Chapter 15

# The Impact of the Eye in Dementia: The Eye and its Role in Diagnosis and Follow-up

Elena Salobrar-García, Ana I. Ramírez, Rosa de Hoz, Pilar Rojas, Juan J. Salazar, Blanca Rojas, Raquel Yubero, Pedro Gil, Alberto Triviño and José M. Ramírez

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**Abstract**

Over the last few decades, the importance of ophthalmic examination in neurodegenerative diseases of the CNS has reportedly increased. The retina is an extension of the CNS and thus should not be surprising to find abnormal results in both the test exploring visual processing and those examining the retina of patients with CNS degeneration. Current in vivo imaging techniques are allowing ophthalmologists to detect and quantify data consistent with the histopathological findings described in the retinas of Alzheimer's disease (AD) patients and may help to reveal unsuspected retinal and optic-nerve repercussions of other CNS diseases. In this chapter, we perform an analysis of the physiological changes in ocular and cerebral ageing. We analyse the ocular manifestations in CNS disorders such as stroke, AD and Parkinson's disease. In addition, the pathophysiology of both the eye and the visual pathway in AD are described. The value of the visual psychophysical tests in AD diagnosis is reviewed as well as the main findings of the optical coherence tomography as a contribution to the diagnosis and monitoring of the disease. Finally, we examine the association of two neurodegenerative diseases, AD and glaucoma, as mere coincidence or possible role in the progression of the neurodegeneration.

**Keywords:** neurodegenerative disease, Alzheimer, optical coherence tomography, contrast sensitivity test

## 1. Introduction

The eye is a special sensory organ, as the retina is an extension of the brain. Both brain and retina derive from the neural tube and consist of neurons and glial cells. As with the CNS, any insult to the retina and optic nerve cause anterograde and retrograde axon degeneration, myelin destruction, and scar formation. Chronic progressive retinal neurodegeneration is involved in the pathophysiology of ocular diseases [1] such as glaucoma, age-related macular degeneration (ARMD) and diabetic retinopathy (DR).

In the brain, neurodegeneration is a key event in disorders such as Parkinson's disease (PD) and Alzheimer's disease (AD). PD is a neurodegenerative disease of middle and old age; the origin of defect lies in the basal ganglia and it is characterised by deficiency of dopamine in the mid-brain area.

AD, the most common cause of dementia, afflicts 67 in 1000 people over the age of 65 and more than 26 million people worldwide, its prevalence and incidence increasing exponentially with age [2, 3]. In 2006, the worldwide prevalence of Alzheimer's was 26.6 million, and by 2050, the prevalence is expected to quadruple [3]. A chronic progressive degenerative neurological disorder affecting cognition and memory [4], AD is characterised by the formation of extracellular amyloid beta (Aβ) plaques and intracellular neurofibrillary tangles (made of hyperphosphorylated tau), primarily in the cerebral cortex [5, 6]. Currently, there is no definitive antemortem diagnosis for AD, and therefore new biomarkers for diagnosis are needed. It can be argued that improved methods of screening and early detection are essential to identify patients without cognitive impairment but with a high risk of developing AD. Thus, protocols for early treatment could be established to help slow the disease progression [7]. Over the last few decades, the importance of ophthalmic examination in neurodegenerative diseases of the CNS has reportedly increased. As mentioned above, the retina is an extension of the CNS and thus the impairment of ocular function in patients with CNS degeneration should not be surprising. In fact, both the test exploring visual processing/visual pathways and those examining the retina of such patients display abnormal results. Current in vivo imaging techniques are allowing ophthalmologists to detect and quantify data consistent with the histopathological findings described in the retinas of AD patients years ago [8] and may help to reveal unsuspected retinal and optic-nerve repercussions of other CNS diseases. Specifically, over the last decades, accurate tools for analysing the eye fundus such as optical coherence tomography (OCT) and laser polarimetry have been developed, opening new ways of examining the retina in vivo. The retinal nerve-fibre layer (RNFL) is composed of retinal ganglion-cell axons, which form the optic nerve. Decreased thickness of the RNFL can reflect retinal neuronal ganglion-cell death and axonal loss in the optic nerve [9, 10], and RNFL reportedly thins with ageing [11, 12]. Notably, some studies have shown that AD patients show greater RNFL thinning than is normal for their age [9, 10, 13–20]. In this context, Hinton et al. [8] were the first to show histopathological evidence of retinal ganglion-cell loss and optic-nerve degeneration in AD patients. These findings were later confirmed in several follow-up studies [21–24]. Indeed, axonal degeneration of the large M-cells in AD has been documented [22, 25, 26]. Nevertheless, other histopathological studies [27–33] have failed to confirm these

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findings, suggesting that methodological differences were responsible for the different results. In addition to the anatomical findings in AD, this disease can exert an impact on most aspects of visual processing, such as visual-field abnormalities [34–36], colour-perception deficits [37–40], pattern electroretinogram changes [26, 41, 42] and reduced contrast sensitivity (CS) [43–46]. Psychophysical investigations of CS in AD patients have demonstrated results consistent with the neuropathological evidence [47]. However, studies of CS in patients with AD have reported no AD-related deficits in spatial CS [48, 49], while others have found deficits at all spatial frequencies tested [40, 50].

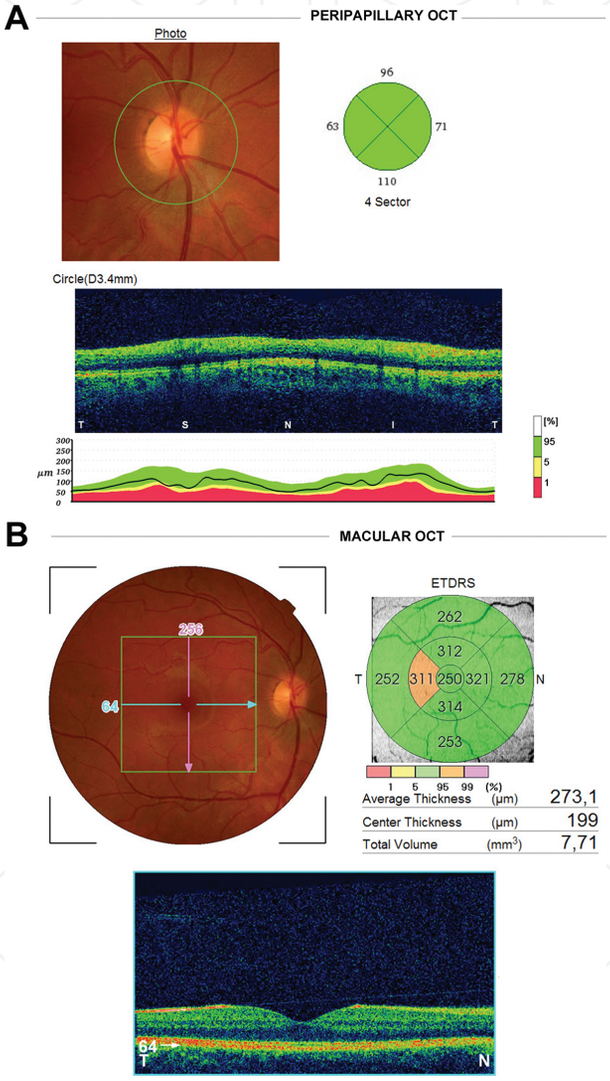


**Figure 1.** Retinal nerve fibre layer (RNFL) thickness analysis. Optical coherence tomography (OCT) study. (**A**) Peripapillary OCT. Upper left: peripapillary retinography with a green circle marking the retinal tissue considered for analysis. Upper right: diagram of the peripapillary quadrants analysed: temporal quadrant (316–45), superior quadrant (46–135), nasal quadrant (136–225), inferior quadrant (226–315). Bottom: retinal b-scan and diagram of thickness normality. (**B**) Macular OCT. Upper left: central retinography with a green square marking the retinal tissue considered for analysis. Upper right: diagram showing the concentric rings and quadrants considered for analysis of the macular RNFL thickness and measurements automatically provided by the analyser. Bottom: retinal b-scan of the macula. ETDRS: Early Treatment Diabetic Retinopathy Study (from Figure 1 of [19] with permission).

Diagnosis and follow-up of AD, especially the early-onset cases, become difficult, due to imprecise neuropsychological testing, sophisticated but expensive neuroimaging techniques, and invasive sampling of cerebrospinal fluid [31, 32]. OCT is a reliable noninvasive technique, routinely used in ophthalmology to visualise and quantify the layers of the retina. This technique enables quantitative cross-sectional imaging of the RNFL and macular volume. As a measure of neuronal degeneration, changes in longitudinal OCT measurements of the RNFL can act as a surrogate marker of axonal health. Thus, OCT could become an invaluable tool for measuring axonal loss, as a biomarker, in different neurological conditions [33, 51–61] (**Figure 1**).

In a review of a meta-analysis which investigates the role of OCT in detecting RNFL thinning in AD patients, it was found that the OCT is a well-suited paraclinical methodology to assess RNFL thickness in both AD and mild cognitive impairment (MCI) disorders [19]. Macular studies in AD using OCT have recently reported that mild AD patients with a high average score (23.3 ± 3.1) on the Mini-Mental State Examination (MMSE) had significantly reduced macular nerve-fibre-layer thickness with or without significant peripapillary involvement [19, 40, 62, 63]. OCT thus offers the clinician a fast, reliable, reproducible, noninvasive method to evaluate and monitor several neurological diseases [64].

## 2. Search strategy and selection criteria

A literature search was performed up to April 2016 using the MEDLINE database, PubMed and Google Scholar search services with the following key words and word combinations: dementia, Alzheimer's disease, ageing, vision, eye, physiopathology, visual pathway, visual psychophysical test, optical coherence tomography, glaucoma.

After filtering by author criteria, English or Spanish language, and the condition that they all addressed dementia and vision as the main theme, 325 articles were included after a full text review. All the abstracts were then carefully divided into subcategories covering topics including ageing and vision, visual pathway, physiopathology, visual psychophysical test, Alzheimer's and glaucoma.

This review covers systematic reviews, original articles and letters to the editor. We did not contact other authors for further articles inclusion.

## 3. Ageing and vision

The term 'ageing' refers to the process of morphofunctional changes that organisms experience as time goes by. That process can be analysed from two main perspectives. On the one hand, there is the view that takes into account the physiological changes that happen to any individual, regardless of life experiences. On the other hand, there is the perspective referring to pathological changes, unique in each individual and related to alterations on the organic

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balance [65]. The eye is not an exception to this process, and indeed the eye is one of the organs most affected by ageing.

### 3.1. Theories on ageing

Many theories and classifications have been proposed to explain human ageing, although a combination of several of them may explain the process. In 2013, in a review called 'The hallmarks of ageing' [66], the current theories were widely discussed and nine fundamental traits of ageing were described: genomic instability, telomere shortening, epigenetic changes, loss of proteostasis, deregulation of the detection of nutrients, mitochondrial dysfunction, cell ageing, depletion of stem cells, and altered intercellular communication. Additionally, it is clear that there are other environmental and behavioural factors that can contribute to this degradation process, such as, for instance, smoking and regular exposure to UV light.

### 3.2. The ageing eye

As the eye ages, some morphological, structural, and functional changes take place in both the eye itself and other extraocular structures. This process is generically referred to as 'eye ageing'.

#### *3.2.1. Structural changes in the ageing eye*

In the orbit and the adjacent tissue, there is a reduction of the adipose tissue with relative preservation of the nasal fat pad [67]. This generates eyeball sinking (enophthalmos).

The eyelids progressively lose their elastic properties, with an increase in palpebral skin laxity [68].

In the lacrimal gland, there is a proliferation of connective tissue and an atrophy of glandular elements resulting in a decrease in lacrimal tear production [69]. The lacrimal pathology in elderly patients involves different situations ranging from 'dry eye' to profuse lacrimation or epiphora. The result is an alteration in the lacrimal film with its corresponding discomfort and decline in visual acuity (VA).

The conjunctiva undergoes a decrease in density of dendritic cells due to ageing, as well as the degeneration of the subepithelial structures. There is an increase in conjunctival microcysts, indicating that the Goblet cell function is failing, since it has been demonstrated that the Goblet cell population does not decrease in number [70].

The ageing sclera shows hyaline plaques, fat deposits, and loss of aqueous content, hence provoking biomechanical changes due to greater rigidity [71, 72].

Refractively, the ageing cornea suffers a change in keratometry resulting in against-the-rule astigmatism. Ageing results in corneal degeneration with a progressive deposit of lipid material that provokes gerontoxon or arcus senilis. Some calcifications appear in the Bowman's membrane periphery while Descemet's membrane thickens. The cornea becomes more rigid and edematous, with a tendency to opacity, causing a sensitivity loss [72, 73]. There is also a reduction in the number of corneal endothelial cells, and hence the development of Fuchs

endothelial dystrophy is common. This endothelial loss provokes a dysregulation in corneal homeostasis, which diminishes VA and even leads to blindness [72, 74].

The trabecular meshwork alters its shape due to the ageing process, changing from a wedge-shaped structure into a more rhomboidal one [72, 75]. The trabeculae thicken and an ultrastructural examination shows a change in the appearance of the extracellular materials [75]. There is a lower number of endothelial trabecular cells as well as of giant vacuoles and intracellular pores in Schelmm's canal [72]. Gonioscopy shows an increase in the trabecular meshwork pigmentation. All of these factors could result in greater resistance to the aqueous outflow, which may favour the onset of glaucoma [76].

The pupil tends to become smaller and the iris is less reactive. There are also more difficulties in terms of pharmacologic dilation of the pupil. Iris pigment is lost with ageing, resulting in iris transillumination in the slit-lamp examination, especially in the pupillary margin.

The changes in size and tone of the ciliary body, together with the loss of elasticity of the lens capsule and a packing in its fibres, weaken accommodative capacity, causing presbyopia [77].

With age, the lens tends to absorb more blue light (410 nm) due to the accumulation of yellow pigment caused by the oxidation of lens proteins [72]. This is called 'blue blindness' in the cataractogenic processes.

Clinical data from studies on the choroid, using OCT, show an inverse correlation between age and choroid volume [78]. Some histopathological studies have shown a negative correlation between age and choriocapillaris density [79]. Bruch's membrane is the structure that presents the most changes due to ageing, becoming thicker, with changes in the elastic fibres (calcification among others) and collagen [72]. The major proportion of thickening appears to be due to the deposits of lipids [80] and fibrillar and amorphous material [81]. The basal laminar deposits, material that accumulates between the Bruch's membrane and the retinal pigment epithelium (RPE), are located mainly in the macular area and occasionally appear as drusen [76, 82]. The aforementioned changes in Bruch's membrane lead to the appearance of waste accumulation in the overlying retina. The retinal pigment epithelium, which is vital for the integrity of the rods and cones, shows greater pleomorphism, a lower number of epithelial cells in the posterior pole, a loss of melanin content, an increase in lipofuscin, and a reduction of the cytoplasmic volume [72, 76, 82]. With age, photoreceptor density reduces in the retina [86]. An age-related loss of rods in the macula occurs with a decline in scotopic sensitivity [72]. In the astroglial plexus of the ganglion-cell layer and RNFL, the number of astrocytes significantly drops. These cells show stronger GFAP immunoreactivity, more cytoplasmic organelles, glial filaments and lipofuscin deposits [82]. As a result of the ageing process, the retinal-blood flow diminishes and macular microcirculation diminishes by an estimated 20% [83]. The number of retinal capillaries around the fovea falls and arteriosclerotic changes occur in retinal vessels [72].

In the optic nerve (ON), the number of ON axons reportedly declines [72, 84]. The connective tissue within the fibrovascular pial septae becomes more abundant. As a result, the exchange of nutrients between the capillaries and the nerve fibres is impaired [72]. With ageing, Corpora

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amylacea may be seen in the ON, appearing as accumulations of intracellular organelles (neurotubules, dense bodies, and mitochondria) in the axons [72].

In the vitreous humour, changes appear in the components of the collagen fibres and hyaluronic acid, causing vitreous floaters [85]. As a result of ageing, the vitreous attachment to the retina weakens, provoking posterior vitreous detachment. This may trigger a contraction at its base, leading to traction on the peripheral retina, which may result in retinal tears [72].

#### *3.2.2. Functional changes in the ageing eye*

Normal ageing implies changes in the functionality of the visual system, since there is less light transmission and scattering inside the eye. Also efficiency in phototransduction and photopigment regeneration declines. The quality of transmission and its synaptic processing in the retina and in the entire visual pathway diminishes [86]. Due to all these changes, vision is affected in different ways. The elderly population experiences significant refractive changes with age. Usually, a change of against-the-rule astigmatism takes place as a result of corneal flattening. Moreover, the spherical component becomes more hyperopic due to sclera rigidity, senile myosis and changes in the ageing lens, the latter resulting in a loss of the refractive capacity. The prevalence of oblique astigmatism and anisometropia also increase with age [87].

Visual acuity (VA) worsens with age for many reasons, the standard being a vision of 0.8. Regarding the ageing process, this reduction in near VA may be due to presbyopia or physiological loss of accommodation because of ciliary muscle-tone loss. Likewise, the changes in the lens can cause alterations in VA: late-onset myopia can appear, owing to the rigidity in the lens nucleus that is related to the senile cataract; also, early nuclear sclerosis can cause eye glare.

Contrast sensitivity (CS) undergoes small changes starting in childhood up until the age of 65. After that, the decline is more pronounced, especially in medium and high spatial frequencies. This decline in CS is due partially to the opacity in the media of the eye, which decreases depth perception [87, 88].

With age, the normal visual field (VF) is impaired due to a retraction. The blind spot size enlarges. Additionally, the reduction in the number of cones in the fovea causes a general decline in colour vision [76].

Old people experience trouble with light and dark adaptation and they are incapable of tolerating glare [76].

There are also age-related binocular problems that affect the neuromuscular mechanisms and the structures of the tissues adjacent to the eye. Patients suffer from accommodation-convergence problems and thus, they show greater exophoria in near vision. Vertical deviations and poor stereopsis are very frequent with ageing [89].

### 3.3. Brain ageing

The nervous system is particularly vulnerable to ageing due to the main cellular elements of this tissue are post-mitotic cells and thus their regeneration capacity is limited.

Age-related worsening of cognitive functions occurs both in humans and in animals. This is especially true for the functions related to executive capacities, attention processes, and the learning and storage of new information. Also, the senescent brain is capable of using functional strategies to compensate for functional and/or structural deficiencies. This brain plasticity observed in senescence can decrease or mask the clinical expression of brain ageing [90].

### *3.3.1. Structural changes in the brain*

Research conducted a few years ago on anatomical brain changes seems to demonstrate a clear reduction in brain volume due to neuronal death [91]. The greatest part of this volume loss is the reduction of synaptic density [92] and volume of white matter in the frontal lobes [93]. Even so, the most recent studies indicate that age-related changes do not affect the brain globally. On the contrary, these changes would be highly limited to the dorsolateral prefrontal cortex and, to a lesser extent, to some subdivisions within the medial temporal lobe, such as the subiculum and the dentate gyrus [94]. It is believed that the age-related drop in cognitive skills is the consequence of a selective alteration in the corticocortical pathways that connect the temporal and frontal association areas to the corticostriatal pathways [93, 94].

Age-related microscopic changes include regional brain atrophy [93], axonal cortical dystrophy [95], lipofuscin accumulation [96], astrogliosis [91], neurofibrillary degeneration, senile plaques [97, 98] and scattered vascular or dystrophic focal changes in the white matter [99]. Many of these changes cannot be regarded as being specific to ageing. For instance, most cases of cortical atrophy could indicate an underlying degenerative brain [100] or vascular [101] disease. Changes in the periventricular white matter (leukoaraiosis or subcortical leukoencephalopathy) occur in patients with vascular risk factors, reflecting an insufficiency of the deep vessels of the brain secondary to a hypertensive, diabetic or multifactorial degenerative arteriopathy [102]. Perhaps the only brain change attributable to the passage of time is lipofuscin accumulation; this indicates oxidative stress and lipid peroxidation [96], as well as local synaptic loss [93, 94].

The vascular volume in the brain decreases, specifically the surface of the capillaries [103]. The blood-brain barrier is selective place for the exchange of nutrients between the blood and the brain parenchyma. With ageing, the molecular transport systems operating at this level are reduced. This has some metabolic consequences for the normal functioning of the nervous system [104].

One of the least known aspects in the ageing process is the role of the brain glial cells [105]. The glia is a group of CNS cells whose main function is to maintain the homeostasis of the neural environment (astrocytes), immunosurveillance (microglia) and the formation of myelin (oligodendrocytes).

It has been demonstrated that, in the ageing brain of experimental animals as well as humans, there is a proliferation of astrocytes which is called reactive gliosis. Its purpose is to mitigate the effects of the physiological age-related neuronal degeneration [106].

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*3.3.2. Cognitive functional changes*

Age-related neuromorphological changes trigger cognitive alterations. Cognition is the set of brain activities that enable humans to be aware of themselves, of the others, and of the environment [107]. One of the most important features of cognitive ageing is memory loss. Learning and memory have their neurobiological origin in the hippocampus. The hippocampus is composed of a series of cell populations that establish certain very precise and well-organised synaptic pathways. The information received is processed and sent to the brain cortex for storage and for use in the long-term memory [108, 109]. Learning processes are based on neuroplasticity, whose neurophysiological basis is long-term potentiation. This is achieved by a proliferation of AMPA glutamate receptors as well as an increase in dendritic spine density in hippocampal postsynaptic neurons [110]. During the ageing process, a reduction may occur in the neural capacity to synthesise neurotransmitters involved in synapses [111]. The most common neurotransmitters are glutamate, GABA, acetylcholine and dopamine. Changes in the homeostatic levels of these neurotransmitters cause different pathologies that are accentuated during ageing [112]. For instance, the lowering of acetylcholine levels is one of the most striking features of AD [113].

## 4. The eye as an extension of the central nervous system

Given that the eye is an extension of the CNS, evidence is being sought to determine whether the retina is a window to the brain and whether eye research could improve our understanding of CNS disorders [114]. The retina is made up of specialised neuron layers that are interconnected via synapses. The light that enters the eye is captured by the photoreceptor cells in the outer retina, initiating a cascade of neural signals that finally reach the retinal ganglion cells (RGCs), whose axons form the ON. These axons project to the lateral geniculate nucleus (LGN) in the thalamus and to the superior colliculus (SC) in the midbrain, whose information is then transmitted to more specialised visual processing centres that provide a perception of the world [114, 115].

Most of the RGC axons come together to form the ON. After passing through the lamina cribrosa of the eye the ON is covered by a myelin sheath produced by the oligodendrocytes and surrounded by the three meningeal layers. As in the CNS, ON injury may result in anterograde and retrograde degeneration of the damaged axons, scarring, myelin destruction and creation of a neurotoxic environment involving oxidative stress, deprivation of neurotrophic factors, raised levels of excitotoxic neurotransmitters and abnormal aggregation of proteins and waste products. Such a hostile environment often provokes the death of the initially undamaged neighbouring neurons in a process called secondary degeneration [116–121].

Axonal regeneration after injury is limited both in the CNS and ON. In fact, most of our knowledge on axonal response to traumatic brain injury stems from studies of the ON [122–128]. The factors responsible for creating an environment that is non-permissive for axonal growth are the same by CNS and ON. The first discoveries of CNS axon regeneration in the

presence of peripheral nerve grafts were performed in experimental models of ON transection and of spinal-cord injury [122, 123, 129]. We should underline that there are similar restrictive growth conditions in these two structures of the nervous system.

The eye, and especially the retina as a part of the CNS, must maintain regulated interactions with the immune system. In fact, the retina occupies a special immune site. The eyeball is made up of some unique physical structures and contains a set of surface molecules and cytokines responsible of some specialised immune responses, similar to those observed in the brain and the spinal cord [130, 131]. The eye possesses the blood-retinal barrier, whose structure, characteristics and mechanisms are similar to those of the blood-brain barrier. The anterior chamber of the eye contains the aqueous humour, a fluid with anti-inflammatory and immunoregulatory mediators. This fluid resembles the cerebrospinal fluid circulating around the brain and the spinal cord parenchyma [132, 133]. Besides the similarities with the CNS, the ocular immunoprivilege involves a unique phenomenon called 'anterior chamber associated immune deviation' (ACAID), wherein the antigen-presenting cells entering the anterior chamber capture the antigen and then migrate to the spleen. There the effector leukocytes become regulatory leukocytes. This process establishes a tightly regulated immune response towards ocular antigens [130]. The combination of the aforementioned mechanisms allows the eye to benefit from the immune defence machinery that would eliminate the risk of tissue damage due to uncontrolled inflammation [114].

### 4.1. Visual pathway

The visual information collected by the photoreceptors (rods, sensitive to contrast; and cones, sensitive to colour) goes through the inner plexiform layer of the retina (bipolar, horizontal and amacrine cells) to the RGC layer (midget, parasol and bistratified cells) [134]. The layout of these three different RGC types forms different receptive fields, which help in segregating and coding visual information [135]. Then, the RGC are projected through different pathways (parvocellular (P), magnocellular (M) and koniocellular (K)) to the sub-cortical region of the LGN and to the V1 cortical area [135–137]. The P-pathway receives colour and shape information from the midget cells. The K-pathway receives some blue-on/yellow-off opponent colour information from the bistratified cells. Finally, the M-pathway carries the luminance and motion data from the parasol cells. Thus, the visual information segregated in the V1 region is projected into the V2 region for processing [135, 138, 139]. The information about colour, orientation and spatial frequency continues ventrally through V2 and V4. This route continues to the infero-temporal cortex, where more-complex aspects of the visual processing of objects are carried out, such as face perception. Motion and location follow the dorsal pathway through V2 and V3. The V3 dorsal area seems to be specialised in the detection of global motion [140, 141]. The V5 is specialised in local movement [142]. The dorsal pathway continues to the posterior parietal cortex, where the complex aspects of spatial perception, e.g. details within a scene as an integrated perception are processed [141].

### 4.2. Ocular manifestations of CNS disorders

As mentioned above, the eye is an extension of the brain, and therefore it seems reasonable to look for some ocular manifestations of brain pathologies. In fact, in patients with CNS pathologies such as EP, multiple sclerosis (MS), amyotrophic lateral sclerosis, and AD, ophthalmological changes have been observed. Notably, many of these changes are not exclusive to a certain disease, highlighting the relationship between the retina and the brain. Likewise, in many of these CNS disorders the ocular symptoms precede the cerebral symptoms. Therefore, eye examinations could help in the early diagnosis of these CNS diseases.

#### *4.2.1. Stroke*

Prospective studies have shown that retinal microvascular abnormalities (formation of arteriovenous crossings, bleeding, and arteriolar narrowing) could predict the risk of cerebral ischemic changes and stroke [143–145]. In addition, the presence of a retinopathy with arteriovenous crossings has been linked to an increased risk of stroke, especially when these retinal abnormalities were associated with lesions in the cerebral white matter, a feature which is usually indicative of stroke [143, 145, 146]. Beyond these prospective studies, other research on the eyes in some animal models have shown that stroke is associated with functional impairment of the retina, including thinning of the retinal layers, reactive gliosis, increased expression of genes associated with cell damage, restricted oxygen supply, DNA fragmentation and ON neurodegeneration [147].

Ocular manifestations are to be expected in stroke, because the small vessels of the retina and the brain have similar embryological origins, anatomical characteristics and physiological properties [148, 149]. Some dysfunctions in the blood-brain and the blood-retinal barriers are suspected of playing a central role in the development of brain and retinal microangiopathy, respectively [131, 150, 151].

#### *4.2.2. Multiple sclerosis (MS)*

Visual impairment in MS is a major cause of disability. Visual loss is a symptom that occurs in up to 50% of patients with MS, resulting in some degree of visual impairment throughout the course of the disease for most cases [152–154].

It is not surprising that MS is related to eye disease, since the myelin components, which are essential in both the brain and the visual pathway, are the major autoimmune targets in MS. Visual defects are usually the result of axonal demyelination along the visual pathway [155]. It has been found that some internal areas of the retina, which are not associated with myelin, are also affected in MS. This suggests that the autoimmune response is also directed against other antigens in the eye [156].

Retrobulbar optic neuritis is an inflammatory optic neuropathy associated with demyelination and degeneration of the RGC. Diagnosed in 75% of patients with MS, this is often the first symptom of the disease [154, 155, 157]. It is important to highlight that visual deficits in MS also occur in patients without an optic neuritis diagnosis. Several studies have shown that,

although the VA is not affected [158–160], there is a decrease in CS [158–160] and the RNFL thickness in MS patients in comparison with healthy individuals [160, 161]. RNFL thickening occurs in both the peripapillary [60, 160, 162, 163] and the macular area [54, 60]. Furthermore, RNFL thinning in MS patients directly correlates with the progression of neurological impairment and disease duration [160].

*4.2.3. Parkinson's disease (PD)*

PD is a chronic neurodegenerative disorder that is associated mainly with motor dysfunction, although it can also involve some non-motor symptoms, including visual deficits. These deficiencies may manifest as decreased CS [59, 163], impaired colour vision (the tritan axis is altered first) [57], and abnormal electrophysiological responses [57, 164]. The retinas of PD patients show photoreceptor and RGC dysfunction, morphological deterioration of the perifoveal dopaminergic plexus [165], and thinning of the RNFL [52, 53, 164, 166, 167]. According to the hypothesis that the disease results from a dopamine imbalance, it seems that visual deficits in PD could also be caused by dopamine depletion. In fact, some of the visual deficits experienced by PD patients can be improved by levodopa treatment [168].

*4.2.4. Alzheimer's disease (AD)*

The first abnormalities in the visual system for AD, observed in the 1970s, were regarded strictly as a dysfunction at the cortical level. Subsequent studies over the past 25 years have revealed that all parts of the visual system, including the ON and the retina, may be affected in AD. Some aspects of this involvement are still not well understood and are still the subject of recent research. Anatomical changes along the visual pathways and their corresponding functional changes have been detected and analysed by psychophysical procedures. AD can affect different aspects of the visual processing in line with the impact of the disease in the dorsal and ventral regions of the brain. Patients with dorsal-region damage suffer alterations in functions such as discrimination and angular-motion perception [169–172]. Those with damage in the ventral region show difficulty in discriminating faces, colours, and shapes [37, 173, 174].

## 5. Physiopathology of AD manifestations in the eye and the visual pathway

Changes in the visual system associated with AD have been the focus of the scientific community over many years, with some extensive reviews focus on different aspects of the problem [7, 47, 175–188]. All this evidence emphasises that visual changes may in medical practice help in the assessment of these patients and may even provide a predictive value potentially useful in diagnosis.

### 5.1. The lens

β-Amyloid deposits in the brain are a pathologic marker for AD. Amyloid β-peptides Aβ1–42 and Aβ1–40 have been identified in the human lens. Aβ1–40 was found in the aqueous humour,

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and its concentration is comparable to that found in the cerebral cortex and in the cerebrospinal fluid of AD patients [189]. On the one hand, it was recently discovered that there is an increase in β-amyloid deposits in the supranuclear lens fibres, which may be linked to the equatorial supranuclear cataracts more frequently found in these patients [1]. On the other hand, the study by Bei et al. determined that the measuring of the lens opacity was unlikely to provide a noninvasive measure of the risk of developing AD [190].

## 5.2. Retina

### *5.2.1. Retinal ganglion cells (RGCs)*

The first histopathological studies on human-donor retinas of AD patients were made in the 1980s. Hinton et al. [8] examined four eyes from AD patients, finding a loss on the number of RGC, but a shortcoming of the study was that they did not provide numerical values in their results. However, Curcio et al. [27] found no significant difference in the number of RGC between the AD group and the age-matched controls. In the mid-1990s, Blanks et al. [23, 24] confirmed the initial observations of Hinton et al. These researchers compared the postmortem number of RGC from 12 retinas of nine patients with severe AD and 15 retinas from 12 age-matched controls. These studies found a 25% decrease in the number of RGC ($p < 0.001$) and an 82% increase in the astrocyte ratio per neuron in the retina ($p < 0.001$). However, a study with AD transgenic mice did not show a significant difference in the number of CGR compared to controls [191].

All the histopathological studies carried out so far involve a relatively small number of subjects. Therefore, it would be advisable to undertake more studies with larger numbers of subjects in order to verify the RGC decline in AD.

### *5.2.2. Vascularisation and retinal blood flow*

Recent data suggest the vascular involvement of the retina in AD patients. Vascular changes in the retina are thought to share similar pathogenic mechanisms with cerebral vasculature [15, 192]. In fact, it is known that cerebral vascular insufficiency is one of the earliest pathological signs in the development of AD [193, 194].

Currently, there are few studies on vascularisation and retinal blood flow in AD. In 2007, Berisha et al. [15] studied the retinal vascularisation and blood flow in patients with AD. These researchers used Doppler laser in nine patients with probable mild ($n = 6$) and moderate AD ($n = 3$) plus eight age-matched controls. They detected a significant narrowing in the diameter of the retinal veins and decreased blood flow in AD patients, compared with controls. Mroczkowska et al. analysed the dynamic retinal vascularisation, noting that there were some signs of microvascular dysfunction that were correlated with the extent of cognitive impairment [195]. However, the study published by Tsai et al. found no differences either in the vascular structure or the calibre of retinal vessels in AD transgenic mice, compared to control animals [191].

*5.2.3. Amyloid plaques, neurofibrillary tangles and vascular angiopathy*

The first unsuccessful attempts to find amyloid plaques, neurofibrillary tangles or vascular retinal angiopathy in eyes of AD patients were performed in 1989 by Blanks et al. [21]. Although none of these typical AD signs were detected in the retina, their findings showed different levels of degeneration in RGC correlated with the degree of impairment of the patient.

In the last few years, β-amyloid deposits and hyperphosphorylated tau proteins have been detected in elderly retinas in a model of AD in double transgenic mice [196–198]. These β-amyloid plaques are distributed from the ganglion-cell layer to the inner plexiform layer. Some of these are also located in the outer nuclear layer, in the outer segments of the photoreceptors and in the ON [197]. These deposits, analysed with immunohistochemical techniques, are found to be accompanied by an increase in MCP-1+ immunoreactivity and F4/80+ in RGC layer. These results suggest that β-amyloid deposits cause neurodegeneration in the retina of these mice. This idea is further supported by the presence of TUNEL+ immunostaining in the RGC layer, so that there is some histological evidence of apoptosis in this layer [196]. In 2009, a β-amyloid vaccine was tested in the experimental mice model mentioned above, resulting in a lower number of retinal β-amyloid deposits. Nevertheless, there was a marked increase in retinal microvascular β-amyloid deposits as well as local neuroinflammation due to microglial infiltration and astrogliosis linked to a disorder in the organisation of the retina [197].

A postmortem study in human retinas showed for the first time the presence of β-amyloid plaques in AD patients [199]. Subsequently, other authors have confirmed the presence of β-amyloid deposits, which were more prevalent in perivascular and perimacular areas, both in AD patients and in those with mild cognitive impairment (MCI) [191, 200]. Campbell et al. recognised β-amyloid plaques in the retina by observing its polarisation properties and proposing it as a new diagnostic method [201].

**5.3. Choroid**

The latest improvement in OCT technology has enabled us to study the thickness of the choroid in vivo in patients with mild to moderate AD. A statistically significant generalised loss of foveal choroid thickness was found in these patients [191, 202, 203]. According to the authors, this choroidal thinning in AD may be associated with hypoperfusion and/or atrophic changes in this vascular layer. Several immunohistochemical studies in AD transgenic animals have reported a higher frequency of RPE hypertrophy and binucleated cells, but these changes were not seen in human retinas [191]. Previous studies have shown an Aβ accumulation in the choroidal vasculature in ageing mice and in a transgenic mouse model of AD [196, 204]. As happens in the brain, Aβ accumulation in the choroid may induce an inflammatory response and complement activation, which would lead to progressive vasoregression of the choroidal vasculature (and subsequent retinal neurodegeneration), through the same pathological cascade that has already been described in AD brains [191, 205–207].

### 5.4. The optic nerve

Hinton et al. [8] described widespread axonal degeneration of the optic nerves in 8 out of 10 AD patients that were analysed postmortem. In an additional study, a morphometric analysis of the ON suggested a predominant loss of magnocellular neurons that contribute large-calibre fibres. In a study published in 2005 by Syed et al. [208], some significant differences in axonal density were found by dyeing axon contours with toluidine blue, both in the central and in the peripheral areas of the ON. The analysis was performed on 12 AD patients, compared with 13 advanced-age control subjects. It should be pointed out that Syed's study found a decrease in smaller axons, with transversal section areas measuring less than 1.99 $\mu m^2$. Studies using magnetic resonance imaging (MRI) have found a statistically significant decrease in the ON volume in AD patients. However, this reduction does not correlate with brain volume [209].

Neurofibrillary tangles of tau protein have also been observed in ON [211], although this may not be specific for AD. Low-density lipoprotein receptor-related protein (LRP) is involved in the pathogenesis of AD by mediating the transport of amyloid-β (Aβ) out of the brain into the systemic circulation. Recently, Cuzzo et al. [210] found a decrease in the expression of LRP in the optic nerves of 11 patients with AD, compared to 10 control subjects. This would support the theory that LRP may play a role in the physiopathology of the optic neuropathy in AD. In the same study, the group of Cuzzo observed a decrease in neurofilament immunostaining in AD patients in comparison with control, thus confirming the previous findings by Hinton et al. [8]. Also, an increase in the receptor expression of advanced glycation end-products in the astrocytes near microvasculature has been reported in ON samples from AD patients [211].

Different studies have also pointed out some differences between the control group and the AD patients in the appearance of the ON head, both with red-free photography [13, 212, 213] and with scanning laser ophthalmoscope [214]. However, other studies failed to find such differences between AD patients and controls using the latter technique [31].

### 5.5. Lateral geniculate nucleus (LGN)

Scholtz et al. [215] noted a myelin loss and reduced function of neurons in the LGN in AD patients. The presence of β-amyloid plaques and neurofibrillary tangles of tau protein are also shown to be more abundant in the parvocellular than in the magnocellular layers of the LGN [218, 219]. On the contrary, a recent study found that tau pathology was scarce in the LGN and it did not differ significantly with age-matched control patients [216].

### 5.6. Other brain nuclei

#### *5.6.1. Superior coliculus (SC)*

The SC, sometimes referred to as the optic tectum, is a paired and laminated structure with a retinotopic organisation in the medium brain, which receives about 10% of RGC axons and is involved in the control of eye movements. Numerous amyloid plaques were found in the SC of AD patients [217]. Furthermore, subsequent studies identified abundant neuropathological

neurofibrillary tangles [216, 218, 219] in this nucleus. These pathological changes in the SC may explain the problems of ocular motility frequently found in patients with AD [220].

*5.6.2. Suprachiasmatic nucleus*

The suprachiasmatic nucleus (SCN) is a paired structure formed by a group of neurons in the medial hypothalamus, above the optic chiasm, which receives direct RGC input through a retinal-hypothalamic tract [221]. In addition, it is a primary control centre of circadian rhythms by stimulating melatonin secretion by the pineal gland. It has been seen that there may be marked changes in the SCN in AD, such as decreases in the volume and number of cells (including specific neuronal subpopulations, such as vasopressin and neurotensin neurons) and the formation of neurofibrillary tangles [222–225]. These neuropathological findings may be correlated with the misalignment of the circadian rhythm in AD [226].

*5.6.3. Pulvinar nuclei*

Pulvinar nuclei, are a collection of nuclei located in the pulvinar thalamus, have reciprocal connections with association areas of the cerebral cortex, in the parietal, occipital and temporal lobes. They consist of several divisions that receive multiple inputs from the visual cortex subdivisions, from the SC and the retina (to a limited extent) [227]. This area is involved in visual attention and the control of eye movements.

Numerous amyloid plaques and some neuritic plaques (extracellular deposits within the brain grey matter which are a mixture between amyloid and death neuronal processes) were found along the various subdivisions of the pulvinar nuclei in nine AD patients compared with younger patients and age-matched controls [228]. This could explain the deterioration of visual attention in AD patients [174].

**5.7. Visual cortex**

The visual cortex is located in the occipital lobe. It comprises the striate cortex or V1 (primary visual cortex) and visual cortical extrastriate areas such as V2, V3, V4, V5, etc. (secondary visual cortex). Together, the primary and secondary visual cortex consists of a mosaic of several dozen visual areas occupying a large part of the cerebral cortex, approximately 20–25% in humans [229, 230].

In AD, the primary visual cortex is affected after the involvement of other cortical regions [231–233], except in a variant that manifests with early visual symptoms [234, 235]. Nevertheless, the accumulation of amyloid plaques and neurofibrillary tangles, the decrease in the number of neurons and capillary density, and the reduction of certain enzymes in V1 of AD patients are well documented [191, 233–236].

Although some preliminary studies claimed that there are minimal neurofibrillary tangles and amyloid plaques in primary and secondary visual cortex [237], subsequent studies have found abundant neurofibrillary tangles and plaques in the secondary visual cortex (mostly in the extrastriate 18 and 19 areas) [238, 239]. In both areas 17 and 18, the average neuronal density

decreases to a similar degree (~30%) [240]. However, the difference between the two areas was the concentration of neurofibrillary tangles (2% of the neurons present tangles in area 17 vs. 10% in area 18) [240]. The reason for such discrepancy in neuronal loss could be related to the vulnerability of some neurons to the presence of neurofibrillary tangles or to the possibility of some cell loss unrelated to the degeneration of neurofibrillary tangles [47]. In addition to amyloid plaques and tangles, astrocytic gliosis was found in the primary visual cortex [241]. A likely associated dendritic pathology has also been observed in AD: dystrophic dendrites, loss of dendritic branches, and pathological alteration of dendritic spines [242, 243].

## 6. Visual psychophysical tests in Alzheimer's disease

To perform psychophysical tests in pathology such as AD can be a great challenge, because most of these tests require understanding and memorisation of the protocol for proper test performance. Therefore, without supervision by an experienced examiner, anomalies detected in testing may actually be the result of a failure to perform the task and not a visual deficit.

### 6.1. Visual acuity

The analysis of VA in AD patients was one of the most controversial tests. Although several studies claim that VA is not altered in this neurodegenerative condition [44, 48, 49, 239, 241, 244–246], other researchers find not only a decrease in VA [40, 247] (**Figure 2A**), but they also link this reduction to visual hallucinations when VA is severely decreased [248, 249]. A

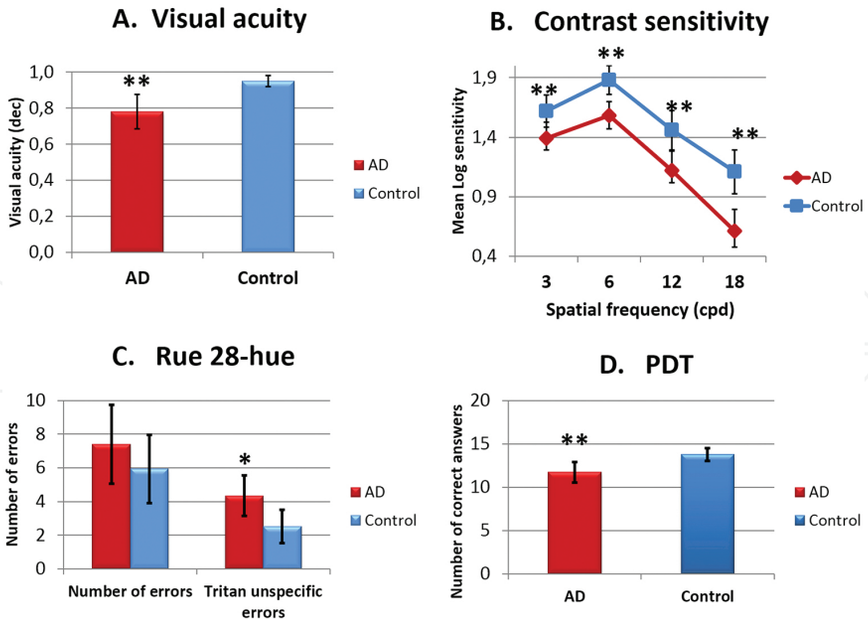


**Figure 2.** Mean data of the psychophysical tests. (**a**) Visual acuity, (**b**) contrast sensitivity, (**c**) desaturated Rue 28-hue colour test, and (**d**) perception digital test. Each bar represents the mean ± SD. *$p < 0.05$ versus control. **$p < 0.01$ versus control. Mann-Whitney *U* test (from **Figure 1** of [40] with permission).

correlation between the worsening in VA and the progression of AD has been described [250], together with a decline in AD patients and in AD patients with vascular dementia under low-luminosity conditions [44].

### 6.2. Colour vision

To perform the colour test in clinical practice in patients with AD is controversial because these patients have a naming deficit and therefore may have trouble verbalizing colours that they see or they might incorrectly name numbers or shapes. Despite this, some colour-vision tests do not require verbalisation, although they require concentration and memorisation of the task.

Some published studies which used Farsworth's test and Ishihara's test [251–253] found no differences in colour perception between the AD group and the control one. However, other authors found some tritan-axis defects, showing a correlation with the degree of dementia [37, 40, 238, 244] (**Figure 2C**). These data agree with the results of other authors [173, 240, 247, 254]. Pacheco et al., in their analysis with Ishihara test and PV-16, found impaired colour vision consisting of non-specific mistakes. Such responses were more prevalent in AD patients compared with controls, and were unrelated to the severity of the disease [38]. The disparity in the results may be due to the fact that each study used a different method for studying colour vision, so that comparisons of the results are difficult to interpret. Notably, Salamone et al. claimed that the problem of colour discrimination in AD patients is not purely cognitive but rather seems to be related to the damage of the structures responsible for colour perception [39].

### 6.3. Visual field

Like other psychophysical measures, automated perimetry requires considerable cooperation from the patient; therefore the reports on VF and AD are scarce and most are case reports. VF defects in AD vary from homonymous quadrantanopsia [255, 256] to non-hemianopic VF loss [239]. VF impairment in AD has been found both with manual perimetry [35] and with automated perimetry [34]. The latter showed a significant reduction in differential luminance sensitivity between AD and controls. This study additionally reported that AD patient underwent a diffuse sensitivity loss and, although VF defects involved the central field, deficits were more pronounced in the inferior field, appearing mostly as arcuate defects. They also found that the patients exhibited progressive VF loss 18 months after the initial examination.

### 6.4. Contrast sensitivity (CS)

CS tests evaluate the ability of the visual system to discriminate an object from the background in which it is located. This allows us to assess the integration of the information by the RGC and its cortical processing. The CS is measured by a threshold curve in which the spatial frequencies examined are depicted. High spatial frequencies examine the role of parvocellular cells, while low spatial frequencies represent the function of magnocellular cells.

The study of CS in AD has given rise to discrepancies in the results. Most reports have shown that CS function is affected in AD patients, the impairment ranging from a reduction in all

spatial frequencies [26, 40, 43, 44, 245, 247, 251, 257–259], to a greater decline in high [26, 40, 258, 260] or low spatial frequencies [239, 244, 261, 262] (**Figure 2B**). By contrast, two studies found no differences between AD patients and controls [48, 246]. Such discrepancies in the results could be due to differences among the patients included in the studies as well as the CS test used [45]. Some CS tests are influenced by VA, such as the Regan chart, a low-contrast letter, and the Vistech VCTS 6500 whereas others are independent on VA, such as the Pelli-Robson test and the Freiburg test [45]. CS impairment in AD patients has consequences for daily functions and cognitive abilities, given that the spatial frequencies most affected appear to be those corresponding to macular function. An example of the importance of CS loss in AD patients is the capacity to predict the risk of falling [45].

### 6.5. Perception digital test (PDT)

The PDT is a quick, easy, and sensitive method recently developed for evaluating visual-perception disorders in mild AD patients [263]. The test aimed to assess the visual recognition of familiar situations, masked by geometric special effects that hinder perception. Each of the 15 sheets comprising the test shows the same picture at different positions in space. Special effects such as geometric effect (tile) or the effect of the frame 24/48 of MGI Photo Suite III program are used to distort the pictures. The test consists on a set of images that are shown to the patient to identify which one is properly oriented in space. Among the photographs are six common objects, five landscapes, two people, one letter, and one animal. The study of Rami et al. [263] showed that there were significant differences in PDT between mild-AD patients and control as well as a significant correlation with the MMSE. These results have been recently confirmed by Salobrar-García et al. [40] indicating that patients with mild AD had significantly more failures than controls and that there was a significant linear association with the MMSE [40] (**Figure 2D**).

### 6.6. Critical fusion frequency

The critical fusion frequency (CFF), also called temporal resolution, is a psychophysical threshold and in psychological terms is regarded as a measure of information-processing capacity [264]. It is defined as the frequency at which an intermittent light stimulus appears to be completely steady to the average human observer [265]. The CFF threshold is determined by the processing in the magnocellular pathway and frontal and parietal cortex [266]. In some studies the CFF appears normal in AD patients [244, 254, 267] with no retinocalcarine abnormality specific to AD patients [254]. By contrast, other authors found significantly lower CFF and descending scores compared with healthy elderly subjects [239, 264, 268].

### 6.7. Dark adaptation

Older adults have serious difficulty seeing under low illumination and at night, even in the absence of ocular disease. This fact can be attributed to delayed rhodopsin regeneration [269]. The study of Rizzo et al. showed that 7 of the 10 AD patients studied had a worse adaptation to darkness than did the control group of slightly younger patients [254].

### 6.8. Depth perception

The ability of the human eye to see in three dimensions and judge the distance of an object is called depth perception. Depth perception is grounded in both stereopsis and monocular cues. Because measuring monocular tracks is difficult, studies typically assess stereopsis. When an object is observed, each eye sees it from a slightly different angle. Those images are then sent back to the brain to be integrated into a single image, creating the 3D effect or stereopsis. Stereopsis relies mainly in the primary visual cortex. However, a more detailed analysis reveals that stereoscopic depth takes place in visual-association areas in the dorsal and ventral cortical pathways [270]. AD patients have been found to have abnormal depth perception in comparison with controls [238, 251, 254, 271, 272]. Disturbances in stereopsis, motion parallax and interpretation of static monocular cues may result from neuropathology in the AD visual cortex [272]. Other studies investigating stereopsis in AD were inconclusive [267] or found normal operation [171]. More recently, the link between worsening depth perception and AD has been demonstrated by means of functional magnetic resonance imaging (fMRI). The fMRI has revealed hypoactivation in the areas responsible for depth perception [273].

### 6.9. Motion perception

Motion perception is the process of deducing the speed and direction of different elements in a scene based on different sensory stimuli: visual, vestibular and proprioceptive. Visual sensory information for motion perception is based on retina [274], LGN [275] and primary and secondary visual cortex processing [276]. There is controversy in the reports on motion perception in AD patients, as some studies have found no differences in this regard [174, 246, 267] while others have identified several deficiencies in the motion perception [173, 277]. Specifically, patients with an early-stage of AD have great difficulty interpreting the movement of objects, a condition that worsens as the disease progresses [47]. The discrepancy of the results could be related to the test used, since some require discrimination of motion direction while others simply demand the recognition of the occurrence of motion.

### 6.10. Pupillary response to light

Pupillary response is controlled by a balance between the cholinergic and adrenergic innervation being influenced directly or indirectly by the input from the central and autonomic nervous system.

As an impairment of the cholinergic system is known to occur in dementia and AD [278], it would be expected for the pupillary light reflex to be affected in AD [279, 280]. The constriction at the onset of bright light relative to the resting amplitude was significantly reduced in AD compared with healthy age-matched older adults and young adults [279]. These findings point to the presence of a cholinergic deficit in AD patients [280, 281], as shown by the fact that pharmacological treatment with donepezil, an anticholinesterase agent, partially improves this deficit [280]. However, it is still a challenge to develop a pupillary-response-sensitivity test specific to clinical diagnosis of early AD.

In 1994, Scinto et al. reported that AD patients had hypersensitivity of the pupil dilation after diluted tropicamide instillation [282]. Since the publication of this work, numerous studies have been performed, with several results showing both negative [283–291] and positive results [281, 282, 292–297]. Some of these studies point to a lack of specificity to the pupil tropicamide test in AD [288, 298].

### 6.11. Ocular motility

For the proper coordination of eye movements the retina, the brain integration of the image, and the extraocular muscles need to be coordinated [299]. It has been reported that in post-mortem studies of AD patients, the oculomotor nuclei of the brain are affected [300, 301]. Boxer et al. reported that AD patients displayed reflexive visually guided saccade abnormalities, specifically, prominent increases in horizontal saccade latency [301].

### 6.12. The electroretinogram (ERG)

The electroretinogram (ERG) is a record of the bioelectrical response towards light stimuli. The three types used in daily practice are full-field ERG, pattern ERG (PERG) and multifocal ERG (mfERG). For clinical purposes, full-field ERG has been standardised so that the results of different researchers can be compared [302].

There is intense controversy with respect ERG impairment in AD patients. Some studies have found that the amplitude and latency of the retinal potentials did not differ between AD and control groups [29, 32, 254, 303, 304], indicating that the PERG may not be valuable in establishing an early diagnosis of AD [304]. In the study of Kergoat et al., amplitude and latency of ERG was not affected but there was a delay on the latency of the visual evoked potentials (VEP) [32]. Other studies have reported a significant amplitude reduction in AD patients [25, 26, 305] and postulated that this result is consistent with RGC dysfunction [26].

In PERG examination, increased implicit time of P50-wave and amplitude reduction in P50- and N95-waves were observed in AD patients [41, 42, 306], and this could reflect an impairment of the magnocellular stream [306]. In addition to PERG, Krasodomska et al. studied pattern VEP in patients with early stages of AD, and normal routine ophthalmological examination results. Their most prevalent findings were amplitude reduction in N95-wave and increased latency of P100-wave. Such results showed a dysfunction of RGC and optic nerve in early stages of AD [41]. The mfERG measures macular function [337], and a decrease in electrical activity has been found in the macula of AD patients [307].

### 6.13. Optical coherence tomography (OCT)

OCT is a non-invasive imaging technique that works in a similar way to ultrasound, except that it uses low-coherence light waves instead of sound waves. The light waves are used to take cross-section images of the retina. As OCT allows visualisation of the retinal layers, their thickness can be mapped and measured. In fact, this technique has already been established as the standard image model for retinal tests (**Figure 1**).

Currently, RNFL, RGC and inner layers of the retina are considered indirect biomarkers of the CNS, enabling the prediction of brain pathology in patients suffering from different neurological diseases [184, 308]. Since the development of OCT, this tool has been used to measure the thickness of the RNFL in different neurodegenerative pathologies. Despite that OCT was first developed in 1991 and commercially distributed in 1995, it was not until 2001 when a study was first published on the thickness of the RNFL in patients with AD [42].

During those first years, many studies appeared focusing on the peripapillary RNFL thickness in AD patients. In every study, a significant decrease in RNFL thickness was objectified in AD patients and compared with age-matched controls. These analyses were carried out by segmenting the measures of the peripapillary thickness according to the area (superior, inferior, nasal and temporal). Several studies showed a decrease in the peripapillary RNFL thickness in all areas [10, 14, 16, 18, 42, 309]; others found that the thinning occurred in the inferior and superior regions [17, 307, 310], while in still other studies this significant decrease appeared only in the superior peripapillary region [15, 213, 311–313]. Some studies reported a certain thinning in the RNFL associated with the progressive cognitive decline [203, 312, 314]. Some authors even suggest that the inferior peripapillary quadrants might be the area with most specificity and sensitivity regarding the detection of the cognitive decline in the initial stages of the AD [17]. However, Salobrar-García et al. [20] reported that their group of patients with mild AD showed no significant difference with respect to control subjects in terms of RNFL thickness of the peripapillary region (**Figure 3A**). These authors postulated that although no statistically significant differences in peripapillary RNFL were found between control and AD eyes, the increase in peripapillary thickness observed in mild-AD patients could be secondary to an inflammatory process that may represent an early stage of degeneration and could lead to progressive peripapillary fibre damage. The variability in peripapillary RNFL thickness reported in AD might be due to differences in disease progression among patients studied, since patients with greater involvement of the peripapillary region were those with a more advanced stage of AD.

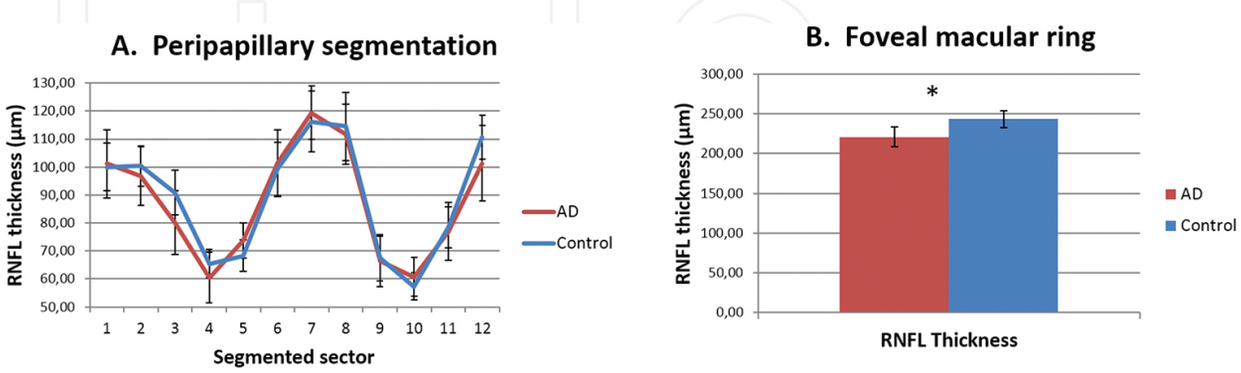


**Figure 3.** Mean data of RNFL thickness against eye quadrants assessed with optical coherence tomography (OCT). (**a**) Peripapillary segmentation retinal nerve fibre layer, (**b**) central macular ring (1 mm away from the fovea). *$p$ value < 0.01 (modified from **Figure 2** [20] with permission).

Recently, some studies focusing on the analysis of patients with mild cognitive impairment (MCI) found a thinning of the peripapillary region [62, 314–316]. MCI patients also have a thinning in the macular ganglion cell-inner plexiform layer [317]. By contrast, Ascaso et al., reported an increase in the macular volume in MCI when compared to control subjects and AD patients [315]. These findings could be explained as an increase in the macular volume caused by a possible inflammation and gliosis prior to neuronal cell death.

Recently, studies in AD analysed the measurement of not only the peripapillary RNFL thickness but also the RNFL thickness in the macular region. They demonstrated a significant RNFL thinning in the macular region of AD patients compared with age-matched controls [14, 19, 62, 63, 307, 311, 315] (**Figure 3B**). A study carried out using the latest OCT technology, which allows an analysis of the different retinal layers separately, noted that the thickness reduction occurred in the inner layers of the retina (RNFL-RGC complex), whereas the outer layers were not affected [63, 203].

In the most incipient AD stages (mild AD), psychophysical tests having the greatest predictive value are reportedly the CS, VA, unspecific errors in tritan region and the PDT [40]. In addition, the macular RNFL thickness and total macular volume measured by OCT have highly significant sensitivity and specificity for differentiating mild AD patients from healthy subjects, the thickness of the inner upper macular RNFL seeming to have the highest diagnostic value in mild AD neurodegeneration. Probably, the first affected area of the retina in mild AD is the macular area, where, due to the arrangement of the multilayer bodies of the ganglion cells, the decrease is easier to detect [19, 20]. These observations highlight the importance of applying psychophysical tests and OCT in patients with incipient AD stages.

Due to the ageing population increasing, the incidence of neurodegenerative diseases such as AD is growing. As demonstrated by the results of the visual psychophysical test mentioned above, the eye gives us a valuable window for evaluating these neurodegenerations. Therefore, the inclusion of ophthalmological examination could become an important tool in early diagnosis and follow-up of these patients.

## 7. Alzheimer's disease and glaucoma

In the last decade, several studies have been made on some AD patients and experimental models of glaucoma. These studies have shown some significant similarities between the two pathologies [318–320]. Furthermore, in some clinical studies where the prevalence of primary open-angle glaucoma (POAG) in AD patients was studied, an increase was observed in the incidence rate of POAG in AD patients [321, 322]. Tamura et al. identified an increase in the prevalence of the ε 4 allele of the APOE in POAG patients, similar to those that occur in patients suffering from AD. This suggests that common mechanisms could contribute to both pathologies [322]. Lipton et al. [323] have postulated that treatment with memantine, a NMDA receptor blocker used in AD could help to slow the advance of glaucomatous neurodegeneration. This hypothesis is based on the fact that the apoptosis, mediated by excitotoxic cell death, is a factor in the physiopathology of many neurodegenerative diseases, including glaucoma.

This kind of excitotoxicity is caused by the excessive activation of NMDA glutamate receptors, at least partially. This excessive activity in the NMDA receptor entails an abnormally high influx of calcium ions in the neurons, which triggers multiple outcomes resulting in apoptosis. Thus, pharmacological blockage of NMDA receptor activity would prevent apoptosis related to excitotoxicity. However, the use of a neuroprotective drug (memantine) in patients with POAG gave discouraging results [324]. On the other hand, in a recent 12.7-year longitudinal study, no direct link was found between normotensive glaucoma and increase risk of developing dementia or AD, compared with the general population [325].

Whether or not glaucomatous optic neuropathy can be considered an ocular extension during Alzheimer's progression deserves further investigation.

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## Author details

Elena Salobrar-García[1], Ana I. Ramírez[2], Rosa de Hoz[2], Pilar Rojas[3], Juan J. Salazar[2], Blanca Rojas[1], Raquel Yubero[4], Pedro Gil[4], Alberto Triviño[1] and José M. Ramírez[1*]

*Address all correspondence to: ramirezs@med.ucm.es

1 Ramon Castroviejo Institute of Ophthalmologic Research, School of Medicine, Complutense University of Madrid (UCM), Spain

2 Ramon Castroviejo Institute of Ophthalmologic Research, School of Optics and Optometry, Complutense University of Madrid (UCM), Spain

3 Service of Ophthalmology Hospital Gregorio Marañon, Ramon Castroviejo Institute of Ophthalmologic Research, Complutense University of Madrid (UCM), Spain

4 Service of Geriatrics, University Hospital Clinico San Carlos, Complutense University of Madrid (UCM), Spain

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