The retina as a window to the brain
—from eye research to CNS disorders

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Abstract | Philosophers defined the eye as a window to the soul long before scientists addressed this cliché to determine its scientific basis and clinical relevance. Anatomically and developmentally, the retina is known as an extension of the CNS; it consists of retinal ganglion cells, the axons of which form the optic nerve, whose fibres are, in effect, CNS axons. The eye has unique physical structures and a local array of surface molecules and cytokines, and is host to specialized immune responses similar to those in the brain and spinal cord. Several well-defined neurodegenerative conditions that affect the brain and spinal cord have manifestations in the eye, and ocular symptoms often precede conventional diagnosis of such CNS disorders. Furthermore, various eye-specific pathologies share characteristics of other CNS pathologies. In this Review, we summarize data that support examination of the eye as a noninvasive approach to the diagnosis of select CNS diseases, and the use of the eye as a valuable model to study the CNS. Translation of eye research to CNS disease, and deciphering the role of immune cells in these two systems, could improve our understanding and, potentially, the treatment of neurodegenerative disorders.

Introduction

Cicero (106–43 BC) was first to declare “ut imago est animi voltus sic indices oculi”—the face is a picture of the mind as the eyes are its interpreter. Many different versions of this phrase have since been quoted by philosophers, orators, politicians and writers. Over the years, scientists have struggled with the concept that the eyes are the window to our soul, searching for scientific evidence to determine whether eye research could be useful for investigating the brain and diagnosis of its diseases.

During embryonic development, the retina and optic nerve extend from the diencephalon, and are thus considered part of the CNS. The retina is composed of layers of specialized neurons that are interconnected through synapses. Light that enters the eye is captured by photoreceptor cells in the outermost layer of the retina, which initiates a cascade of neuronal signals that eventually reach the retinal ganglion cells (RGCs), the axons of which form the optic nerve. These axons extend to the lateral geniculate nucleus in the thalamus and the superior colliculus in the midbrain, from which information is further relayed to the higher visual processing centres that enable us to perceive an image of our world.¹

Despite their diverse morphology,² RGCs display the typical properties of CNS neurons, and generally comprise a cell body, dendrites and an axon. The axons of many RGCs collect to form the optic nerve. Posterior to the globe, the optic nerve, similar to all fibre tracts in the CNS, is covered with oligodendrocyte-produced myelin, and is ensheathed in all three meningeal layers. Like insult to other CNS axons, insult to the optic nerve results in retrograde and anterograde degeneration of the severed axons, scar formation, myelin destruction, and the creation of a neurotoxic environment that involves oxidative stress, deprivation of neurotrophic factors, excitotoxic levels of neurotransmitters, and abnormal aggregation of proteins and debris. Such a hostile milieu often results in death of neighbouring neurons that were spared in the initial damage—a phenomenon that is termed secondary degeneration.³⁻⁴

In the CNS, including the optic nerve, axonal regeneration after injury is limited. Indeed, much of our knowledge about axonal response to CNS trauma has emerged from studies of the optic nerve.⁵⁻¹⁰ The factors deemed responsible for creation of an environment that is nonpermissive for axonal growth are shared between the injured optic nerve and other CNS axons. Such factors include molecules that inhibit neurite outgrowth—among which are myelin debris and myelin-associated inhibitors (such as reticulon-4 [also known as Nogo A], myelin-associated glycoprotein and oligodendrocyte myelin glycoprotein)—reactive astrocytes and chondroitin sulphate proteoglycans that form the glial scar, as well as the lack of growth-promoting factors.¹¹⁻¹⁵ Early discoveries that CNS axons can regrow in the presence of peripheral nerve grafts were made in models of optic nerve transection and of spinal cord injury,¹⁰,¹²,¹² highlighting that similar growth-restrictive conditions exist in these two CNS compartments (Figure 1).

As a part of the CNS, the eye—particularly the retina—must maintain regulated interactions with the immune system, and is, in fact, an immune-privileged
The eye consists of unique physical structures, a local collection of surface molecules and cytokines, and is host to specialized immune responses similar to those seen in the brain and spinal cord. The eye is also surrounded by an array of blood–ocular barriers that share structures, characteristics and mechanisms with the CNS gating system. For example, the inner blood–retinal barrier (BRB) is composed of nonfenestrated endothelial cells that are firmly connected by tight junctions and surrounded by astroglial and Müller cell endfeet, and thus strongly resembles the blood–brain barrier (BBB). The anterior chamber of the eye is filled with aqueous humour, a fluid enriched with anti-inflammatory and immunoregulatory mediators that is reminiscent of the cerebrospinal fluid that circulates around brain and spinal cord parenchymas. In addition to these similarities with CNS defences, immune privilege in the eye involves a unique phenomenon termed anterior chamber–associated immune deviation, in which antigen-presenting cells that enter the anterior chamber of the eye capture antigen and then migrate to the spleen where they convert effector leukocytes into regulatory ones. This process thereby establishes a tightly regulated immune response towards ocular antigens. In combination, the mechanisms described above enable the eye to benefit from immune-defence machinery while avoiding the risk of tissue damage owing to uncontrolled inflammation (Figure 1).

Given the features common to the eye and the rest of the CNS, much of what is learned from eye research could be applicable to the brain and spinal cord, and vice versa. In this Review, we summarize how the eye, as an extension of the brain, presents manifestations of major neurodegenerative diseases, and argue that several ocular diseases should be viewed as forms of neurodegenerative disorders. As a corollary, we describe the benefits of the eye as a research and diagnostic tool, presenting it as a valuable model for CNS research and an important aid in the search for new therapeutic avenues to alleviate CNS pathologies.

Ocular manifestations of CNS disorders

As the eye is an extension of the brain, to search for ocular manifestations of brain pathologies seems reasonable. Indeed, various ocular changes have been detected and characterized through ophthalmological assessments in patients with CNS disorders such as stroke, multiple sclerosis (MS), Parkinson disease (PD) and Alzheimer disease (AD). Although some eye manifestations are not specific to a particular disease, their existence emphasizes the strong link between the retina and the brain. Furthermore, in many of these disorders, ocular manifestations often precede symptoms in the brain, indicating that eye investigations could offer a means of early diagnosis.

Stroke

Prospective studies have shown that retinal microvascular abnormalities, including arteriovenous nicking, retinal haemorrhage and arteriolar narrowing, could predict the risk of ischaemic brain changes (such as cerebral infarcts and white matter lesions), clinical stroke events and stroke mortality. In addition, retinopathy or retinal arteriovenous nicking were linked to increased risk of incident cerebral infarction, especially when such retinal abnormalities were associated with cerebral white matter lesions—a characteristic that is often predictive of clinical stroke. Beyond this prospective evidence, studies of the eye in animal models have revealed that stroke is associated with functional retinal impairment including retinal layer thinning, reactive gliosis, increased expression of genes associated with cellular injury and restricted oxygen supply, DNA fragmentation, and neurodegeneration of the optic nerve (Figure 2a). Ocular manifestations are to be expected in stroke, as retinal and cerebral small vessels have similar embryological origins, anatomical features and physiological properties. Dysfunction of the BBB or the BRB is suspected to have a central role in the development of cerebral and retinal microangiopathy, respectively. Importantly, whereas BBB breakdown usually remains undetected until marked vasogenic oedema and brain damage has occurred, changes in retinal vascularization can be visualized early in the disease process, and in a direct and noninvasive manner.

Multiple sclerosis

In MS, another major neurodegenerative disease—visual dysfunction is a leading cause of disability. Visual loss is a presenting symptom in up to 50% of patients with MS, and some degree of visual impairment develops along the course of disease in most cases. Optic neuritis, an inflammatory optic neuropathy associated with demyelination and RGC degeneration, is diagnosed in 75% of patients with MS, and is often the presenting symptom. Anecdotally, the earliest record of MS was found in the 19th century diaries of Sir Augustus d’Este, in which he described symptoms of optic neuritis and diplopia followed by severe disability—a constellation of symptoms that, in the present day, would be immediately suggestive of MS. Importantly, visual deficits in MS also occur in patients without a diagnosis of optic neuritis. Measures of visual acuity and contrast sensitivity are decreased in such patients, and the retinal nerve fibre layer (RNFL) is thinner than in healthy individuals. Moreover, in patients with MS, decline in

Key points

- As an extension of the CNS, the retina displays similarities to the brain and spinal cord in terms of anatomy, functionality, response to insult, and immunology
- Several major neurodegenerative disorders have manifestations in the retina, suggesting that the eye is a ‘window’ into the brain
- Neurodegenerative processes that have been characterized in CNS disorders are also detected in some classic ocular pathologies
- The accessibility and organization of the retina makes it a convenient research tool with which to study processes in the CNS
- Advances in ocular imaging techniques support the potential of these approaches as effective aids in noninvasive diagnosis of CNS disorders
- Future research should be aimed at testing whether therapies that are beneficial in brain disorders could also alleviate diseases of the eye, and vice versa
RNFL thickness correlates directly with progression of neurological impairment and with disease duration.45 Patients with MS often present with additional ocular abnormalities, such as inflammation and BRB dysfunction, as well as retinal atrophy in the form of RGC and axonal loss (with a shrunken appearance of surviving cells), and pathological cupping of the optic disc—the site at which RGCs exit the eye and form the optic nerve (Figure 2b).45,46

That MS and ocular pathology are associated is not surprising given that myelin components, which are essential in both the brain and the visual tract, are major autoimmune targets in MS. Visual defects commonly result from demyelination of axons along the visual pathway.39 Interestingly, however, inner parts of the retina, which are not myelin-associated, are also affected in MS, suggesting that the autoimmune response is also directed against other antigens in the eye.47

Parkinson disease
PD is mainly associated with motor dysfunction, but also involves nonmotor symptoms that can include visual deficits. Such deficits can manifest as deterioration in visual acuity, low sensitivity to contrast, and/or disturbed colour vision, and can lead to abnormal responses on electrophysiological testing. The retinas of patients with PD display swelling of photoreceptors and RGCs, and morphological deterioration of the perifoveal dopaminergic plexus48–51 with thinning of the RNFL.52–55 In agreement with the hypothesis that PD results from an imbalance of dopamine, it seems that visual deficits in PD are also caused by dopaminergic deficiency, resulting at least in part from reduced expression of tyrosine hydroxylase—the rate-limiting enzyme in dopamine synthesis (Figure 2c).49,50 Indeed, some of the visual deficits experienced by patients with PD can be ameliorated by treatment with levodopa.56

Figure 1 | The eye as an extension of the CNS. a | The retinal layers are composed of several neuronal types including retinal ganglion cells, which share structural morphology with other CNS neurons. b | The axons of these cells are myelinated by oligodendrocytes posterior to the globe, and form the optic nerve, which extends to the LGN and SC of the brain. c | Injury to the optic nerve produces, in a manner similar to other CNS neurons, an environment that is both hostile to survival of neurons that were spared in the primary insult and inhibitory to regeneration of severed axons. d–e | Similar to the CNS, the eye has a unique relationship with the immune system that involves specialized barriers such as the inner blood–retinal barrier, the retinal counterpart of the CNS blood–brain barrier (d), and the constitutive presence of immunoregulatory molecules (e). Abbreviations: CSPG, chondroitin sulphate proteoglycan; LGN, lateral geniculate nucleus; NgR, Nogo receptor; SC, superior colliculus.
Alzheimer disease

Ocular manifestations of AD have been studied extensively over the past few decades.\(^ {57,58} \) A case–control study comparing the optic nerves of patients with AD with those of controls found epidemiological support for RGC atrophy in AD.\(^ {59} \) Compared with healthy individuals, patients with AD displayed narrowing of retinal veins, reduced retinal blood flow and RGC numbers.
and thinner RNFLs, and such retinal abnormalities in AD correlated with retinal dysfunction.\textsuperscript{60–65} Importantly, a reduction in macular volume in patients with AD was found to correlate with cognitive impairment, as measured using the Mini-Mental State Examination.\textsuperscript{66} Previous findings showed that ocular degeneration in AD was most severe at the posterior parts of the optic nerve (close to the optic chiasm), suggesting that, although pathology is observed in the eye, the primary site of damage is intracranial.\textsuperscript{67}

Pathological accumulation of amyloid-β (Aβ) and phosphorylated tau (p-tau)—the classic manifestations of AD in the brain—has also been reported in the eyes of patients with AD and in the eyes of transgenic mouse models of this disease.\textsuperscript{57,68–72} Similar to their pathological activities in the brain, Aβ and p-tau in the eye have been associated with ocular damage including the formation of cataracts, loss of retinal neurons, RNFL thinning and impaired axonal outgrowth.\textsuperscript{57,68–72} Taken together, the robust manifestations of AD in the eye emphasize the close relationship between this organ and the brain (Figure 2d).

**Lymphoma**

Ocular manifestations of CNS pathologies are not confined to neurodegenerative conditions. In primary CNS lymphoma (PCNSL), an extranodal non-Hodgkin lymphoma, 60–80\% of patients are initially diagnosed with primary intraocular lymphoma, which presents with symptoms such as ‘floaters’ (deposits within the vitreous that cast shadows onto the retina, resulting in the appearance of spots, threads or fragments of cobwebs floating in the visual field), decreased vision, and ocular inflammation.\textsuperscript{73} As PCNSL is a multifocal disease that often presents with symptoms in the eye, ophthalmologists and neuro-oncologists should join forces in research and development of therapeutic strategies for this disorder.

**Eye disease as neurodegeneration**

Beyond the fact that major brain diseases manifest within the eye, several diseases that are unique to the eye display characteristics of neurodegenerative disorders. Such overlap is probably explained by the similarities between the eye and the brain in terms of tissue structure and interactions with the immune system.

**Glaucoma**

In glaucoma—a primary cause of irreversible vision loss associated with RGC death—the loss of RGC bodies is suggested to be preceded by axonal atrophy and deficits in axonal transport.\textsuperscript{74,75} This pattern of disease progression (that is, beginning with axonal degeneration and progressing through secondary degeneration) is also seen in AD, PD and amyotrophic lateral sclerosis, suggesting that similarities exist between the aetiology of glaucoma and these neurodegenerative disorders.\textsuperscript{4,75–79} Studies in primates and humans have shown that glaucomatous damage spreads within the central visual pathways, beyond the eye and the optic nerve. This damage includes trans-synaptic degeneration in the brain, similar to that seen in AD and PD, and again indicates that glaucoma should be considered a neurodegenerative disease of the CNS.\textsuperscript{80,81} Aβ and p-tau, the major pathological features of AD, have also been detected in patients with glaucoma, and are thought to have a role in neuronal death and progression of vision loss in this disease.\textsuperscript{82–87}

**Age-related macular degeneration**

In age-related macular degeneration (AMD), the leading cause of blindness among the elderly, Aβ is found in drusen—the extracellular deposits that are characteristic of this disease.\textsuperscript{88,89} Similar to its roles in AD, Aβ in drusen might contribute to AMD progression by mediating oxidative stress, uncontrolled inflammation and imbalanced angiogenesis.\textsuperscript{88–91} Interestingly, many of the other proteins and molecules present in drusen are also components of AD plaques, and it is possible that protein misfolding contributes to the pathology of both AD and AMD.\textsuperscript{92,93}

**Genetic similarities**

The commonality in mechanisms that underlie disorders of the eye and the brain is also reflected in the genetics of disorders of these CNS compartments. For example, genes related to iron metabolism are involved in a series of neurodegenerative disorders that affect the brain and spinal cord, as well as the retina. One such example is the ceruloplasmin (CP) gene, which is expressed in both the brain and the retina. Mutations in this gene are associated with aceruloplasminaemia, an autosomal dominant disorder characterized by degeneration of the retina and basal nuclei.\textsuperscript{94,95} Mutations in the CP gene were also detected in patients with PD, and the finding that ceruloplasmin protein colocalized with Lewy bodies—a characteristic pathological feature of PD—indicates a role for ceruloplasmin in PD pathogenesis.\textsuperscript{96} Elevated expression of the CP gene has been reported in experimental and human glaucoma, and following optic nerve crush.\textsuperscript{97,98}

Another disease that highlights the shared genetics of brain and eye disorders is posterior column ataxia and retinitis pigmentosa—an autosomal recessive neurodegenerative disorder characterized by retinitis pigmentosa and sensory ataxia. This condition has been mapped to a mutation in the \textit{FLVCR1} gene on chromosome 1, and is also possibly related to dysregulation of iron homeostasis.\textsuperscript{99–100}

A comprehensive report of genetic mutations that are common to conditions affecting the eye and other parts of the CNS is beyond the scope of this Review, but could be a useful tool to aid in the diagnosis and, possibly, the treatment of some of these conditions. Such genetic data, together with the evidence presented above, gives credence to the view that some ocular pathologies are neurodegenerative disorders, and highlights the advantage of using research on eye pathologies as a means to obtain insight into CNS disorders.

**The eye as a model of the CNS**

The similarity of the eye to other parts of the CNS makes it a viable model for the study of CNS processes in both...
health and disease. The eye is a particularly convenient research model for several reasons. First, compared with other parts of the CNS, the eye is relatively accessible for manipulation and imaging in live individuals. Second, as the neurons in the retina are clearly recognizable, neuronal death can be directly quantified. Third, the unique organization of the retinal layers enables the various retinal neurons and their interactions to be distinguished; thus, damage that manifests as distortion of the normal structure is easily detectable. Fourth, administration of various compounds (either therapeutic or experimental) to the eye is fairly simple, and injections into the vitreous or the subretinal space can be performed without directly penetrating the parenchyma. Fifth, the optic nerve consists of a long, continuous tract of axons that are uninterrupted by interneurons, which makes it ideally suited for regeneration studies. Finally, as the retina is a well-defined neuronal compartment, it can be isolated in an intact form and used to study molecular mechanisms of pathology and reaction to various pharmacological agents, either using retinal explant cultures or through whole-mount immunohistochemical staining.

Given these features of the eye, it is not surprising that much of our understanding regarding the processes of neuroprotection, cell renewal and axonal regeneration in the CNS, and how these processes are influenced by the immune system, has emerged from studies of the retina and optic nerve.9,10,12,13,15,101–106

Eye-based diagnosis of CNS disorders

On the basis of the evidence described above, ocular imaging and visual tests could have substantial benefits as diagnostic tools for CNS disorders. Although such eye-based diagnostics are not yet in routine clinical use, accumulating evidence on associations between retinal abnormalities and the risk of developing neurological disorders suggests that ocular imaging techniques may be useful to assist in the diagnosis of these disorders.

Stroke

The Atherosclerosis Risk in Communities (ARIC) study—a prospective study to investigate cardiovascular disease and its risk factors—included retinal photography to detect retinal microvascular changes in the enrolled individuals. The ARIC investigators reported that participants whose retinal photographs showed lesions in the form of microaneurysms, retinal hemorrhages and soft exudates had a higher risk of developing incident stroke over 3 years than did patients without lesions.26 These findings and those of other studies demonstrate that retinal photography is a potentially valuable tool to study the microvascular aetiology of cerebrovascular disease, and suggest that this method could be used in individuals at risk of stroke to investigate subclinical microangiopathy or to predict the risk of stroke recurrence.33,107,108

Multiple sclerosis

Optical coherence tomography (OCT) is a retinal imaging technique used to measure changes in RNFL thickness and macular volume, both of which are decreased in several neurodegenerative disorders, including MS. Reports indicate that many patients with MS exhibit optic neuritis as a presenting symptom; consequently, methods used for the diagnosis of optic neuritis, such as OCT and visual evoked potentials, may be beneficial in enabling early diagnosis of MS.43,111,112 Indeed, patients diagnosed with optic neuritis should be referred to a neurologist for an MS-directed examination. Notably, OCT has enabled quantitative measurement of RNFL thinning even in patients with MS who do not have a history of optic neuritis.43,111,112 and OCT measures were found to correlate with MRI outcomes in MS.113,114

To distinguish between MS and neuromyelitis optica (NMO)—an inflammatory demyelinating disease of the spinal cord and optic nerve that is often misdiagnosed as MS—is important.115 Studies using OCT have shown that after episodes of optic neuritis, which tend to be more severe in NMO, thinning of the RNFL is more pronounced in patients with NMO than in those with MS.46,116–118 OCT could, therefore, aid in the differentiation of these two conditions.

Alzheimer disease

OCT has also been used to assess RNFL thickness in patients with mild cognitive impairment (MCI) and AD.65,119,120 Interestingly, RNFL thickness was reduced both in patients with MCI and in those with AD of different severities compared with healthy controls, but the difference in RNFL thickness between patients with MCI and those with mild AD was not statistically significant. This finding suggests that RNFL thinning is an early event in AD pathology.119,120

In a recent study in which curcumin was administered to label plaques of Aβ, such plaques were detected in retinas of live AD transgenic mice before they could be detected in the brains of these animals. As retinal Aβ plaques were also found in the eyes from patients with AD during postmortem analyses, live imaging of the retina could be a useful tool for early diagnosis of AD.72 Moreover, treatment that effectively restricted Aβ plaque burden in brains of AD transgenic mice also caused a substantial reduction in retinal plaque burden,72 which suggests that monitoring the eye can be useful not only in the diagnosis of AD, but also for follow-up analysis of therapeutic efficacy.

Therapies for eye and brain diseases

Given the various associations and similarities between the eye and the brain, to test whether therapies that are beneficial in brain disorders could alleviate diseases of the eye (and vice versa) is tempting. Indeed, approaches that reduce Aβ load and improve cognitive performance in models of AD and, to some extent, patients,121–123 have proved successful in decreasing visual deficits in mouse models of AMD124,125 and reducing RGC loss in experimental glaucoma.87

Humanin, a brain-derived peptide that was originally discovered in the occipital lobe of a patient with AD...
and was shown to suppress neuronal death in various AD models,126 was recently found to attenuate RGC loss induced by hypoxia—a condition that is characteristic of many ocular pathologies, including glaucoma.127 Glatiramer acetate (also known as copolymer-1), a synthetic polypeptide approved for the treatment of MS that was found to be efficacious in experimental models of several other neurodegenerative disorders,128,129 was protective against ocular neurodegeneration in various animal models.14,130,131 This polypeptide preserved RNFL thickness in patients with diabetic retinopathy who underwent pan-retinal photocoagulation,132 and is currently under clinical investigation for acute optic neuritis and AMD.133–135

A good example of the growing understanding that several eye diseases are neurodegenerative disorders, and should be treated as such, is the case of memantine. This neuroprotective drug, which is approved for treatment of AD, showed beneficial effects in animal models of glaucoma,136 and was recently evaluated in a clinical trial in patients with this disorder. Although the trial failed to meet its primary end point,57,137 (the reasons for which are expected to be clarified in the full report), the concept underlying the basis of this trial—namely the application of neuroprotective drugs for the treatment of ocular disorders—holds great promise.

Interestingly, some patients with AD display irregularities in intracranial pressure (ICP).139 This finding, in analogy to the major role attributed to elevated intraocular pressure (IOP) in the aetiology of glaucoma, raises the question of whether AD could be considered as a form of cerebral glaucoma.138 If so, testing whether therapies that modulate IOP can reduce the risk of developing AD by manipulating ICP would be valuable.

Conclusions

The eye, itself an intriguing organ, is an extension of the brain. These two compartments share functional building blocks in the form of neurons and axons, as well as common degenerative and regenerative processes, and unique mechanisms of crosstalk with the immune system. In this Review, in appreciation of the similarities and interrelationships between these organs, we have surveyed several major CNS disorders that present ocular manifestations, and classic eye diseases that display neurodegenerative features. Taken together, the similarities between these CNS compartments suggest that knowledge acquired from studying and visualizing the eye should be regarded as a means to obtain insight into mechanisms and processes taking place in the brain in health and disease, as well as to assist in the diagnosis of CNS pathologies. In addition, this knowledge could facilitate the development of shared therapies for diseases of the eye and the brain, and such therapeutic attempts are already under way for several conditions. When addressing data obtained from studies on human populations, inherent limitations, such as differences in sample sizes, selection bias and exclusion criteria, should be considered. Nevertheless, the fact that similar results have been reported by several independent research groups gives these data additional validity.

Finally, we emphasize that potential cross-benefit could arise from collaboration between researchers and clinicians who are experts in the physiology and pathology of the eye and those with expertise in the brain. The transfer of knowledge and therapeutic approaches from one field to the other will necessitate some adaptations that take into account the unique characteristics of each organ and condition, but we believe that understanding similarities in disease manifestations and mechanisms will advance research in both disciplines, and could eventually improve the welfare of patients.

References for this Review were selected by searching PubMed and Google Scholar for full-text articles and abstracts in English, with no limitations on the date of publication, using various combinations of the terms “eye”, “retina”, “optic nerve”, “CNS”, “multiple sclerosis”, “Alzheimer”, “Parkinson”, “stroke”, “cerebral infarct”, “glaucoma”, “age-related macular degeneration”, “optical coherence tomography”, “retinal imaging”, “diagnosis”, “neurodegeneration” and “pathology”. Additional relevant papers were identified from the reference lists of selected articles.

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