AD.<sup>43-45</sup> Although OCTA may represent an indirect valuable biomarker showing vascular changes in AD,<sup>46</sup> the variability of its parameters is large and its disease specificity is not yet known, thus prompting additional prospective and methodologically robust studies.

Retinal fundus photography might represent even an interest in this context, because it can be easily implemented in non-ophthalmic clinics, including in neurology clinics. Zhang et al.<sup>47</sup> studied whether ML could discriminate patients with dementia and MCI, from normal individuals on standard retinal fundus photographs. This small study, which included 15 patients with dementia, 17 patients with MCI and 26 individuals

with normal cognitive function, used both SVM and extreme learning machine to classify these populations. The best model achieved an AUROC of 0.86, sensitivity of 92.8% and specificity of 69.6% in classifying patients with dementia and normal individuals. In addition, the model was able to discriminate patients with MCI from normal individuals with an AUROC of 0.87, sensitivity of 69.0% and specificity of 98.4%.

Tian et al.<sup>48</sup> also attempted to develop a classification model based on retinal photographs, focusing particularly on the architecture of retinal vessels. For this purpose, they used convolutional neural networks (CNN) to generate segmented retinal vascular images from fundus photographs, followed by the use of SVM for classification purposes. A total of 122 images of AD dementia patients and 122 images of age-matched normal controls from the UK Biobank database were enrolled for training of the model using 5-fold cross-validation. In the testing dataset, the model could discriminate AD dementia patients from normal controls with an accuracy of 82.4%, sensitivity of 79.2% and specificity of 84.8%. Among the various limitations of this study, the clinical diagnostic criteria for AD dementia and cognitive impairment were not well defined.

Wisely et al.<sup>49</sup> investigated a mix of multimodal retinal images and patient data to create a CNN to identify symptomatic AD. Colour maps of ganglion cell-inner plexiform layer (GC-IPL) thickness, OCT and OCTA images of the superficial capillary plexus, and ultra-widefield colour and fundus autofluorescence scanning laser ophthalmoscopy images were taken in patients with confirmed AD dementia and in healthy controls. Altogether, the study included 284 eyes from 159 patients, 36 of whom were clinically diagnosed with AD dementia by expert neurologists. All medical records were reviewed by 1 of 2 expert neurologists to confirm a clinical diagnosis of AD dementia using the National Institute of Aging and Alzheimer's Association standards. On the validation set, the best-performing model—which included GC-IPL maps, quantitative data and patient data—reached an AUROC of 0.861 (95% confidence interval [CI] 0.73–0.995); on the testing set, an AUROC of 0.84 (95% CI 0.74–0.94) was reached. However, this study had a few limitations, including a small sample size.<sup>50</sup>

In the UK, several studies have aimed to link routinely collected multimodal retinal images with systemic and neurodegenerative disease data from hospital admissions, including the ongoing AlzEye study.<sup>51</sup> This study, which includes more than 6 million retinal images collected from hundreds of thousands of patients, is currently aiming

to identify novel retinal signatures in patients with AD dementia and cardiovascular diseases.

These initial studies share common limitations, such as small numbers of included patients, same ethnicity and lack of testing the system's performance on external and independent datasets. More generally, the results of these studies do not yet have a strong explainability, i.e. identification of well-identified features to distinguish between retinas in AD dementia versus cognitively healthy individuals. It is possible for DL algorithms to take into account several retinal features associated with AD dementia, such as: (1) visible retina drusen (or other retinal changes due to AMD or glaucoma, which are statistically associated with AD dementia); (2) retinal axonal and neuronal changes; and (3) retinal vascular changes.

A recent, largest-to-date study aiming to test a retinal photograph-based DL algorithm for AD dementia identification, has tried to address a few of these questions in retrospectively collected data from multiethnic and multinational datasets, including a total of 12,949 retinal photographs from 648 AD dementia patients and 3,240 controls with no dementia.<sup>52</sup> Using advanced techniques of unsupervised domain adaptation and feature fusion, the classification performance of the DLS in 5 independent external cohorts achieved accuracies ranging from 79.6% to 92.1%, and AUROCs ranging from 0.73 to 0.91. Interestingly, the DLS performed well even in the presence of concomitant eye diseases, suggesting that AD dementia might be associated with specific retinal features. In the cohorts with PET scan data, the model could discriminate A $\beta$ -positive from A $\beta$ -negative patients with accuracies ranging from 80.6% to 89.3%, and AUROCs ranging from 0.68 to 0.86, supporting the concept that a retinal photograph-based DL algorithm might have considerable potential for screening AD dementia at community levels.

Altogether, these recent preliminary studies suggest that DL methods applied to retinal imaging may contribute to identify AD, although not as the only or the primary AD dementia diagnostic criteria. There is a need for further validation with higher accuracy and specificity in prospective studies. If validated, implemented and adopted, AI-based retinal imaging may represent an interesting objective modality to screen elderly patients, at best in combination with other validated modalities (i.e. exploring cognition). This could be particularly useful at community levels, and especially if novel therapies are introduced for treating AD dementia. Early AD dementia diagnosis improves

the life quality of affected patients, and it is an opportune time to strive towards this goal as large resources are currently being allocated for AD dementia prevention and pharmacological treatment.<sup>33</sup>

## CONCLUSION

The application of AI to retinal imaging in neurology is at its beginnings, with focus mainly on detecting ONH abnormalities associated with life-threatening and debilitating neurological disorders, as well as on identifying neurodegenerative conditions including AD dementia. The currently growing interest of this approach is due to the fact that retinal imaging technologies, being non-invasive, are becoming more widely accessible, often affordable and simple to use. Novel handheld, easy-to-use retinal cameras have recently become largely available, providing high-resolution images that can be acquired without pupillary dilation (non-mydratic cameras). These encouraging initial achievements may soon translate to new forms of practice in neurology, particularly when ophthalmologists are not readily available. However, more robust replication studies are required to validate this new technology for use in clinical practice. These new concepts suggest AI-assisted interpretation of retinal imaging might become a useful, complementary tool for screening or even identification of neurological diseases in the future.

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