Invited review

Oculovisual changes and clinical considerations affecting older patients with dementia.

R.A. Armstrong[1]

H. Kergoat[2]

[1] Vision Sciences, Aston University, Birmingham, B4 7ET, U.K.

[2] École d'optométrie, Université de Montréal, Montréal, P.Q., Canada H3C 3J7

Corresponding author: Dr R.A. Armstrong, Vision Sciences, Aston University, Birmingham, B4 7ET, U.K. (Tel: 0121-204-4102; Fax 0121-204-3892; Email: R.A.Armstrong@aston.ac.uk)

Abstract

Purpose: Dementia is associated with various alterations of the eye and visual function. Over 60% of cases are attributable to Alzheimer's disease (AD), a significant proportion of the remainder to vascular dementia (VD) or dementia with Lewy bodies (DLB), while frontotemporal dementia (FTD), and Parkinson's disease dementia (PDD) are less common. This review describes the oculovisual problems of these five dementias and the pathological changes which may explain these symptoms. It further discusses clinical considerations to help the clinician care for older patients affected by dementia.

Recent findings: Visual problems in dementia include loss of visual acuity (VA), defects in colour vision and visual masking tests, changes in pupillary response to mydriatics, defects in fixation and smooth and saccadic eye movements, changes in contrast sensitivity function (CSF) and visual evoked potentials (VEP), and disturbance of complex visual functions such as in reading ability, visuospatial function, and the naming and identification of objects. Pathological changes have also been reported affecting the crystalline lens, retina, optic nerve, and visual cortex. Clinically, issues such as cataract surgery, correcting the refractive error, quality of life, falls, visual impairment and eye care for dementia have been addressed.

Summary: Many visual changes occur across dementias, are controversial, often based on limited patient numbers, and no single feature can be regarded as diagnostic of any specific dementia. Nevertheless, visual hallucinations may be more characteristic of DLB and PDD than AD or FTD. Differences in saccadic eye movement dysfunction may also help to distinguish AD from FTD and PDD from DLB. Eye care professionals need to keep informed of the growing literature in vision/dementia, be attentive to signs and symptoms suggestive of cognitive impairment, and be able to adapt their practice and clinical interventions to best serve patients with dementia.

Key words: Dementia, Visual dysfunction, Alzheimer's disease (AD), Vascular dementia (VD), Dementia with Lewy bodies (DLB)

Introduction

A significant part of current optometric practice is concerned with examining older individuals[1] and this trend is likely to continue given the predicted increase in the life-span worldwide. A major disorder causing changes in the oculovisual system in the older population is dementia defined as 'a major degenerative disorder with evidence of substantial cognitive decline from a previous level of performance in one or more domains such as short-term memory, abstract thinking, judgment, language, and personality changes sufficiently severe to interfere with independence.'[2] The majority of cases of dementia are due to Alzheimer's disease (AD)[3], a significant proportion of the remainder to vascular dementia (VD)[4], either alone or in combination with AD (mixed dementia), and to dementia with Lewy bodies (DLB)[5], while other causes such as frontotemporal dementia (FTD)[6], dementia associated with Parkinson's disease (PDD)[7,8], Creutzfeldt-Jakob disease (CJD)[9], systemic disease, or to drug use are rare.[10] FTD is a particularly complex disorder and is associated with a number of clinical conditions such as behavioural variant FTD (bvFTD), FTD with motor neuron disease (FTD-MND), progressive non-fluent aphasia (PNFA), semantic dementia (SD), and progressive apraxia (PAX).[11] FTD is therefore a clinical diagnosis and its associated pathological variants are termed frontotemporal lobar degeneration (FTLD).[12]

Dementia is associated with a characteristic brain pathology which can also affect the eye and visual pathway, resulting in visual dysfunction.[13] This review describes the major alterations in visual function that may occur in dementia and the pathological changes which may explain them. Some aspects of visual dysfunction described cannot be measured easily in clinical practice and the study of dementia is frequently carried out by multidisciplinary teams involving the collaboration of many types of professional. In addition, the review concentrates on types of dementia more likely to be encountered in practice, e.g., AD, VD, and DLB, but also includes some less common disorders such as FTD and PDD.[7] Particularly rare dementias such as CJD[9], corticobasal degeneration (CBD)[14], and progressive supranuclear palsy (PSP)[15], however, have not been included.

Prevalence of dementia

It is estimated that 24.3 million individuals worldwide have dementia and that there are 4.6 million new cases recorded each year.[16-18] The overall prevalence of dementia calculated by the European dementia meta-analysis (EURDEM) of all European studies is 1.6% and 1% for males and females respectively in the 65-69 age class, rising to 11% and 12.6% for males and females in the 85-89 age class.[17] Various estimates have also been made of the prevalence of dementia attributable specifically to AD.[18-20] With advancing age, the prevalence of AD is estimated at 19% in individuals 75-84 yrs, and at 30-35% for those older than 85 yrs. Of the different types of dementia, approximately 62% of cases are due to AD and 17% to VD alone, 10% to a combination of VD and AD, while DLB accounts for 4%, FTD for 2%, PDD for 2%, and all other causes collectively for 3% of dementias.[16-20]

Diagnosis of dementia

There are many conditions which can result in dementia (Table 1) and clinical diagnosis of any specific disorder can be challenging. However, using rigorous criteria, the viability of current clinical diagnosis compared with the pathological standard can be 90% or higher in certain studies.[21] Diagnosis of a dementia is frequently based on 'consensus criteria', i.e., on the opinions of leading experts in the field regarding the clinical and pathological features most important in diagnosis. For example, diagnostic criteria for AD were developed originally by the 'National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association' (NINCDS-ADRDA) work group[22] and subsequently modified by the National Institute on Aging (NIA) - Reagan Institute.[23] In addition, criteria for DLB are based on those of the 'Consortium on Dementia with Lewy bodies (CDLB)'.[24] The definitive diagnosis of a dementia, however, usually requires neuropathological examination of brain tissue, either at biopsy or post-mortem, and the identification of a specific molecular pathology.[25] Hence, the deposition of aggregated or misfolded proteins in the brain either as intracellular neuronal cytoplasmic 'inclusions' (NCI), e.g., neurofibrillary tangles (NFT) and Lewy bodies (LB), or extracellular protein deposits in

the form of 'senile plaques' (SP) is characteristic of many dementias and an important feature in the pathological diagnosis of individual disorders.[24]

Many changes affect the brain in AD but few of them are specific, most appearing as exacerbations of normal aging. Hence, there is atrophy of the cerebral hemispheres with narrowed gyri and expanded sulci accompanying a widening of the subarachnoid space.[26] These gross changes mainly affect frontal, temporal, and parietal lobes but may spare the occipital cortex, at least until later in the disease. The meninges are thickened by fibrosis and the ventricles dilated.[27] White matter undergoes discolouration and may become vacuolated ('spongiosis') and there is a proliferation of glial cells ('gliosis') affecting the gray matter.[27] The formation of SP and NFT is regarded as the defining histological feature of AD and these lesions occur in various cerebral cortical regions, including the visual cortex, and in the hippocampus.[23,28,29] The most important molecular constituents of the SP and NFT are the abnormally aggregated proteins β-amyloid (Aβ)[30] and the microtubule associated protein (MAP) tau, respectively.[25]

Similar types of pathology can be observed in other dementias. Hence, Aβ deposits are also found in VD[4], PDD[8], and DLB.[31,32] In addition, both PDD and DLB possess LB, the major molecular constituent of which is α-synuclein and these disorders are therefore termed 'synucleinopathies'.[33] In addition, abnormally aggregated tau and transactive response (TAR) DNA-binding protein of 43kDa (TDP-43) are important in various forms of FTD.[12] Recent research suggests that many of these pathological proteins may propagate through the brain along anatomical pathways by direct cell to cell transfer.[34-36] Hence, visual dysfunction due to degenerative brain disease could be dictated by topography, i.e., which visual areas of brain become affected and at what stage of the disease, and ultimately be determined by the spread of these proteins.[37] Nevertheless, some of these results are still controversial and not sufficiently documented to be certain of their validity.

Visual dysfunction in dementia

Visual dysfunction in AD, VD, FTD, DLB, and PDD is summarized in Table 2. Aspects of visual function are divided into various categories based largely on those described in AD, the disorder with the most extensive literature. Several factors need to be taken into account in interpreting these findings. First, most studies rely on clinical diagnosis of a dementia and therefore, on the criteria used and should be viewed with caution if the most rigorous consensus criteria have not been applied. In addition, it can be difficult to separate AD from VD and PDD from DLB and there are 'mixed' cases exhibiting features of these disorders. Second, clinical testing frequently involves a small number of dementia participants not graded according to degree of cognitive impairment while other studies may classify participants into a small number of categories, e.g., early, middle, and late stage AD or into mild, moderate and severe cognitive impairment. Hence, studies on small numbers of ungraded individuals should be viewed with considerable caution. Third, visual testing may be carried out using a variety of different objective and subjective methods. Hence, the effectiveness of some of these methods in testing participants especially those with severe dementia should be taken into account. Fourth, participants may have been visually assessed without having had an eye examination, and thus, without knowing if the optimal refraction has been used or if an ocular pathology was present. Koch et al.[38], for example, investigated the prevalence of uncorrected visual disorders in AD individuals residing in two nursing homes in the USA. In 85 residents with dementia, 80 needed spectacle correction for presbyopia, myopia, or both. Of these, 25 had not been using their spectacles regularly, nine with severe cognitive impairment did not request them, eight had lost or damaged their glasses, and eight had inappropriate prescriptions for correcting their vision. Minor refractive blur may not affect performance on testing such as visual field, critical flicker fusion frequency (CFFF), low spatial frequency contrast sensitivity (CS), motion detection, and colour vision tasks but is likely to significantly affect visual acuity (VA), high spatial frequency CS, and stereoacuity. It should also be noted that many aspects of visual function can be affected by age-related conditions such as cataract, age-related macular degeneration, and glaucoma.

Visual acuity

In one of the earliest studies of VA in dementia, Teller cards were used to measure VA binocularly in non communicative nursing home residents.[39] The authors reported that VA can be measured in about 20-30 minutes and suggested that this technique should be used for those residents in whom conventional acuity measurements are not possible. Shortly after, the results from a study where VA was measured on equal groups (n= 87) of AD individuals with mild to moderate dementia and controls showed a higher prevalence of near- and far-vision impairment in AD.[40] In addition, the authors reported that poor VA was significantly correlated with the severity of cognitive dysfunction. A parallel study using a HOTV chart failed to demonstrate VA deficits in individuals with mild to severe AD,[41] and a more recent investigation using Snellen type letters failed to find differences in near or far VA in community-dwelling individuals with mild dementia, both in comparison to control subjects.[42] Later on, in a large scale research investigation, two types of VA charts (recognition *vs* grating acuity) were compared in nursing home residents.[43] Of all participants (n= 656) studied, 86% responded to VA testing in at least one eye, 84% could be tested using Teller cards while 73% were testable using ETDRS letters or Lea symbols. Of the participants with a mini mental state examination (MMSE) score of less than 10, and thus having more severe dementia, 41% were testable by recognition acuity and 61% by grating acuity (Teller cards). It was concluded that Teller cards could be used to test vision in cognitively impaired individuals not testable by conventional means. Another study presented clinical data based on eye examinations provided to older individuals (65 to 104 yrs of age) residing in long-term care units.[44] From the 105 residents referred for an optometric eye examination, 92 (87.6%) had dementia (MMSE between 0 to 23). It was possible to do an ocular refraction with VA measurement in 78 (84.8%) of these 92 residents. For those in whom VA could be improved, it increased on average from 6/27 (20/90) to 6/12 (20/40). This study clearly indicated that VA can be measured clinically in a large proportion of institutionalized older residents with mild to severe dementia,[44] findings that parallel the research results presented by Friedman.[43] More recently, Teller cards and Lea symbols were used to measure grating and recognition acuity respectively, in subjects with AD (n= 20) and age-matched controls (n= 24).[45] The results indicated that VA measured with

the 2 techniques were well correlated, in agreement with earlier data.[43] Finally, VA has been compared using six validated acuity charts in older residents (n= 30) from long-term care units suffering from mild to severe dementia.[46] The results showed that it was possible to measure VA in all, but one, subjects with severe dementia. The charts that provided the lowest level of VA were the Teller cards and the ETDRS Patty pics, regardless of the level of dementia. On the other hand, the charts that provided the highest level of VA as well as the fastest responses were those displaying letters (ETDRS or Snellen). The authors hypothesized that letters are usually learned very early in life and thus, may be more easily retrieved from long-term memory compared to the other optotypes, in older individuals with dementia. Therefore, the results from this study suggest that VA should be measured with the regular letter charts in individuals with dementia, but that other charts can be used for those not able to respond to letters. Overall, these studies indicate that even if it is more challenging and if it requires more time to measure VA in older individuals with dementia,[46] this test can be performed in most of them. These studies further agree that alternative VA charts, such as the Teller cards, should be used for those not able to respond to standard letter acuity charts. Finally, studies comparing VA in individuals with *vs* without dementia present controversial data indicating either no decrease in VA, or alternatively, a decrease in VA that is more important with the severity of the disease.

Colour vision

Some early studies of dementia suggested defective colour vision may be present in approximately 50% of individuals with AD.[47,48] Studies of colour vision, however, have frequently not taken into account the presence of cataract, intraocular lenses and aphakia, or have not been using appropriate controls. Colour perception was compared in cognitively intact 80 and 95 yr old individuals and in participants with AD.[49] Performance of the 95 yr olds was poorer than the 80 yr olds but similar to the AD participants, overall lower colour perception ability in the 95 yr olds being attributable to age rather than any additional factor. In a further study, although the number of participants was small (n= 10), colour deficits identified in AD by L'Anthony D-15 desaturated colour test could be accounted for by age-related changes.[50] Another study has also suggested that colour vision is normal in mild to moderate AD[51], however, the authors acknowledged that their sample size was very limited (n= 12) and that the Ishihara and Ishikawa plates used

provide only a rudimentory measure of colour vision. In a study by Pache et al.[52], both Ishihara plates and the saturated PV-16 choice test were used, the latter originally designed for children. Hence, there were significantly more unspecific errors made by individuals with mild to moderate AD (n= 26) compared to age-matched controls (n= 25), using both tests, but no relationship was detected between test performance and severity of AD. As the authors acknowledged, however, their VA scores were quite different after having balanced the groups for the presence of cataract. The authors suggest that this may be due to poor collaboration on the VA test, although only one subject had severe dementia. Other studies also identified colour vision deficiencies in mild dementia using the SPP2 plates[42] and in mild to severe dementia using the City University test plates[41]. Unfortunately, the results of the various studies remain controversial and the strength of the evidence does not permit any real conclusion on the potential effect of AD on colour vision. Colour vision deficits may also occur in DLB[53] but this disorder has been much less studied than AD.

Stereoacuity

In AD individuals, defects in binocular depth perception ('stereoacuity') have been found using the Randot dot stereograms,[41,54] but another study using the Titmus test did not find differences.[42] In a further study, functional magnetic resonance imaging (fMRI) was carried out on newly diagnosed (mild) AD individuals (n= 12) not taking anti-cholinesterase medication while they viewed various types of stimuli including stereomotion.[55] AD individuals exhibited hypoactivation in area V5, and in the superior parietal lobule, parietal occipital areas, and premotor cortex compared with controls but with greater activity in the inferior parietal lobule, while viewing visuospatial stimuli. The authors conclude that these results are evidence for a pathophysiological basis for the visuospatial disorientation experienced by individuals with AD. Stereoacuity may be impaired more significantly in VD than in AD, pathology in the right hemisphere of the brain having a greater effect than in the left and by cortical rather than subcortical vascular pathology.[56] Impairment in stereoacuity was related to the severity of dementia. Stereoacuity is mediated by various neural pathways involving the thalamus and posterior parietal lobe, areas likely to be affected in both AD and VD. Overall, these studies present some functional and pathophysiological evidence for a

deficit in stereoacuity in AD and VD.

Contrast sensitivity function

Contrast sensitivity (CS) provides a measure of visual performance for various spatial frequencies and contrasts. The CS performance of individuals with AD is controversial, some studies not reporting changes in the CS function (CSF)[57,58] while others found reduced CS over all spatial frequencies[59,60] and particularly at lower spatial frequencies.[41] Such differences have been attributed to variations in the population under study, the method used to measure CS, or the failure to account for VA differences.[61] Additionally, not all studies checked for adequate ocular refraction, test distance or ocular health of participants. Spatial CS performance across a range of frequencies has been shown to be similar in AD, VD and mixed AD/VD cases.[62] A study of spatial CS at frequencies 1, 5, and 8 cycles deg^{-1} using the sweep visual evoked potential (VEP),[60] an objective method that minimizes the subjects' collaboration, showed a deficit in CS in mild to moderate AD (n= 16) *vs* control (n= 9) subjects. The authors concluded that defects in spatial CSF were likely attributable to dysfunction of the primary afferent visual pathway since they were not related to the severity of the disease. A more recent study used frequency doubling technology (FDT) to measure temporal CS in AD, amnestic mild cognitive impairment (MCI), older adults with cognitive complaints (CC) but without MCI, and healthy controls.[63] CS deficits were found in all quadrants for AD, MCI and CC subjects, but the largest differences between AD and MCI compared to controls were found in the upper right visual field in both eyes. From these results, it was concluded that FDT based measures of temporal CS are sensitive to early AD changes and it was suggested that this type of testing may have promise as a biomarker for AD.[63] The authors, however, were very careful in acknowledging the limitations of their results and the need for additional studies before this type of CS measurement can effectively be used as a biomarker of the disease. Although not universal, deficits have been reported in the vast majority of studies having investigated CS in AD. Deficits in CS were even hypothesized as leading to impaired cognitive performance in AD. This was demonstrated using a test of temporal CS at high frequency when enhancing the signal strength through an increase in stimulus contrast was shown to improve performance on a letter recognition task in subjects with

probable AD.[64] An earlier study also demonstrated that increasing contrast improved the speed of letter identification while reading in AD.[65]

Motion perception

There are many aspects to motion perception such as detection, direction discrimination, perception of structure from motion. Earlier studies indicated that motion direction discrimination[66,67] and perception of structure from motion[42,57] are impaired in AD. It has been suggested that defective motion processing in AD individuals may have retinal, cortical and subcortical neuronal origin.[57] Such anomalies in motion processing may explain visuospatial disorientation in AD[68] and it has been suggested that it can also lead to unsafe driving behavior.[69,70]

Critical flicker fusion frequency

The CFFF threshold represents the lowest frequency at which a person can no longer perceive a flickering light as a steady light.[71] The CFFF is a well-established research tool in psychopharmacology, with possible application in detecting early AD.[71,72] Neurons from the retina and various cortical areas contribute to the CFFF.[41,72] In a study of mild to moderate AD participants (n= 26), CFFF was highly correlated with standard clinical assessment, cognitive function, and psychomotor performance.[73] However, CFFF has also been reported to be normal in AD.[41] By contrast, Mentis et al.[74] obtained positron emission tomography (PET) scans in mild to severe AD individuals (n= 21) while wearing goggles containing grids of red lights. In AD, there were significantly smaller cerebral blood flow responses at the frequency producing the largest responses in control subjects, which may indicate a deficit in CFFF. In one study, CFFF was able to differentiate between AD (n= 30) and VaD (n= 16), but these results need to be replicated.[75]

Visual masking

Psychophysical thresholds are regarded as more reliable than psychometric tests in assessing cognitive dysfunction in the elderly, and visual masking has been a particularly

useful test.[76] Visual masking involves the presentation of a second stimulus, such as illumination or a checkerboard, immediately before ('forward masking') or after ('backward masking') a test stimulus. This type of testing helps probing spatial and temporal aspects of the visual-cognitive system at various levels of processing.[77] It has been shown that the performance of AD individuals on a backward patterned mask stimulus is impaired compared with controls.[58,78] This result suggests that the speed of central visual processing is further reduced in AD subjects compared to age-matched controls. In addition, it was shown that adaptation to the backward masking task may occur at different speeds in individuals with AD (n= 21) and VD (n= 16).[79] Furthermore, in AD individuals (n= 38) with deficits on a backward masking task, 13 were tested electrophysiologically, the flash electroretinogram (fERG) and pattern VEP being normal, suggesting the involvement of visual association areas rather than precortical visual pathway.[80] 'Visual crowding' is a specific form of masking in which the identification of a given letter is compromised by the presence of other letters in close proximity to the target.[81] In one individual with a posterior form of AD (posterior cortical atrophy-PCA), recognition accuracy decreased significantly in the presence of flanking letters and hence, 'crowding' could constitute a specific form of early-visual processing deficit impairing reading. Overall, these results have shown that visual masking can reveal cortical as well as precortical visual deficits.

Visual fields

One earlier study reported an overall reduction in sensitivity in the visual field of AD individuals, with greater deficits inferiorly.[82] Follow up studies demonstrated a progression of visual field loss over time.[82] This result is in contrast to those in a more recent study[63] where deficits in older individuals with AD (n= 10) and MCI (n= 28), were found especially in the upper right visual field, using frequency doubling technology (FDT). Although additional studies are essential to reconcile these results, such visual field deficits could reflect differential thinning of the retina in AD or differences in pathology affecting primary visual cortex (VI).[83] The feasibility of using FDT to screen for AD biomarkers was discussed in a recent paper.[84] Although it was demonstrated that

AD individuals can respond well to the test, further larger-scale studies are required to confirm these results in individuals with AD and MCI.

In addition, a number of imaging studies have been carried out on individuals with clinically diagnosed DLB and the results compared with AD. For example, regional cerebral blood flow (rCBF) is usually lower in occipital cortex[85,86] and higher in the medial temporal lobe[86] in DLB than in AD. In both DLB and AD, there are significant reductions in metabolism in parietal and temporal cortex, the posterior cingulate gyrus, and frontal association areas.[87] However, a significant reduction in occipital cortex and especially in area V1 occurred only in DLB, and therefore, there is considerable potential for visual field deficits in this disorder. Consistent with this suggestion, a study of a single 66 yr old person diagnosed with DLB, revealed a left homonymous hemianopia early in the disease.[88] Although neuropathologic findings met the criteria for DLB, large numbers of NFT were also found in the right striate, peristriate, and inferior temporal cortex of this person, possibly explaining the visual field deficits. In addition, occipital hypometabolism may be a useful potential method of distinguishing DLB from AD.[85-87]

Pupillary function

Earlier reports suggested that individuals with AD displayed a specific response to low doses (typically 0.01%) of the muscarinic receptor antagonist tropicamide, with pupils dilating on average by 23.4% compared to 5% for controls.[89] Although these findings could be replicated in some studies[90,91], others did not find similar results.[92,93] Increased pupillary sensitivity to tropicamide could be due to loss of noradrenergic neurons in the locus caeruleus observed in AD and a number of dementias.[94]

Hypersensitivity pupillary responses have also been reported using dilute solutions of the sympathetic agonist phenylephrine and the cholinergic agonist pilocarpine.[95] Phenylephrine 0.5% induced a larger mydriasis in LBD subjects compared to AD and control participants, a result attributed to the dysfunction in sympathetic innervation to the iris. Pilocarpine 0.0625% induced more miosis in DLB and AD subjects compared to controls, a result attributed to the dysfunction of the cholinergic system in both diseases.

Hence, it was concluded that a combination of the pilocarpine and phenylephrine pupil tests may help detect the two disorders as well as distinguish between them. Reduction in the pupillary constriction to bright light has also been reported in AD individuals but the responses were highly variable between subjects.[96]

Up to now, the results of these studies have not been sufficiently convincing to find their way within the clinical setting.

Eye movements

Eye movement problems are particularly characteristic of dementia especially in the parkinsonian syndromes DLB and PDD.[5,7] Assessment of oculomotor function has usually been carried out using equipment able to measure precisely spatial and temporal eye movement events, and employing electro-oculography (EOG) on individuals in whom cognitive impairment was not serious enough to compromise the tests.

The ability of some individuals to fixate a target is affected in AD[97,98], defects of fixation control being associated with parietal lobe degeneration, a region involved in maintaining fixation stability. Several changes in saccadic eye movements have also been reported in AD. Saccadic latency is prolonged in AD[97-102] and it was even found that longer latencies correlated with lower MMSE scores.[102] The velocity of saccades is reduced and the degree of reduction correlates with the severity of dementia.[97] Individuals with AD make hypometric saccades[97] and many have difficulty initiating or maintaining saccadic eye movements.[103] In AD individuals, the duration of fixation during visual saccades increased in the early stages of the disease.[104] By contrast, some VD individuals were slower to adapt to this task and required longer center to target distances, believed to be attributable to a general slowing of cognitive processes in VD.[104]

Smooth pursuits, a sensitive indicator of brain function, may also be affected in AD.[105] Hence, a gradual deterioration of these movements has been reported necessitating 'catch-up saccades' to maintain fixation.[100,106] Degeneration and atrophy of frontal and parietal lobes have been implicated in these changes.[3] In particular, dorsal frontal lobe

damage impairs smooth pursuits and the ability to suppress visually guided saccades on the antisaccade task.[107]

Abnormalities of saccadic eye movements are also characteristic of various forms of FTD. Hence, in a study comparing FTD (n= 22) and control (n= 23) subjects, saccadic latency was prolonged and early saccades were increased, reflecting increased atrophy of the left frontal eye field and reduced speed of decision making processes.[108] In addition, a study demonstrated that FTD (n= 28) subjects presented abnormalities in reflexive visually guided saccades, as did AD (n= 10) participants.[109] In a smaller size study of FTD associated with motor neuron disease (MND), and in whom gross ocular abnormalities were present, slowing of both vertical and horizontal saccades was observed.[110] In a much larger study (n> 100) comparing various forms of FTD and other related disorders, an overlap was observed between most groups, but only in FTD were there spontaneous selfcorrecting anti-saccade errors.[111] In addition, mutual gaze ('eye contact'), which is important in social interactions, is impaired in a number of dementias including FTD, but was preserved in AD subjects.[112] There is also a significant difference in the ability of control and AD subjects to reaccelerate their eyes in a predictive fashion before the predicted time of target reappearance, FTD being unable to carry out this task. Moreover, in FTD, anticipatory eye movements are triggered by the disappearance of the fixation point before the onset of target motion.[113]

In a study comparing DLB (n= 20), PDD (n= 20) and AD (n= 22) subjects, DLB and PDD participants showed impairment in reflexive and saccadic execution as well as in the performance of more complex saccadic eye movements, differentiating them from those with AD.[114] In addition, albeit in a single case with DLB, problems in convergence were followed by bradykinesia and rigidity.[115] There have also been cases of DLB presenting with vertical and horizontal gaze palsy, a sign frequently associated with PSP, thus potentially confusing the two disorders.[116] Caution is therefore required in the interpretation of vertical gaze palsy when distinguishing parkinsonian syndromes.[117]

Electroencephalogram

Studies of six electroencephalogram (EEG) frequency bands in FTD (n= 19) and AD (n= 16) subjects indicate that there was no increase in slow activity and a larger decrease in fast activity in FTD, while there was an increase in slow activity and a smaller decrease in fast activity in AD, in comparison to age-matched controls.[118] Quantitative EEG alone, however, could not differentiate well FTD and AD. In a study of VD (n= 12), there was a reduction in synchrony of the slow frequency bands during a target detection task, more neurons presumably having to be activated.[119] It was concluded that this type of EEG recording can be useful to evaluate cognitive dysfunction in individuals with VD. EEG in response to eye opening and to 12 Hz photic stimulation was also studied in a relatively small number of DLB (n= 10) and PDD (n= 7) subjects using global field synchronization (GFS).[120] When eyes were closed, theta-GFS increased in PDD and alpha-1 GFS was decreased in DLB. In addition, using 12 Hz intermittent photic stimulation, reactivity of posterior electrodes was decreased in DLB, suggesting disruption of posterior anatomical pathways.[120] Further studies are required, however, to evaluate if EEG can distinguish LBD from PDD.

Electroretinogram

Changes in the electroretinogram (ERG) have been reported in various dementias. The pattern ERG (PERG) reflects the activity of the retinal and pre-retinal ganglion cells.[121] It has been reported that the amplitude and latency of the PERG response are reduced in AD,[122-125] although these results are not universal.[126,127] The flash ERG (fERG) measures the activity of the photoreceptors, bipolar, Mueller and amacrine cells. Studies have indicated that the scotopic and photopic fERG are largely unaffected in AD.[80,127,128] It has further been shown that the scotopic and photopic oscillatory potentials are also preserved in AD.[128]

The fERG has also been used to demonstrate dysfunction of the scotopic and photopic systems of the retina in DLB subjects.[129] The deficits were attributed to pathological alterations in the photoreceptors which were accompanied by ‘pale inclusions’ in the outer plexiform layer, particularly in the peripheral retina. Immunohistochemistry and

structural analyses indicated that these inclusions differed from LB.[130]

Visual evoked potentials

The visual evoked potentials (VEP) provide an objective measure of the functionality of the maculo-cortical pathways. In AD, a number of studies suggest that the latency of the P2 component of the cortical flash VEP is delayed, while the P100 component to a reversing checkerboard stimulus is unaffected.[131-134] This combination of abnormalities, however, is controversial and has not been confirmed by all studies.[135] Others have found that the P100 is delayed and that the retinocortical time is prolonged in AD.[125,136]

Visual event-related potentials

A number of studies of event-related potentials which elicit the 'P3' (P300) response believed to reflect orientation, attention, stimulus evaluation, and memory have been carried out in dementia. It is also believed that P300 is an indication of the level of cognitive resources used for processing a stimulus.[137] Using a facial discrimination task[138], mean latency of the visual P3 response was greater in PDD with visual hallucinations (n= 11) and DLB (n= 24) compared to AD (n= 21) subjects. Furthermore, mean latency of the P2 response was greater in PDD with and without VH and in DLB subjects, but not in AD, compared with controls. The results suggest that visual cognitive function is selectively impaired in PDD and DLB, and this, at an early stage of visual processing. In VD, the latency of P3 is delayed and its amplitude decreased, suggesting that these individuals may have fewer attention resources to devote to processing stimuli.[139]

Complex visual functions

Individuals with dementia exhibit a variety of more complex visual problems. This is the case for example with reading[103,140] or visuospatial function.[48,141,142] Three types of reading problem are common in AD: 1. 'semantic alexia', caused by a failure to understand words, primary vision being unimpaired, 2. 'surface alexia', caused by difficulties in pronouncing words, and 3. 'letter by letter reading', a difficulty in decoding words that are presented visually, not reading complete words but their constituent letters

in sequence.[143] Individuals with AD also show deficits in eye-head coordination[144], difficulties with finding objects that are surrounded by other items[145], and in finding known objects in an unknown location.[146] AD and VD individuals often exhibit very similar deficits on more complex visual tasks, with the possible exception of word recall, which is frequently better in VD.[147]

In some cases of FTD, difficulties in recognizing faces from photographs, including those of well-known personalities and family members, have been observed.[148,149] Facial recognition problems may by characteristic of FTD and therefore, a useful potential diagnostic indicator. In addition, the drawing performance of four artists with FTD was investigated, none with facial recognition problems, and in three out of four, drawings of faces were 'distorted' or 'menacing'.[150] These individuals exhibit cortical degeneration specifically affecting frontal and temporal regions and which could affect those areas involved in processing facial data. Hence, in SD, pathology in the anterior and inferior lateral right temporal lobe may be responsible.[151]

Individuals with DLB (n= 24) had a poorer performance than those with AD (n= 48) on object size discrimination, form discrimination, overlapping figure identification, and on visual counting tasks.[152] This was concluded to play a role in the perceptual deficits observed in DLB, such as visual hallucinations. Other complex visual tasks such as colour integration and rotated object comparison are also impaired in DLB, which corresponds with the cortical areas affected by the disease.[153] Significant defects in the 'trail-making task', a test of visual attention in which the subject is asked to 'connect the dots' and on the DMS-48, a test of visual object recognition memory, were observed in DLB (n= 10) compared to PDD (n= 12) individuals.[154] Although further studies are required, the authors concluded that such tests can be useful for characterizing the two diseases.

Individuals with DLB may exhibit a variety of deficits in visuospatial function including difficulty in judging verticals and the position of body parts, and in carrying out a route-walking task.[5] Hence, inability to copy the shape of a pentagon was often worse in DLB

(n= 17) than AD (n= 27) individuals suggesting greater visuospatial deficits.[155] By contrast, in a large study of FTD participants (n= 44), seven of whom were pathologically confirmed, there was relative preservation of visuospatial function[156], although such deficits have been reported in late-onset cases.[157] Individuals with AD, although rarely, may develop a complex combination of visual symptoms called 'Balint's syndrome', usually before any signs of overt dementia are apparent.[158] These include ocular apraxia, a psychic paralysis of gaze, optic ataxia, a defective visually controlled hand movement, and simultanagnosia, a visuospatial disorder of attention.[158] Simultanagnosia can be accompanied by visual field constriction, the fading of centrally fixated objects, and impaired reading ability, despite normal VA.

Visual hallucinations

Visual hallucinations (VH) have been reported in several types of dementias, especially in individuals with decreased VA or those with advanced cognitive impairment.[159] Hence, in a study of PDD (n= 26), hallucinations were very common.[160] Hallucinations are also common in DLB[161] but are less frequent in AD.[162-165] VH have also been reported in some genetic subtypes of FTD, especially those caused by chromosome 9 open reading frame 72 (C9ORF72) gene mutations.[166] In a small study of DLB individuals (n= 9), six developed VH and it was the presenting sign in one case.[161] VH in DLB are recurrent, well formed and detailed[167] and may be the only psychotic symptom which can reliably differentiate DLB and AD.[5] Hallucinations in DLB are usually colourful and complex,[168] and involve people or animals invading the person's home.[161] The hallucinations are often seen in great detail and although they do not often trouble the person, they can evoke considerable fear in some.[161,169]

Various factors may be involved in VH in DLB (Fig 1). Although pathology affecting the thalamus may be a contributory factor[170], changes in cerebral cortex are more likely to be the cause. Hence, hallucinations are abolished by eye closure indicating a primary cortical pathology.[171] Hypometabolism in area V1 of the visual cortex and relatively preserved metabolism in the temporal and parietal lobes may be associated with these

symptoms. Well formed VH are also evident in a pathological study of subjects (n= 63) with extensive development of LB in the temporal lobe[172] and are rarely reported in parkinsonian syndromes without LB, such as PSP.[173] Furthermore, cholinergic activity, especially the enzyme choline acetyltransferase (CAT) is reduced in the cerebral cortex of individuals with DLB.[174] More extensive cholinergic abnormalities are associated with an increased risk of VH. Hence, hallucinations in DLB could result from a change in the balance of neurotransmitter activity between the cholinergic and monoaminergic systems as a consequence of LB pathology in brain stem nuclei.[165] Nevertheless, ocular and retinal pathology could also contribute to hallucinations by reducing occipital stimulation.[130,175,176] Hence, the 'pale inclusions' which have been observed in the outer plexiform layer of the retina in DLB may suggest disruption of the cytoskeleton of cone cells.[129] As a consequence, ventral association areas may increase their activity as a result of cortical disinhibition resulting in hallucination.

Visual hallucinations have been linked with decreased visual acuity in AD[177-179], and observational data indicate that adjusting the ophthalmic correction can reduce VH.[179] A case reports study showed that providing optical aids decreased VH in three older individuals affected by VD and mild dementia.[180] Another case report presented an older patient incorrectly assumed to have a form of senile psychosis, in whom VH ceased completely after having had cataract surgery.[181] Further studies are required, however, before solid conclusions can be drawn regarding the effectiveness improving vision has on reducing VH in the various forms of dementia.

Pathological changes in the eye and visual system

Anterior segment of the eye

Some studies have reported Aβ deposits, which are widespread in AD brain in the form of SP, in the crystalline lens of the eye. Hence, Aβ deposits were observed in the equatorial supranuclear region of the lens, a mitotically active region not usually affected by cataract, in postmortem eyes of all AD subjects (n= 9) and in none of the controls.[182] Hence, a fluorescent compound which binds to Aβ deposits could be used *in vivo* as a potential early test for AD[183], the fluorescent material being applied as an eye ointment

and a laser scanning device used to measure the amount of fluorescence. However, Michael et al.[184] studied the presence of Aβ in postmortem eyes of AD individuals using confocal Raman microspectroscopy and observed that cortical lens opacities were not typical of AD and not characterized by the accumulation of Aβ and hence, the occurrence of Aβ in the lens in AD remains controversial.

Posterior segment of the eye

Whether or not pathological changes occur within the posterior segment of the eye in dementia is also controversial. In an earlier study, the authors did not detect fundus abnormalities linked with AD.[54] Nevertheless, others have reported abnormalities in some individuals with AD, including disc pallor, optic atrophy, and disc cupping.[103]

In various dementias, transynaptic degeneration involving the posterior visual pathway may cause pathological changes in the eye and retina.[185] Hence, the retina could provide an easily accessible site for non-invasive examination of brain pathology.[186] Retinal nerve fibre layer (RNFL) abnormalities in AD and controls have been studied using optical coherence tomography (OCT), a simple, high resolution method of quantifying the thickness of the RNFL.[187] This technique was originally used to study glaucoma and non-glaucomatous neuropathies.[188] A number of studies of RNFL using OCT have been carried out in AD. Hence, a study of AD (n= 21) and control (n= 21) subjects revealed thinning of RNFL and RNFL plus ganglion cell layer[189], while thinning of RNFL in all retinal quadrants was apparent in a meta-analysis of seven studies involving 324 eyes[190], and in other studies thinning most significantly affected the superior and/or inferior quadrants of the retina.[191,192] RNFL thinning has also been observed at the macula in a study of 28 eyes from AD individuals (n= 14).[193] RNFL thinning at the macula may also be accompanied by decreased electrical activity of the macula.[194] In addition, retinal thinning has been recorded in MCI, a condition which may precede AD, suggesting that the retina may be affected early in the disease.[195,196] Thinning of RNFL has also been recorded in 10 cases each of PDD and DLB.[187]

Post-mortem studies of the retina in AD also suggest a decreased number of ganglion

cells and a thinning of the RNFL.[197] There is a swelling and shrinking of ganglion cells with some containing vacuoles. A decline in the number of retinal ganglion cells could explain the disc abnormalities observed in a study of individuals with AD (n= 26).[198] It was unlikely that primary open-angle glaucoma (POAG) explained these changes as the intraocular pressures were in the normal range, and there was no family history of glaucoma[198], but low tension glaucoma could not be ruled out. SP-like structures have also been recorded in the human retina and in transgenic rodent models of AD[199] suggesting that retinal imaging techniques could eventually be applied to monitor retinal SP.[200] AD-related pathological changes have also been observed in normal-pressure hydrocephalus, traumatic brain injury, and glaucoma; all of which may be associated with elevated intracranial or intraocular pressure.[201] These results suggest that AD-type changes could result in part from exposure of the central nervous system to elevated mechanical stress[202] and that such progressive changes in pressure gradients affecting the intracranial optic nerve might be a further cause of visual field changes in AD.

Optic nerve

POAG may be present in approximately a quarter of individuals with AD compared with 5-10% of controls,[203,204] the authors suggesting that similar pathological processes could occur in the two diseases. By contrast, in a large Danish study, no association was found between POAG and AD.[205] Abnormal tau proteins have also been observed in the retina and optic nerve in AD, FTD, and in glaucoma.[206]

There is a decline in the density of optic nerve axons in AD. Studies have reported either a preferential reduction in large-diameter axons[197,207] or a decline in small-diameter axons in individuals with AD (n= 12).[208] Whether this degeneration is caused by a loss of retinal ganglion cells, retrograde degeneration affecting the retina, or both of these processes is yet to be established.

A reduction in large-diameter axons in the optic nerve suggests that the magnocellular (M) pathway is impaired in AD. The M-pathway, stimulated using high temporal - low spatial frequency, low contrast and luminance stimuli, is essentially a ‘luminance’

channel involved in motion detection.[209] Its preferential degeneration could explain reported anomalies in the cortical flash VEP[210,211] and loss of motion perception observed in AD. If small-diameter axons in the optic nerve are affected, then it suggests that the parvocellular (P) pathway is impaired in AD. This would likely impair the detection of fine details or colour.[209] Consistent with this, impairment of colour vision has been reported in AD.[48]

Lateral geniculate nucleus

Neurons in the lateral geniculate nucleus rarely develop NFT, although cells in this area accumulate lipofuscin, a pigment found in increasing amounts in nerve cells with age.[212] In an earlier study, however, SP were observed in all AD individuals (n= 12) evaluated.[213]

Visual cortex

Functional magnetic resonance imaging (fMRI) studies of young and healthy older adults suggest no major changes in visual cortex due to aging, but changes have been reported in some AD cases.[214] The transition between normal aging, MCI, and AD is often indistinct but pathological changes suggest early changes in medial temporal lobe spreading to affect neocortical regions[215] while brain imaging studies often suggest early changes in the posterior/temporal parietal region and in occipital cortex with NFT affecting B19 (V3).[216] These observations support the hypothesis that retinal pathology in AD may result from retrograde degeneration from association areas reducing axonal input to the eye. Pathological changes when they affect the visual cortex usually involve visual association areas (V2, V3 etc.) more significantly than area V1. Hence, SP and NFT were found in the visual cortex in 72% and 27% of AD individuals (n= 106), respectively.[217] The density of SP and especially NFT was more important in area V2 than in V1, particularly in early-onset cases. In V1, SP with distinct amyloid cores accompanied by small numbers of NFT can be seen, whereas in V2, numerous NFT and uncored 'neuritic-type' SP are usually found.[218] Additional studies are required to evaluate whether or not the differences in cortical pathology in V1 and V2 can explain the cortical VEP responses reported in AD.[219] In addition, in many cases of AD, the density of SP and/or NFT in V1

is significantly greater in the cuneal *vs* the lingual gyrus.[83] These findings could help explain the predominantly inferior visual field deficits that have been reported in some cases of AD.[82] Furthermore, a reduction in myelin as well as a loss of neurons and neurotransmitters have also been reported in the outer laminae of the visual cortex.[218]

Clinical considerations

Cataract surgery

Studies indicate that much of the vision loss in individuals residing in nursing homes may be correctable, due to causes such as inappropriately corrected refractive error or unoperated cataract. Cataracts are highly prevalent with advancing age[220] and the incidence of cataract surgery is increasing in many developed countries.[221] The benefits cataract surgery has on functional vision and quality of life have been well documented for community-dwelling aging individuals,[222,223] including the oldest-old.[224] This latter study showed that those 90 yrs of age or older were the most unsatisfied with their vision prior to surgery and that 79% fared better in their activities of daily living after the surgery. Additionally, the surgery improved VA in more than 90%, and further showed that 43% and 62% of those 90 yrs of age or older and 85-89 yrs of age respectively, were still alive 4 years after surgery. The authors concluded that not only was surgery beneficial for improving vision, but it was also beneficial when you take life expectancy into account. Other studies also demonstrated the benefits of cataract surgery,[225] as well as its safety[221] for the very elderly. These studies, however, did not address such outcomes in older individuals with cognitive deficits, an issue of particular importance, as the prevalence of cognitive deficits and dementia increases with advancing age. It is likely that many of the older individuals seen by ophthalmologists for cataract surgery are affected by undetected cognitive decline, MCI or even dementia. Recently, Jefferis[227] presented data on community-dwelling participants 75 yrs of age or older, capable of providing consent (MMSE > 12), having bilateral cataracts and being scheduled for first eye surgery. Their participants (n= 112) were all recruited from eye clinics, many had impaired cognition, and there were even 9 (8%) and 23 (20.5%) who met the clinical diagnosis of dementia and MCI, respectively, although only 3 had been seen in a memory

clinic prior to the study. All participants (n= 46 with intact and n= 45 with impaired cognition) seen at the 1 yr post-surgery follow-up had improvements in VA and visual quality of life. Those with MCI and dementia also improved, although to a lesser degree than those with cognitive decline but without these diagnoses. Although the outcomes of surgery were beneficial, the authors carefully concluded that these results cannot be extrapolated to individuals with severe cognitive impairment, as none were included in the study.

Many studies have documented a high prevalence of cataract in elderly residents living in nursing homes and long term care facilities[228,229], however, much less attention has been given to the uptake of cataract surgery and its benefits for that population. Although no study seems to have documented this issue in an older institutionalized population comprised exclusively of individuals with dementia, the SEEING study included a good proportion of older individuals with the disease.[230] This study reported data on the uptake of cataract surgery in nursing homes where assistance with access to the surgery was offered to the residents (i.e. intervention), compared to nursing homes where regular care was provided to the residents (i.e. usual care). Their results clearly demonstrated that there is a better uptake of cataract surgery in nursing homes receiving intervention compared to those where usual care is provided (30% *vs* 2% of residents had surgery). The authors, however, found many unexpected barriers to cataract surgery for cognitively impaired nursing home residents. The lack of transportation and patients' advocates to coordinate the appointments were important barriers in nursing homes where usual care was provided. Another important barrier, in 50% of those requiring cataract extraction, was the non acceptance of the surgery by the family, the guardians or the residents themselves. The rate of refusal was similar when consent was provided by residents compared to family/guardians. An additionnal barrier was community ophthalmologists refusing to perform the surgery although they had accepted to see residents who would be sent to them by the research staff. The authors rightly conclude that if studies can demonstrate that cataract surgery improves the quality of life of institutionalized frail elderly residents, then programs aimed at removing barriers to surgery will have to be implemented. Since, at least one study has been able to make this demonstration. Owsley

et al[231] showed that nursing home residents undergoing cataract surgery, compared to other residents refusing surgery, had improvements in their distance and near VA, contrast sensitivity as well as many aspects of their vision-targeted health-related quality of life. Their study included residents with mild to moderate dementia, but excluded those with more advanced stages of the disease. Thus, as the authors acknowledged, their results can unfortunately not be generalized to that nursing home sub-population and further studies are required to address this important issue. Importantly, however, their study demonstrated the overall benefits of cataract surgery for older institutionalized individuals with mild to moderate dementia. Taken together, the studies by Friedman[230] and Owsley[231] provide evidence-based data that can be used by clinicians to inform residents, family members and guardians on the benefits of cataract surgery for those individuals, whenever cataract surgery is required.

There are many issues to consider clinically when facing older residents with advanced dementia having visually debilitating cataracts, more so in developed countries where health services are readily available. One legitimate question is why was the surgery not performed earlier in the person's life, prior to institutionalization or before a cognitive deficit evolved into severe dementia. This question brings along the issues of prevention and education. Did the person develop the cataract during institutionalization or was it a pre-existing undiagnosed cataract that continued evolving ? In either case, a diagnosis of cataract should have been made early on after the person had been admitted to the nursing home. Therefore, it is suggested that for each newly-admitted resident, the nursing home should request a copy of the last eye examination if performed within the previous 1-2 yrs, or should ensure that a complete eye examination is offered to the resident. This would help in the detection and optimization of any uncorrected or not appropriately corrected ocular refraction, the detection and treatment of any active ocular pathology, and the adjustment of the environment as well as the way care is provided if a visual impairment is present. The studies described earlier clearly indicate that cataract surgery improves VA and vision-related quality of life in older community-dwelling and institutionalized individuals with mild to moderate dementia. One study also demonstrated the VA benefits for older institutionalized individuals having more

advanced dementia.[230] The difficulty the clinician faces in the presence of a resident with advanced dementia needing cataract surgery is to help the resident, family, guardian, make an informed decision regarding the surgery. This information has to be evidence-based. There is now some evidence that VA will be improved in these residents,[230] but there are no data on the overall quality of life provided by this gain in VA. More often than not, this is what the family or guardian wants to address. This is really about weighing the benefits *vs* the risks, more so since general anesthesia will usually be required for the surgery. As of yet, these data do not exist in the literature because there is no vision-related quality of life questionnaire specifically addressing this issue for people with more advanced dementia.[232] Such a questionnaire has to be built and validated in order to evaluate how changes in vision impact the quality of life of institutionalized individuals with more advanced dementia.

Eye care professionals keep on stressing the importance of providing regular eye examinations every 1-2 yrs for people 65 yrs of age or older.[233-236] This is true for community-dwelling individuals and it is particularly important for older instutionalized people for whom studies have repeatedly reported a higher prevalence of visual impairment. Eye care professionals should keep reinforcing this message among older patients consulting them, in order to detect and address any oculovisual problem as early as possible. If the oculovisual health of older individuals can be optimized when they live in the community, then it is hoped that eventually the prevalence of correctable visual impairment in those needing institutionalization will not be as high as it is currently. Meanwhile, eye care professionals could also assume a more pro-active role in their community, reaching out for nursing homes to provide eye care services to residents as well as educational programs, knowing that such services are currently not optimal.[237] Educational institutions should also ensure that their curriculum contains the necessary theoretical and clinical training in geriatrics so that eye care professionals can confidently deliver the special care required by older frail individuals, including those with dementia.[238,239] In parallel, licensure and certification boards should ensure competency of their members in the care of older adults.[238,239]

Correcting refractive error

As indicated earlier, another important cause of vision loss in nursing homes that might be correctable is the inappropriately corrected refractive error. Teresi[240] evaluated 3 groups of older nursing home residents, those receiving optimized ocular refraction, those receiving optimized ocular refraction and where the staff received specific training to help residents, and a control group receiving standard nursing home care. Their data showed less functional decline in residents from the nursing wards where both the optimization of ocular refraction and staff training were implemented. On that basis they recommended a yearly eye examination for nursing home residents, including the optimization of ocular refraction and staff training. Owsley[241] examined the effect of optimizing ocular refraction for nursing home residents, including those with mild to moderate dementia (MMSE≥ 13). In their study, eligible participants had to have an uncorrected refractive error of at least one line on a distance acuity chart, in at least one eye. They showed that adjusting the ocular refraction improved vision related quality of life and decreased symptoms of depression. These results are very important, more so considering that in the clinical setting, it was shown that correcting the ocular refraction improved the distance VA by 5 lines on average on the regular Snellen chart.[44] This latter study was retrospective and did not include vision related quality of life assessments, but more than half the participants had moderate to severe dementia (MMSE< 15). Here again, future studies should evaluate the impact improving VA by optimizing ocular refraction has on nursing home residents having moderate to severe dementia. As indicated above, a vision related quality of life questionnaire needs to be built and validated for that population before such studies can be implemented.[232] There are still many barriers to eye care for residents in nursing homes and, even when eye care services are provided, interventions are not always accepted. Having evidence-based data clearly demonstrating the positive outcomes of optimizing ocular refraction on a resident's vision related quality of life could potentially improve compliance to treatment.

Reflecting on the benefits of improving vision in dementia

The benefits of improving vision through the optimal modality (optical, medical, surgical or rehabilitation treatment) according to an individual's condition has been amply

demonstrated, in multiple domains, for the general older population. Hence, an improvement in vision has been associated with a better quality of life,[231,241,242] a decrease of depressive symptoms[231], as well as a decrease in falls[243] and injury.[244] On the other hand, vision loss can contribute to depression,[245] isolation,[245] disruptive behaviors[246] and falls.[247] Therefore, eye care professionals can confidently offer evidence-based therapies to older individuals having an ocular condition necessitating treatment, knowing that not only will their vision improve, but so will many other aspects of their life.

As indicated earlier, research has now provided some evidence that undergoing cataract surgery improves VA and quality of life in older individuals with MCI, as well as those with mild to moderate dementia.[227, 231] It has also been shown to increase VA in older institutionalized individuals with more advanced dementia.[230] Furthermore, optimizing ocular refraction has been shown to increase VA, improve quality of life and reduce symptoms of depression in older institutionalized individuals with mild to moderate dementia.[233] It has also been shown to increase VA in those with more advanced dementia.[44]

Hence, there is enough evidence for the clinician to confidently indicate to the patient with dementia, their family or guardian, that optimizing ocular refraction or undergoing cataract surgery should improve VA, as is the case for an older person without dementia. There is also enough evidence to inform them that the quality of life of the older individual with mild to moderate dementia should improve. However, evidence is still lacking for indicating that these interventions will improve the quality of life for those affected with more advanced dementia. This certainly should not prevent the clinician from offering an intervention for cataract surgery in advanced dementia, but the risks *vs* benefits to go ahead with the surgery should be well weighed and explained and the final decision taken together with the patient, the family or guardian, the ophthalmologist, the anesthesiologist and the physician caring for this patient. Global peri-surgical care adapted for an older frail population should then be provided.

Optimizing ocular refraction for improving VA in more advanced dementia is a different issue and should not provide too much difficulty, even if evidence for improvement in quality of life or other modalities (eg. social isolation, falls) is lacking. It is not as such an invasive intervention, and this treatment modality is generally well accepted. The clinician can usually base his/her decision to prescribe or modify a prescription based on criteria similar to those used for other frail older individuals, which include special considerations to the amount of dioptric change and the type of corrective lenses that will be prescribed, in view of the risk of falls that is highly prevalent in that population.[248] Falls are effectively a major health problem, knowing that 30% of older individuals 65 yrs of age and older fall at least once a year[249] and that this proportion increases to 48% in those 85 yrs and older living at home.[250] The incidence rates of falls for older persons are greater in nursing homes and hospitals compared to those living in the community.[251] It is also known that 5% of older individuals who fall need to be hospitalized.[252] Additionally, falls leading to trauma represent 10 to 15% of admissions in geriatric evaluation units.[253] Studies further indicate that falls are more prevalent in older individuals having visual impairment.[254] Unfortunately, vision remains overlooked in the global evaluation of older individuals hospitalized following a fall.[255]

No studies have investigated specifically the appropriateness of the degree of dioptric change or type of ophthalmic lenses required for older individuals with dementia. Until these studies are performed, it seems reasonable to apply current evidence-based practice developed for frail older individuals to those affected by dementia. One of the most important issues is to ensure that the person wearing the lenses will be able not only to see well at far and near distance, but will also function optimally and in a secure fashion on a daily basis and for all activities requiring mobility if the person is ambulatory. Elliott[256] has provided a comprehensive overview dealing with that issue for the frail older population, with or without visual impairment, including the difficulties these individuals face when navigating within their environment. He has conducted several studies aimed at understanding the effect of various prescription lenses and their magnification effects on falls, gait and postural control in that population. From his own studies as well as several randomized control trials, he proposes recommendations on

how to prescribe lenses to adjust vision while maintaining safety in frail older individuals at risk of falls. First, the case history should be adapted to identify older individuals at risk of falls; second, changes in an ophthalmic correction should be conservative to avoid magnification effects, distortion or imbalance between the two eyes; third, a change in the type of lenses should not be implemented if the individual is well adapted to the one currently being worn, and fourth, progressive or bifocal lenses should not be offered to those at risk of falls who are used to wearing single vision glasses. In this last instance, it is worth considering prescribing two pairs of glasses, for far and near distance, while ensuring their appropriate identification and use.

A different set of recommendations have been made by Koch et al.[38] to prevent uncorrected VA for nursing home residents with dementia. They recommended to: 1) label eyewear to provide rapid identification of glasses in case of loss or misplacement, 2) provide a second pair of glasses in case they are lost or broken, and 3) ensure that residents receive an eye examintion every one or two years. More recently, Kergoat et al.[257] complemented these with additional recommendations for older institutionalized individuals, such as: 1) ensuring that the proper lens prescription be worn for the proper viewing distance, 2) a sitting position and adequate level of illumination for activities such as reading and television, 3) the regular cleaning of ophthalmic lenses for residents, 4) taking a picture of the glasses as well as the individual while wearing the glasses to place in the clinical file, and 5) an analysis of each resident's prescription glasses and the writing of the prescription and type of lenses (single vision, type of bifocal/multifocal lenses) in the file. For those having visual impairment, they also suggested that adaptations be made, such as keeping objects in the same place within the room, removing obstacles that can impair safe navigation, optimizing illumination and contrast in the room, corridor and for the various activities, minimizing glare, introducing oneself to the resident and explaining the reason of the visit and activities/care to take place. These recommendations and adaptations are particularly important for a person affected by dual visual and cognitive deficiency, since having both deficits can put the individual at increased risk of negative consequences.[258] Not seeing well (vision deficiency) and not being able to judge appropriately the environment (cognitive deficiency) can place these

individuals at more risk, such as being lost in time and space, being socially isolated, or experiencing a sense of insecurity. It is important to remember that the primary objective of care for individuals with dementia is to preserve and promote their quality of life.[259] It is known that optimizing vision contributes to increasing quality of life, and although a person with advanced dementia might not be able to pursue certain activities such as reading, they certainly can benefit from others such as socializing, interacting with relatives, recognizing faces, looking at family pictures, all of which are facilitated by adequate vision.

Eye care for older individuals with cognitive impairment

As mentioned earlier, there is an aging of the population[260,261] that will accelerate in the coming years,[260] the prevalence of dementia is higher in the "oldest old", i.e. those 85 yrs of age or older[16] and additionally, more than 50% of people having dementia remain undiagnosed worldwide.[262] It is therefore reasonable to anticipate that many of the older individuals consulting for eye care will have undiagnosed cognitive deficits or even dementia. Eye care professionals should be aware of these statistics, as well as the pivotal role they can play in helping these individuals, since a large proportion of people who consult them on a regular basis are those 65 yrs of age or older[1,263] Furthermore, visually related symptoms such as difficulty in reading, not recognizing familiar objects, spatio-temporal disorientation, may develop early on in people with dementia[264,265] which may entice them to consult an eye doctor rather than a medical doctor.

As reviewed in this paper, there is a rapidly growing number of studies reporting oculovisual changes in individuals with dementia. Although some of these reports suggest that the data could potentially serve as biomarkers for dementia, the strength of the evidence is not sufficient as of now for any single test to serve as early diagnosis of the disease during the clinical eye examination. In fact, very promising biomarkers for the early diagnosis of various types of dementias have been studied intensively worldwide in several research areas for years but have not yet permeated the primary-care medical clinical environment for many scientific, financial and ethical reasons.[266-270]

In spite of that, eye care clinicians can certainly keep in mind the numerous results that have emerged in the field of vision research in the day-to-day evaluation of older individuals presenting in their office. Case history, VA, colour vision, stereoacuity, visual fields, pupillary function, ocular motilities, evaluation of the anterior and posterior segments of the eye, and even imaging of the ocular structures are performed routinely during an eye examination. The eye doctor can certainly add key questions in the case history to see if a person has difficulty reading such as losing their place, problems with orientation in time and space, difficulty naming or recognizing familiar objects, bumping into objects, VH, etc. At the outcome of the examination, the clinician will be able to judge if any reported symptoms are difficult to match with the results of the eye examination. During the VA testing, can the person easily read the letters in a fluent fashion, are the instructions easy to follow, is the person always starting over and over from the top of the chart when prompted to read the smaller letters, is it taking much longer to read the letters compared to others in the same age-group. Can the person name easily the numbers on the colour plates, if not, can they easily match the coloured capsules on a D15 test. When performing the ocular motilities, are the pursuits smooth or saccadic, when doing saccades are the eyes right on target or always erratic, is fixation easy and sustained. In the evaluation of the fundus, is there a thinning of the RNFL, is the optic nerve head suspicious. In the end, it may not be a single test that can make the clinician suspicious, but rather the way in which the older person perfoms at the various tests, any change in behavior of a person already known to the eye doctor compared to previous visits at the office, as well as the overall performance where test results do not match between themselves and/or with the reported symptoms. When in doubt, the clinician may ask additional open questions allowing the person to voice any concerns with their health, the person can be scheduled for a follow-up evaluation or can also be advised to see his/her family doctor for further investigations. Some studies have even evaluated the possibility of screening for cognitive function in the ophthalmology clinic.[237,245] Additional research is needed to evaluate the ability of such screening to correctly detect older individuals who will in fact be identified as having a cognitive deficit or dementia at the outcome of the medical investigation. If studies demonstrate that this type of screening is effective, then clinicians will have to secure appropriate

mechanisms to ensure access to medical evaluation for individuals testing positive, before using such tests in their office. Ophthalmologists and optometrists see a large proportion of individuals 65 yrs of age or older in consultation[1,263] and they could play a role in helping detect cognitive deficits in the older population. The eye care clinical setting seems particularly adequate for that purpose considering the visual-type symptoms expressed by individuals with cognitive deficits, as well as the large amount of research results linking various aspects of the visual system to dementia. Clinicians trained in the administration and interpretation of these tests could easily screen older individuals for cognitive function with simple validated questions, a short version of the MMSE or the Mini-Cog for example.

The eye examination offered to older individuals residing in nursing homes is a different issue. Here, the cognitive deficit or the diagnosis of dementia is usually known, and dementia is often the reason why a person is being institutionalized.[272] There is also very good agreement in the scientific literature that the prevalence of uncorrected refractive errors and ocular pathology is high and higher than in the community and that eye care services to these residents are not optimal.[237,273] The role of the eye care professional is to provide access to the eye examination, adapt the eye examination to maximize the information obtained while minimizing fatigue, counsel the resident, family, guardian, regarding any diagnosis or treatment, help other health care professionals when differential diagnoses are needed, as well as counsel the nursing home personnel on how to adjust their care and the environment to help the resident whenever a visual impairment is present. Performing an eye examination for residents with mild to moderate dementia does not usually present any major difficulty. It might simply require more time and the instructions need to be provided clearly, in short sentences that are not overcrowded with too many levels of decision-making processes. Additionally, since divided attention is already problematic with aging, the eye examination should be conducted in a calm environment and each step of a different test explained separately. Residents with more advanced dementia, on the other hand, may render the eye examination more challenging in terms of communication and collaboration. Minimally, however, an evaluation of the VA, the ocular refraction and the ocular health should be

provided and vision should be optimized, as much as possible.[44] The examination room has to be physically adapted to accommodate any type of wheelchair and/or bedchair, the ophthalmic chair should ideally be on a sliding platform to be replaced by the wheelchair if required, and each diagnostic instrument chosen to ease access to the patient's eyes, portability being very important. Although for some residents it might not be possible to do any test, it is usually possible to do an eye examination or at least part of it on the majority of residents.[44]

Discussion and conclusion

As reviewed here, dementia has been associated with a variety of visual problems including defects in primary vision such as VA, colour vision, visual fields, eye movements, and more complex aspects of vision such as in reading ability and visuospatial function. VA is not always easy to measure in dementia, especially in the advanced stages, and some studies have indicated that it was impaired in the later stages of the disease. Alternatively, it might also be that we do not have the right tool to measure VA in a person with severe dementia not able to offer sufficient collaboration to perform the test. Defects in pupillary function and in saccadic and smooth pursuit eye movements, are also common in different dementias. In AD, deficits in colour vision, CSF, stereoacuity, backwards masking, reading, and object recognition have been documented, although some results remain controversial. Defects in motion detection, visual fields, CFFF, ERG and VEP have also been reported in AD, but require further study. Visual dysfunction in VD may be very similar to that in AD with the possible exceptions that stereoacuity deficit might be greater and performance on event-related potential tasks poorer than in AD. In FTD, problems involving saccadic eye movement, mutual gaze, and in facial recognition may be especially common. DLB and PDD are both characterized by prominent VH, eye movement problems, and difficulty with visuospatial orientation. When VH are present however, it is important to eliminate 'Charles Bonnet syndrome', and if no diagnosis of this disorder is made, to refer the patient for further investigation.[274,275] Pathological changes have also been reported to affect the retina, optic nerve, and visual areas of the brain in dementia. Many of these oculovisual changes occur across dementias, are controversial, and often based on limited numbers of subjects

and no single oculovisual feature can be regarded as diagnostic of any specific dementia. Nevertheless, VH may be more characteristic of DLB and PDD than AD or FTD and variation in saccadic eye movements may help to distinguish between parkinsonian syndromes and AD from FTD.

Although the oculovisual symptoms summarized above might be quite variable across individuals, although the literature still has many gaps and is often controversial with different studies reporting conflicting conclusions, although individual tests are not specific to particular dementias and cannot really identify individual disorders, and although laboratory-based tests used to investigate vision in dementia do not always translate easily to clinical testing in practice, there is ample evidence in the literature to conclude that vision is affected in dementia. Additional research will need to address the discrepancies reported in the literature in order to provide a clearer picture of the changes affecting the oculovisual system in the various dementias. Research into potential oculovisual biomarkers of various types of dementia should also be pursued, in trying to help with early diagnosis. Finally, research is also needed to continue addressing clinical issues that will help improve the care provided to older individuals affected by dementia.

In conclusion, dementia is a neurodegenerative disease whose prevalence will continue to increase in the next decades along with the aging of the population. The disease is associated with a variety of oculovisual problems for which affected individuals will likely seek eye care services. Eye care professionals will need to keep well informed of the growing literature in the area, be attentive to signs and symptoms that might alert them to potential cognitive impairment, and be able to adapt their practice and clinical interventions to best serve patients with dementia.

References

1. Kergoat H, Leat SJ, Faucher C *et al.* Primary eye care services offered to older adults. *Eur Geriatr Med.* In Press.
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-V). American Psychiatric Association, 2013.
3. Armstrong RA. Alzheimer's disease and the eye. *J Optom* 2009; 2: 103-111.
4. Lewis H, Beher D, Cookson N, *et al*. Quantification of Alzheimer pathology in ageing and dementia: age-related accumulation of amyloid beta (42) peptide in vascular dementia. *Neuropathol Appl Neurobiol* 2006; 32: 103-118.
5. Armstrong RA. Visual signs and symptoms of dementia with Lewy bodies. *Clin Exp Optom* 2012; 95: 621-630.
6. Armstrong RA, Ellis W, Hamilton RL *et al*. Neuropathological heterogeneity in frontotemporal lobar degeneration with TDP-43 proteinopathy: a quantitative study of 94 cases using principal components analysis. *J Neural Transm* 2010; 117: 227-239.
7. Armstrong RA. Visual signs and symptoms of Parkinson's disease. *Clin Exp Optom* 2008; 91: 129-138.
8. Armstrong RA, Kotzbauer PT, Perlmutter JS, *et al*. A quantitative study of a-synuclein pathology in fifteen cases of dementia associated with Parkinson's disease. *J Neural Transm* 2014; 121: 171-181.
9. Armstrong RA. Creutzfeldt-Jakob disease and vision. *Clin Exp Optom* 2004; 89: 3-11.
10. Harvey AM, Bordley J & Barondess JA. Differential Diagnosis: The Interpretation of Clinical Evidence. Third Ed., Saunders, Philadelphia, London, Toronto, 1979.
11. Snowden J, Neary D & Mann D. Frontotemporal lobar degeneration: clinical and pathological relationships. *Acta Neuropathol* 2007; 114: 31-38.
12. Cairns NJ, Bigio EH, Mackenzie IRA *et al*. Neuropathologic diagnostic and nosological criteria for frontotemporal lobar degeneration: consensus of the Consortium for Frontotemporal Lobar Degeneration. *Acta Neuropathol* 2007; 114: 5-22.

13. Armstrong RA & Syed AB. Alzheimer's disease and the eye. *Opthal Physiol Opt (Suppl 1)* 1996; 16: S2-S8.
14. Armstrong RA. Corticobasal degeneration and dementia. In: *Diet and Nutrition in Dementia and Cognitive Decline*. Ed: CR Martin and VR Preedy, Elsevier Inc., pp 35-43, 2015.
15. Armstrong RA. Visual signs and symptoms of progressive supranuclear palsy. *Clin Exp Optom* 2011; 94; 150-160.
16. Ferri CP, Prince M, Brayne C, *et al*. Global prevalence of dementia: a Delphi consensus study. *Lancet* 2005; 366: 2112-2117.
17. Lobo A, Launer LJ, Fratiglioni L, Andersen K, de Carlo A & Breteler MM. Prevalence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. *Neurology* 2000; 54: S4-S9.
18. Fratiglioni L, Launer LJ, Andersen K, Breteler MM, Copeland JR & Dartigues JF. Incidence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. *Neurology* 2000; 54:S10-S15.
19. Evans DA, Funkenstein H, Abert MS *et al*. Prevalence of Alzheimer's disease in a community of older persons - higher than previously reported. *J Am Med Assoc* 1989; 262: 2551-2556.
20. Knopman DS. An overview of common non-Alzheimer dementias. *Clin Geriatr Med* 2001; 17: 281.
21. Dickson DW. Neuropathology of Alzheimer's disease and other dementias. *Clinics in Ger Med* 2001; **17**: 209
22. Tierney MC, Fisher RH, Lewis AJ *et al*. The NINCDS-ADRDA work group criteria for the clinical diagnosis of probable Alzheimer's disease. *Neurology* 1988; 38: 359-364.
23. Jellinger KA & Bancher C. Neuropathology of Alzheimer's disease: a critical update. *J Neural Transm* 1998; 54: 77-95.
24. McKeith IG, Galasko D, Kosaka K *et al*. Consensus guidelines for the clinical and pathological diagnosis of dementia with Lewy bodies (DLB): Report of the consortium on DLB international workshop. *Neurology* 1996; 47: 1113-1124.

25. Armstrong RA, Lantos PL & Cairns NJ. What determines the molecular composition of abnormal protein aggregates in neurodegenerative disease? *Neuropathology* 2008; 28: 351-365.
26. Imhof A, Kovari E, von Gunten A *et al*. Morphological substrates of cognitive decline in nonagenarians and centenarians: A new paradigm? *J Neurol Sci* 2007; 257: 72-79.
27. Brun A. An overview of light and electron microscope changes. In: Reisberg B, editor. Alzheimer's disease: The Standard Reference. London and New York: MacMillan, 1983: 37-45.
28. Khatchaturian ZS. Diagnosis of Alzheimer's disease. *Arch Neurol* 1985; 42: 1097-1005.
29. Mirra SS, Heyman A, McKeel, D *et al*. The consortium to establish a registry for Alzheimer's disease (CERAD). Part II Standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology* 1991; 41: 479-486.
30. Glenner GG & Wong CW. Alzheimer's disease and Down's syndrome: sharing of a unique cerebrovascular amyloid fibril protein. *Biochem Biophys Res Comm* 1984; 122: 1131-1135.
31. Schneider JA, Gearing M, Roblins RS, DeLaune W & Mirra SS. Apolipoprotein E genotype in diverse neurodegenerative disorders. *Ann Neurol* 1995; 38: 131-135.
32. Armstrong RA, Cairns NJ & Lantos PJ. Beta-amyloid deposition in the temporal lobe of patients with dementia with Lewy bodies: Comparison with non-demented cases and Alzheimer's disease. *Dementia* 2000; 11: 187-192.
33. Spillantini MG, Tolnay M, Love S & Goedert M. Microtubule-associated protein tau, heparin sulphate and alpha-synuclein in several neurodegenerative diseases with dementia. *Acta Neuropathol* 1999; 97: 585-594.
34. Goedert M, Clavaguera F & Tolnay M. The propagation of prion-like protein inclusions in neurodegenerative diseases. *Trends Neurosci* 2010; 33: 317-325.
35. Steiner JA, Angot E, Brunden P. A deadly spread: cellular mechanisms of a-synuclein transfer. *Cell Death Differ* 2011; 18: 1425-1433.

36. Armstrong RA & Cairns NJ. Different molecular pathologies result in similar spatial patterns of cellular inclusions in neurodegenerative disease: a comparative study of eight disorders. *J Neural Transm* 2012; 119: 1551-1560.
37. Caselli RJ. Visual syndromes as the presenting feature of degenerative brain disease. *Semin Neurol* 2000; 20: 139-144.
38. Koch JM, Datta G, Makdoom S & Grossberg, GT. Unmet visual needs of Alzheimer's disease patients in long-term care facilities. *J Am Med Dir Assoc* 2005; 6: 233-237.
39. Marx MS, Werner P, Cohen-Mansfield J, Hartmann EE. Visual acuity estimates in noncommunicative elderly persons. Invest Ophthalmol Vis Sci 1990;31:593-6.
40. Uhlmann RF, Larson EB, Koepsell TD, Rees TS & Duckert LG. Visual impairment and cognitive dysfunction in Alzheimer's disease. *J Gen Intern Med* 1991; 6: 126-132.
41. Cronin-Golomb A, Corkin S, Rizzo JF *et al.* Visual dysfunction in Alzheimer's disease: relation to normal aging. *Ann Neurol* 1991; 29: 41-52.
42. Rizzo M, Anderson SW, Dawson J & Nawrot M. Vision and cognition in Alzheimer's disease. *Neuropsychologia* 2000;38:1157-1169.
43. Friedman DS, Munoz B, Massy RW, Bandeen-Roche K & West SK. Grating visual acuity using the preferential-looking method in elderly nursing home residents. *Invest Ophthamol Vis Sci* 2002; 43: 2572-2578.
44. Carcenac G, Hérard MÈ, Kergoat MJ *et al.* Assessment of visual function in institutionalized elderly patients. *J Am Med Dir Assoc* 2009;10:45-49.
45. Ciocler Froiman P, Dantas PEC. Assessment of visual acuity in patients with dementia using teller acuity cards. *Strabismus* 2013; 21: 93-97.
46. Chriqui E, Kergoat MJ, Champoux N, Leclerc BS & Kergoat H. Visual acuity in institutionalized seniors with moderate to severe dementia. *J Am Med Dir Assoc* 2013;14:275-279.
47. Cogan DG. Alzheimer syndromes. *Am J Ophthalmol* 1987; 104: 183-184.
48. Mendez MF, Tomsak RL & Remler B. Disorders of the visual system in Alzheimer's disease. *J Clin Neuroophthalmol* 1990;10:62-69.

49. Wijk H, Berg S, Bergman B, Hanson AB, Sivik L & Steen B. Colour perception among the very elderly related to visual and cognitive function. *Scan J Care Sci* 2002; 16: 91-102.
50. Bassi CJ, Solomon K, Young D. Vision in aging and dementia. *Optom Vis Sci* 1993; 70: 809-813.
51. Wood S, Mortel KF, Hiscock M, Bretmeyer BG & Caroselli JS. Adaptive and maladaptive utilization of color cues by patients with mild to moderate Alzheimer's disease. *Arch Clin Neuropsychol* 1997; 12: 483-489.
52. Pache M, Smeets CHW, Gasio PF, *et al*. Colour vision deficiencies in Alzheimer's disease. *Age and Ageing* 2003; 32: 422-426.
53. Postuma RB, Gagnon JF, Vendette M, Desjardins C & Montplaisir JY. Olfaction and color vision identify impending neurodegeneration in rapid eye movement sleep disorder. *Ann Neurol* 2011; 69: 811-818.
54. Kiyosawa M, Bosley TM, Chawluk J *et al*. Alzheimer's disease with prominent visual symptoms; clinical and metabolic evaluation. *Ophthalmology* 1989; 96: 1077-1085.
55. Thiyagesh SN, Farrow TF, Parks RW *et al*. The neural basis of visuospatial perception in Alzheimer's disease and healthy elderly comparison subjects: An fMRI study. *Psychol Res: Neuroimaging* 2009; 172: 109-116.
56. Mittenberg W, Choi EJ & Apple CC. Stereoscopic visual impairment in vascular dementia. *Arch Clin Neuropsychol* 2000; 15: 561-569.
57. Rizzo M, Nawrot M. Perception of movement and shape in Alzheimer's disease. *Brain* 1998; 121: 2259-2270.
58. Schlotterer G, Mosovitch M, Crapper-McLachlan D. Visual processing deficits as assessed by spatial frequency contrast sensitivity and backward masking in normal ageing and Alzheimer's disease. *Brain* 1984; 107: 309-325.
59. Nissen MJ, Corkin S, Buoanno FJ, Growden JH, Wray SH & Baver J. Spatial vision in Alzheimer's disease; general findings and a case report. *Arch Neurol* 1985; 42: 667-671.

60. Crow RW, Levin LB, LaBree L, Rubin R & Feldon SE. Sweep visual evoked potential evaluation of contrast sensitivity in Alzheimer's dementia. *Invest Opth Vis Sci* 2003; 44: 875-878.
61. Neargarder SA, Stone ER, Cronin-Golomb A & Oriss S. The impact of acuity on performance of four clinical measures of contrast sensitivity in Alzheimer's disease. *J Gerontol Series B* 2003; 58: P54-P62.
62. Lakshminarayanan V, Lagrane J, Kean ML, Dick M & Shankle R. Vision in dementia: contrast effects. *Neurol Res* 1996; 18: 9-15.
63. Risacher SL, WuDunn D, Pepin SM, *et al*. Visual contrast sensitivity in Alzheimer's disease, mild cognitive impairment, and older adults with cognitive complaints. *Neurobiol Aging* 2013; 34: 1133-1144.
64. Gilmore GC, Cronin-Golomb A, Neargarder SA, & Morrision SR. Enhanced stimulus contrast normalizes visual processing of rapidly presented letters in Alzheimer's disease. *Vision Research* 2005; 45: 1013-1020.
65. Gilmore GC, Thomas CW, Klitz T, Persanyi M, Tomsak R. Contrast enhancement eliminates letter identification speed deficits in Alzheimer's disease. *J Clin Geropsychol* 1996;2:307-320.
66. Trick GL, Silverman SE. Visual sensitivity to motion: age-related changes and deficits in senile dementia of the Alzheimer type. *Neurology* 1991;41:1437-1440.
67. Silverman SE, Tran DB, Zimmerman KM & Feldon SE. Dissociation between the detection and perception of motion in Alzheimer's disease. *Neurology* 1994;44:1814-1818.
68. Duffy CJ, Tetewsky SJ, O'Brien H. Cortical motion blindness in visuaospatial AD. *Neurobiol Aging* 2000;21:867-869.
69. Rizzo M, McGehee DV, Dawson JD & Anderson SN. Simulated car crashes at intersections in drivers with Alzheimer's disease. *Alz Dis Assoc Dis* 2001; 15: 10-20.
70. Uc EY, Rizzo M, Anderson SW, Shi Q & Dawson JD. Unsafe rear-end collision avoidance in Alzheimer's disease. *J Neurol Sci* 2006; 251: 35-43.
71. Curran S & Wattis JP. Critical flicker fusion threshold: A useful research tool in patients with Alzheimer's disease. *Hum Psychopharm Clin Exp* 1998; 13: 337-355.

72. Curran S, Wattis J. Critical flicker fusion threshold: a potentially useful measure for the early detection of Alzheimer's disease. *Hum Psychopharmacol* 2000;15:103-112.
73. Curran S, Wattis JP & Hindmarch I. Concurrent validity of critical flicker fusion in patients with primary degenerative dementia of the Alzheimer type. *Int J Ger Psychiatr* 1992; 7: 573-578.
74. Mentis MJ, Alexander GE, Krasuski, J *et al*. Increasing required neural response to expose abnormal brain function in mild versus moderate or severe Alzheimer's disease: PET study using parametric visual stimulation. *Am J Psychiatr* 1998; 155: 785-794.
75. Curran S, Wilson S, Musa S, Wattis J. Critical flicker fusion threshold in patients with Alzheimer's disease and vascular dementia. *Int J Geriatr Psychiatry* 2004;19:575-581.
76. Schlapfer TE, Groner M, Lavoyer E & Fisch HU. Visual masking: A reliable measure for the assessment of cognitive dysfunction in the elderly. *J Gerontol* 1991: 46: P157-P161.
77. Davis C, Kim J. What's in a mask? Information masking with forward and backward visual masks. *Q J Exp Psychol (Hove)* 2011;64:1990-2002.
78. Mendola JD, Cronin-Golomb A, Corkin S & Growdon JH. Prevalence of visual deficits in Alzheimer's disease. *Optom Vis Sci* 1995; 72: 155-167.
79. Muller G, Weisbrod S & Klingberg F. Different influence of backward-masking on visual-pattern recognition in the early stages of presenile-dementia and normal aging. *Int J Geriatr Psych* 1992; 7: 419-426.
80. Rizzo JF, Cronin-Golomb A, Growdon JH, *et al*. Retonocalcarine function in Alzheimer's disease: A clinical and electrophysiological study. *Arch Neurol* 1992; 49: 93-101.
81. Crutch SJ & Warrington EK. Foveal crowding in posterior cortical atrophy: A specific early-visual-processing deficit affecting word reading. *Cog Neuropsychol* 2007; 24: 843-866.
82. Trick GL, Trick LR, Morris P & Wolf M. Visual field loss in senile dementia of the Alzheimer's type. *Neurology* 1995; 45: 68-74.

83. Armstrong RA. Visual field defects in Alzheimer's disease patients may reflect differential pathology in primary visual cortex. *Optometry Vis Sci* 1996; 73: 677-682.
84. Valenti DA. Alzheimer's disease: screening biomarkers using frequency doubling technology visual field. *ISRN Neurology* 2013; 989583.
85. Ishii K, Yamazi S, Kitagaki H, Imamura T, Hirono N & Mori, E. Regional cerebral blood flow difference between dementia with Lewy bodies and Alzheimer's disease. *Neurology* 1999; 53: 413-416.
86. Lobotesis K, Fenwick JD, Phipps A *et al*. Occipital hypoperfusion on SPECT in dementia with Lewy bodies but not Alzheimer's disease. *Neurology* 2001; 56: 643-649.
87. Minoshima S, Foster NL, Sima AAF, Frey KA, Abin RL & Kuhl DE. Alzheimer's disease versus dementia with Lewy bodies: cerebral metabolic distinction with autopsy confirmation. *Ann Neurol* 2001; 50: 358-365.
88. Bashir K, Elbe RJ, Ghabrial M & Struble RG. Hemianopsia in dementia with Lewy bodies. *Arch Neurol* 1998; 55: 1132-1135.
89. Scinto LFM, Daffner KR, Dressler D *et al*. Potential non-invasive neurobiological test for Alzheimer's disease. *Science* 1994; 266: 1051-1054.
90. Arai H, Terajima M, Nakagawa T *et al.* Pupil dilatation assay by tropicamide is modulated by apolipoprotein E ´4 allele dosage in Alzheimer's disease. *Clin Neurosci Neuropathol* 1996;7:918-920.
91. Gomez-Tortosa E, del Barrio A, Jimenez-Alfaro I. Pupil response to tropicamide in Alzheimer's disease and other neurodegenerative disorders. *Acta Neurol Scand* 1996;94:104–109.
92. Ferrario E, Molaschi M, Villa L, *et al.* Is videopupillography useful in the diagnosis of Alzheimer's disease? *Neurology* 1998;50;642-644.
93. Caputo L, Casartelli M, Perrone C, Santori M, Annoni G & Vergaini C. The 'eye-test' in recognition of late-onset Alzheimer's disease. *Arch Gerontol Geriat* 1998; 27: 171-177.

94. Hou RH, Samuels ER, Raisi M, Langley RW, Szabadi E & Bradshaw CM. Why patients with Alzheimer's disease may show increased sensitivity to tropicamide eye drops: role of locus coeruleus. *Psychopharmacology* 2006; 184: 95-106.
95. Hanyu H, Hirao K, Shimizu S, Kanetaka H, Sakurai H & Iwamoto T. Phenylephrine and pilocarpine eye drop test for dementia with Lewy bodies and Alzheimer's disease. *Neurosci Lett* 2007; 414: 174-177.
96. Tales A, Troscianko T, Lush D, Haworth J, Wilcock GK & Butler SR. The pupillary light reflex in aging and Alzheimer's disease. *Aging Clin Exp Res* 2001; 13: 473-478.
97. Fletcher WA, Sharpe JA. Saccadic eye movement dysfunction in Alzheimer's disease. *Ann Neurol* 1986;20:464-471.
98. Pelak VS. Ocular motility of aging and dementia. *Curr Neurol Neurosci* 2010; 10: 440-447.
99. Chang LY, Lowe J, Ardiles A *et al*. Alzheimer's disease in the human eye: Clinical tests that identify ocular and visual information processing deficit as biomarkers. *Alz Dement* 2014; 10: 251-261.
100. Bylsma FW, Rasmusson D, Rebok GW, Keyl PM, Tune L & Brandt J. Changes in visual fixation and saccadic eye movements in Alzheimer's disease. *Int J Psychophysiol* 1995; 19: 33-40.
101. Tsekov R & Mullan M. Vision function abnormalities in Alzheimer's disease. *Surv Ophthalmol* 2013; 59: 414-433.
102. Yang Q, Wang T, Su N, Xiao S & Kapoula Z. Specific saccade deficits in patients with Alzheimer's disease at mid to moderate stage and in patients with amnestic cognitive impairment. *Age* 2013; 35: 1287-1298.
103. Sadun AA, Borchert M, DeVita E, Hinton DR & Bassi CJ. Assessment of visual impairment in patients with Alzheimer's disease. *Am J Ophthalmol* 1987; 104: 113-120.
104. Rosler A, Billino J, Muller NG, Weidauer S, Steinmetz H & Kleinschmidt A. Visual search in patients with subcortical vascular dementia: Short fixations but long reaction times. *Dement Geriatr Cogn Dis* 2005; 20: 375-380.

105. Zaccara G, Gangemi PF, Muscas GC *et al*. Smooth-pursuit eye movements: alterations in Alzheimer's disease. *J Neurol Sci* 1992; 112: 81-89.
106. Fletcher WA & Sharpe JA. Smooth pursuit dysfunction in Alzheimer's disease. *Neurology* 1988; 38: 272-277.
107. Boxer AL, Garbutt S, Rankin KP *et al*. Medial versus lateral frontal lobe contributions to voluntary saccade control as revealed by the study of patients with frontal lobe degeneration. *J Neurosci* 2006; 26: 6354-6363.
108. Burrell JR, Hornberger M, Carpenter RHS, Kiernan MC & Hodges JR. Saccadic abnormalities in frontotemporal dementia. *Neurology* 2012; 78: 1816-1823.
109. Boxer AL, Garbutt S, Seeley WW *et al*. Sacccade abnormalities in autopsy-conformed frontotemporal lobar degeneration and Alzheimer's disease. *Arch Neurol* 2012, 69: 509-517.
110. Moon SY, Lee BH, Seo SW, Kang SJ & Na DL. Slow vertical saccades in the frontotemporal dementia with motor neuron disease. *J Neurol* 2008; 255: 1337-1343.
111. Garbutt S, Matlin A, Hellmuth J *et al*. Oculomotor function in frontotemporal lobar degeneration, related disorders and Alzheimer's disease. *Brain* 2008; 131: 1268-1281.
112. Sturm VE, McCarthy ME, Yun I *et al*. Mutual gaze in Alzheimer's disease, frontotemporal and semantic dementia couples. *Soc Cog Aff Neurosci* 2011; 6: 359-367.
113. Coppe S, de Xivry JJO, Yuksel D, Ivanolu A & Lefevre P. Dramatic impairment of prediction due to frontal lobe degeneration. *J Neurophysiol* 2012; 108: 2957-2966.
114. Mosimann UP, Muri RM, Burn DJ, Felblinger J, O'Brien JT & McKeith IG. Saccadic eye movement changes in Parkinson's disease dementia and dementia with Lewy bodies. *Brain* 2005; 128: 1267-1276.
115. de Bruin VM, Lees AJ & Daniel SE. Diffuse Lewy body disease presenting with supranuclear gaze palsy, Parkinsonism and dementia: a case report. *Movement Disord* 1992; 7: 355-358.

116. Fearnley JM, Revesz T, Brooks DJ, Frackowiak RS & Lees AJ. Diffuse Lewy body disease presenting with a supranuclear gaze palsy. *J Neurol Neurosurg Psychiatr* 1991; 54: 159-161.
117. Brett FM, Henson C & Staunton H. Familial diffuse Lewy body disease, eye movements, eye movement abnormalities and distribution of pathology. *Arch Neurol* 2002; 59: 464-467.
118. Lindau M, Jelic V, Johansson SE, Andersen C, Wahlund LO & Almkvist O. Quantitative EEG abnormalities and cognitive dysfunctions in frontotemporal dementia and Alzheimer's disease. *Dement Geriatr Cogn Dis* 2003; 15: 106-114.
119. Lou WT, Xu J, Sheng HS & Zhao SZ. Multichannel linear descriptor analysis for event-related EEG of vascular dementia patients during visual detection task. *Clin Neurophysiol* 2011; 122: 2151-2156.
120. Pugnetti L, Baglio F, Farina E *et al*. EEG evidence of posterior cortical disconnection in Parkinson's disease and related dementias. *Int J Neurosci* 2010; 120: 88-98.
121. Holder GE, Votruba M, Carter AC et al. Electrophysiological findings in dominant optic atrophy (DOA) linking to the OPA1 locus on chromosome 3q 28-qter. *Doc Ophthalmol* 1999;95:217-228.
122. Katz B, Rimmer S, Iragui V, Katzman R: Abnormal pattern electroretinogram in Alzheimer's disease: evidence for retinal ganglion cell degeneration? *Ann Neurol* 1989;26:221-225.
123. Trick GL, Barris MC & Bickler-Bluth M. Abnormal pattern electroretinogram in patients with senile dementia of the Alzheimer type. *Ann Neurol* 1989; 26: 226-231.
124. Parisi V, Restuccia R, Fattapposta F, Mina C, Bucci M & Pierelli F. Morphological and functional retinal impairment in Alzheimer's disease patients. *Clin Neurophysiol* 2001; 112: 1860-1867.
125. Krasodomska K, Lubiński W, Potemkowski A & Honczarenko K. Pattern electroretinogram (PERG) and pattern visual evoked potentials (PVEP) in the early stages of Alzheimer's disease. *Doc Ophthalmol* 2010; 121: 111-121.
126. Kergoat H, Kergoat MJ, Justino L *et al.* Visual retinocortical function in dementia of the Alzheimer type. *Gerontology* 2002; 48: 197-203.

127. Strenn K, Dalbianco P, Weghaupt H, Koch G, Vass C & Gottlob I. Pattern electroretinogram and luminance electroretinogram in Alzheimer's disease. *J Neural Transm* 1991; Suppl 33: 73-80.
128. Justino L, Kergoat MJ, Bergman H *et al.* Neuroretinal function is normal in early dementia of the Alzheimer type. *Neurobiol Aging* 2001;22:691-695.
129. Devos D, Tir M, Maurage CA, et al. ERG and anatomical abnormalities suggesting retinopathy in dementia with Lewy bodies. *Neurology* 2005; 65: 1107-1110.
130. Maurage CA, Ruchoux MM, de Vos R, Surguchov A & Destee A. Retinal involvement in dementia with Lewy bodies: A clue to hallucinations? *Ann Neurol* 2003; 54: 542-547.
131. Philpot MP, Amin D & Levy R. Visual evoked potentials in Alzheimer's disease: correlations with age and severity. *Electroen Clin Neurol* 1990; 77: 323-329.
132. Harding GFA, Wright CE & Orwin A. Primary presenile dementia: The use of the visual evoked potential as a diagnostic indicator. *Brit J Psychol* 1985; 147: 533-540.
133. O'Neil D, Rowan M, Abrahams D, Feely JB, Walsh JB & Coakley D. The flash visual evoked potential in Alzheimer type dementia. *Israel J Med Sci* 1989; 158: 158.
134. Bajalan AA, Wright CE & Van der Vliet VJ. Changes in the human visual evoked potential (VEP) caused by the anticholinergic agent hyoscine hydrobromide: Comparison with results in Alzheimer's disease. *J Neurol Neurosurg Psychiatr* 1986; 49: 175-182.
135. Coben LA, Danziger WL & Hughes CP. Visual evoked potentials in mild senile dementia of Alzheimer type. *Electroen Clin Neuro* 1983; 55: 121-130.
136. Kergoat H, Kergoat MJ, Justino L *et al.* Visual retinocortical function in dementia of the Alzheimer type. *Gerontology* 2002;48;197-203.
137. Polich J. Updating P300: An integrative theory of P3a and P3b. *Clin Neurophysiol* 2007;118:2128-2148.
138. Kurita A, Murakami M, Takagi S, Matsushima M & Suzuki M. Visual hallucinations and altered visual information processing in Parkinson disease and dementia with Lewy bodies. *Movement Disord* 2010; 25: 167-171.

139. Xu J, Sheng HS, Lou WT & Zhao SZ. Approximate entropy analysis of event-related potentials in patients with early vascular dementia. *J Clin Neurophysiol* 2012; 29: 230-236.
140. Glosser G, Baker KM, de Vries JJ, Alavi A, Grossman M & Clark CM. Disturbed visual processing contributes to impaired reading in Alzheimer's disease. *Neuropsychologia* 2002; 40: 902-909.
141. Fujimori M, Imamura T, Yamashita H, Hirono N & Mori E. The disturbances of object vision and spatial vision in Alzheimer's disease. *Dement Geriatr Cogn Dis* 1997; 8: 228-231.
142. Geldmacher DS. Visuospatial dysfunction in the neurodegenerative diseases. *Front Biosci* 2003; 8: E428-E436.
143. Cronin-Golomb A. Vision in Alzheimer's disease. Karger, Basel, 2004.
144. Nakano N, Hatakeyama Y, Fukatsu R *et al*. Eye-head coordination abnormalities and regional cerebral blood flow in Alzheimer's disease. *Prog Neuro-Psychopharm Biol Psychiatr* 1999; 23: 1053-1062.
145. Tales A, Butler S, Gilchrist I, Jones R & Troscianko T. Visual search in Alzheimer's disease: a deficiency in processing conjunctions of features. *Neuropsychologia* 2002; 40: 1849-1857.
146. Nguyen A, Chubb C & Huff F. Visual identification and spatial location in Alzheimer's disease. *Brain Cognition* 2003; 52: 155-166.
147. Hassing L & Backman L. Episodic memory functioning in population-based samples of very old adults with Alzheimer's disease and vascular dementia. *Dem Ger Cog Disord* 1997; 8: 376-383.
148. Nakachi R, Muramatsu T, Kato M *et al*. Progressive prosopagnosia at an early stage of frontotemporal lobar degeneration. *Psychogeriatrics* 2007; 7: 155-162.
149. Lee ACH, Levi N, Davies RR, Hodges JR & Graham KS. Differing profiles of face and scene discrimination deficits in semantic dementia and Alzheimer's disease. *Neuropsychologia* 2007; 45: 2135-2146.
150. Mendez MF & Perryman KM. Disrupted facial empathy in drawings from artists with frontotemporal dementia. *Neurocase* 2003; 9: 44-50.

151. Snowden JS, Thompson JC & Neary D. Knowledge of famous faces and names in semantic dementia. *Brain* 2004; 127; 860-872.
152. Mori E, Shimomura T, Fujimori M *et al*. Visuoperceptual impairment in dementia with Lewy bodies. *Arch Neurol* 2000; 57: 489-493.
153. Metzler-Baddeley C, Baddeley RJ, Lovell PG, Laffan A & Jones RW. Visual impairment in dementia with Lewy bodies and posterior cortical atrophy. *Neuropsychology* 2010; 24: 35-48.
154. Mondon K, Gochard A, Margue A *et al*. Visual recognition memory differentiates dementia with Lewy bodies and Parkinson's disease dementia. *J Neurol Neurosurg Psychiatr* 2007; 78: 738-741.
155. Ala TA, Hughes LF, Kyrouac GA, Ghobrial MW, & Elble RJ. Pentagon copying is more impaired in dementia with Lewy bodies than in Alzheimer's disease. *J Neurol Neurosurg Psychiatr* 2001; 70: 483-488.
156. Chow TW, Hynan LS & Lipton AM. MMSE scores decline at a greater rate in frontotemporal degeneration than in AD. *Dement Geriatr Cogn Dis* 2006, 22: 194-199.
157. Shinagawa S, Toyota Y, Ishikawa T *et al*. Cognitive function and psychiatric symptoms in early- and late-onset frontotemporal dementia. *Dement Geriatr Cogn Dis* 2008; 25: 439-444.
158. Fletcher WA. Ophthalmological aspects of Alzheimer's disease. *Curr Opin Ophthalmol* 1994; 5: 38-44.
159. Chapman FM, Dickinson J, McKeith I & Ballard C. Association among visual associations, visual acuity, and specific eye pathologies in Alzheimer's disease: Treatment implications. *Am J Psych* 1999; 156: 1983-1985.
160. Archibald NK, Clarke MP, Mosimann UP & Burn DJ. Visual symptoms in Parkinsons' disease and Parkinson's disease dementia. *Movement Disord* 2011; 26: 2387-2395.
161. Hely MA, Reid WG, Halliday GM *et al*. Diffuse Lewy body disease: clinical features in nine cases without coexistant Alzheimer's disease. *J Neurol Neurosurg Psychiatr* 1996; 60: 531-538.

162. Ebersbach G. Hallucinations and psychosis in Parkinson's disease: consequences for diagnosis and management. *Nervenheilkundt* 2008; 27: 709-716.
163. Tiraboschi P, Salmon DP, Hansen LA *et al.* What best differentiates Lewy body from Alzheimer's disease in early-stage dementia ? *Brain* 2006;129:729-735.
164. Yozhizawa H, Consattel JPG, Honig LS. Early neuropsychological discriminants for Lewy body disease: an autopsy series. *J Neurol Neurosurg Psychiatry* 2013;84:1326-1330.
165. Fenelon G, Mahieux F. Hallucinations and dementia: prevalence, clinical presentation and pathophysiology. *Rev Neurol* 2004; 160: S31-S43.
166. Kertesz A, Ang LC, Jesso S *et al*. Psychosis and hallucinations in frontotemporal dementia with the C9ORF72 mutation: A detailed clinical cohort. *Cogn Behav Neurol* 2013; 26: 146-154.
167. McKeith IG, Dickson DW, Lowe J *et al.* Diagnosis and management of dementia with Lewy bodies, Third report of the DLB consortium. *Neurology* 2005;65:1863-1872.
168. Hickey C, Chisholm T, Passmore MJ, O'Brien JD & Johnston J. Differentiating the dementias. Revisiting synucleinopathies and tauopathies. *Curr Alzheimer Res* 2008;5:52-60.
169. McKeith IG. Dementia with Lewy bodies. *Br J Psychiatry* 2002;180:144-147.
170. Perneczky R, Haussermann P, Diehl-Schmid J *et al*. Metabolic correlates of brain reserve power in dementia with Lewy bodies: An FDG PET study. *Dement Geriatr Cogn Dis* 2007; 23: 416-422.
171. Collerton D, Perry E. Thalmocortical dysfunction and complex visual hallucinations in brain disease: are the primary disturbances in the cerebral cortex? *Behav Brain Sci* 2004; 27: 789.
172. Harding AJ, Broe GA & Halliday GM. Visual hallucinations in Lewy body disease relate to Lewy bodies in the temporal lobe. *Brain* 2002; 125: 391-403.
173. Williams DR, Warren JD, Lees AJ. Using the presence of visual hallucinations to differentiate Parkinson's disease from atypical parkinsonism. *J Neurol Neurosurg Psychiatry* 2008;79:652-655.

174. Kaufer DI. Pharmacologic therapy of dementia with Lewy bodies. *J Geriatr Psych Neurol* 2002; 15: 224-232.
175. Manford M & Andermann F. Complex visual hallucinations: clinical and neurobiological insights. *Brain* 1998; 121: 1819-1840.
176. Santhouse AM, Howard RJ & ffytche DH. Visual hallucinatory syndromes and the anatomy of the visual brain. *Brain* 2000; 123: 2055-2064.
177. Holroyd S, Sheldon-Keller A. A study of visual hallucinations in Alzheimer's disease. *Am J Geriatr Psychiatry* 1995;3:198-205.
178. Chapman FM, Dickinson J, McKeith I & Ballard C. Association among visual hallucinations, visual acuity, and specific eye pathologies in Alzheimer's disease: Treatment implications. *Am J Psychiatry* 1999;156:1983-1985.
179. Murgatroyd C, Prettyman R. An investigation of visual hallucinosis and visual sensory status in dementia. *Int J Geriatr Psychiatry* 2001;16:709-713.
180. Pankow L, Pliskin N, Luchins D. An optical intervention for visual hallucinations associated with visual impairment and dementia in elderly patients. *J Neuropsych Clin Neurosciences* 1996;8:88-92.
181. Levine AM. Visual hallucinations and cataracts. *Ophthalmic Surg* 1980;11:95-98.
182. Goldstein L, Muffat J, Cherny R *et al*. Cytosolic b-amyloid deposition and supranuclear cataracts in lenses from people with Alzheimer's disease. *Lancet* 2003; 361: 1258-1265.
183. Kerbage C, Sadowsky CH, Jennings D, Cagle GD & Hartung PD. Alzheimer's disease diagnosis by detecting exogenous fluorescent signal of ligand bound to beta amyloid in the lens of the eye: an exploratory study. *Front Neurol* 2013; 4: 62.
184. Michael R, Otto C, Lenferink A, *et al*. Absence of amyloid-beta in lenses of Alzheimer's patients: A confocal Raman microspectroscopic study. *Exp Eye Res* 2014; 119: 44-53.
185. Simao LM. The contribution off optical coherence tomography in neurodegenerative diseases. *Curr Opin Ophthalmol* 2013; 24: 521-527.
186. Ikram MK, Cheung CY, Wong TY & Chen CPLH. Retinal pathology as biomarker for cognitive impairment and Alzheimer's disease. *J Neurol Neurosurg Psychiatr* 2012; 83: 917-922.

187. Moreno-Ramos T, Benito-Leon J, Villarejo A & Bermejo-Pareja F. Retinal nerve fibre layer thinning in dementia associated with Parkinson's disease, dementia with Lewy bodies, and Alzheimer's disease. *J Alzheimer Dis* 2013; 34: 659-664.
188. Pasol J. Neuro-ophthalmic disease and optical coherence tomography: glaucoma look-alikes. *Curr Opin Ophthalmol* 2011; 22: 124-132.
189. Marziani E, Pomati S, Ramolfo P *et al*. Evaluation of retinal nerve fibre layer and ganglion cell layer thickness in Alzheimer's disease using spectral-domain optical coherence tomography. *Invest Ophth Vis Sci* 2013; 54: 5953-5958.
190. He XF, Liu YT, Peng C, Zhang F, Zhuang S & Zhang JS. Optical coherence tomography assessed retinal nerve fibre layer thickness in patients with Alzheimer's disease: a meta-analysis. *Int J Ophthalmol* 2012; 5: 401-405.
191. Berisha F, Feke GT, Trempe CL, McMeel JW & Schepens CL. Retinal abnormalities in early Alzheimer's disease. *Inv Ophthalmol Vis Sci* 2007; 48: 2285-2289.
192. Lu Y, Li Z, Zhang XQ *et al*. Retinal nerve fibre layer structure abnormalities in early Alzheimer's disease: Evidence in optical coherence tomography. *Neurosci Lett* 2010; 480: 69-72.
193. Iseri PK, Altinas O, Tokay T & Yuksel N, Relationship between cognitive impairment and retinal morphological and visual functional abnormalities in Alzheimer's disease. *J Neuro-Ophthalmol* 2006; 28: 18-24.
194. Moschos MM, Markopoulos I, Chatziralli I *et al*. Structural and functional impairment of the retina and optic nerves in Alzheimer's disease. *Curr Alzheimer Res* 2012; 9: 782-788.
195. Paquet C, Boissonnot M, Roger F, Digiero P, Gil R & Hugon J. Abnormal retinal thickness in patients with mild cognitive impairment and Alzheimer's disease. *Neurosci Lett* 2007; 420: 97-99.
196. Kesler A, Vakhapova V, Korczyn AD, Amos D, Naftaliev E & Neudorfer M. Retinal thickness in patients with mild cognitive impairment and Alzheimer's disease. *Clin Neurol Neurosurg* 2011; 113: 523-526.
197. Hinton DR, Sadun AA, Blancks JC & Miller CA. Optic nerve degeneration in Alzheimer's disease. *New Engl J Med* 1986; 315: 485-488.

198. Tsai CS, Ritch R, Schwartz B *et al*. Optic nerve head and optic nerve fibre layer in Alzheimer's disease. *Arch Ophthalmol* 1991; 109: 199-204.
199. Tsai YC, Lu B, Ljubimov AV *et al*. Ocular changes in TgF344-AD rat model of Alzheimer's disease. *Invest Ophthalmol Vis Sci* 2014; 55: 523-534.
200. Koronyo Y, Salumbides BC, Black KL & Koronyo-Hamaoul M. Alzheimer's disease in the retina: Imaging retinal A beta plaques for early diagnosis and therapy assessment. *Neurodegener Dis* 2012; 10: 285-293.
201. Wostyn P, Audenaert K, De Deyn PP. The Valsava maneuver and Alzheimer's disease: Is there a link? *Curr Alz Res* 2009; 6: 59-68.
202. Valenti DA. Alzheimer's disease and glaucoma: imaging the biomarkers of neurodegenerative disease. *Int J Alzheimers Dis* 2011;2010:793931.
203. Bayer AU, Ferrari F & Erb C. High occurrence rate of glaucoma among patients with Alzheimer's disease. *Eur Neurol* 2002; 47: 165-168.
204. Tamura H, Kawakami H, Kanamoto T *et al*. High frequency of open-angle glaucoma in Japanese patients with Alzheimer's disease. *J Neurol Sci* 2006; 246: 79-83.
205. Kessing LV, Lopez AG, Anderson PK & Kessing SV. No increased risk of developing Alzheimer's disease in patients with glaucoma. *J Glaucoma* 2007; 16: 47-51.
206. Ho WL, Leung Y, Tsang AWT, So KF, Chiu K & Chang RCC. Review: tauopathy in the retina and optic nerve: does it shadow pathological changes in the brain? *Mole Vis* 2012; 18: 2700-2710.
207. Sadun AA, Bassi CJ. Optic nerve damage in Alzheimer's disease. *Ophthalmology* 1990; 97: 9-17.
208. Syed AB, Armstrong RA & Smith CUM. A quantitative analysis of optic nerve axons in elderly control subjects and patients with Alzheimer's disease. *Folia Neuropathol* 2005; 43: 1-6.
209. Kaplan E, Lee BB & Shapeley RM. New views of primate retinal function. In: Osborne N and Chader J, editors. Progress in Retinal Research. New York: Pergamon Press, 1990: 273-336.

210. Wright CE, Harding GF, Orwin A. Presenile dementia--the use of the flash and pattern VEP in diagnosis. *Electroencephalogr Clin Neurophysiol* 1984;57:405-415.
211. Wright CE, Drasdo N, Harding GFA. Pathology of the optic nerve and visual association areas: Information given by the flash and pattern visual evoked potential, and the temporal and spatial contrast sensitivity function. *Brain* 1987; 110: 107-120.
212. Katz B, Rimmer S. Ophthalmologic manifestations of Alzheimer's disease. *Surv Ophthalmol* 1989; 34: 31-43.
213. Leuba G, Saini K. Pathology of subcortical visual centres in relation to cortical degeneration in Alzheimer's disease. *Neuropathol Appl Neurobiol* 1995;21:410-422.
214. Brewer AA & Barton B. Visual cortex in aging and Alzheimer's disease: changes in visual field maps and population receptive fields. *Front Psychol* 2014; 5: Article 74.
215. De Lacoste M & White CL. The role of cortical connectivity in Alzheimer's disease pathogenesis: a review and model system. *Neurobiol Aging* 1993; 14: 1-16.
216. McKee AC, Au R, Cabral HJ, *et al.* Visual association pathology in preclinical Alzheimer's disease. J Neuropath *Exp Neurol* 2006; 65: 621-630.
217. Armstrong RA, Nochlin D, Sumi SM & Alvord EC. Neuropathological changes in the visual cortex in Alzheimer's disease. *Neurosci Res Comm* 1990; 6: 163-171.
218. Hof PR, Morrison JH. Quantitative analysis of a vulnerable subset of pyramidal neurons in Alzheimer's disease. II. Primary and secondary visual cortex. *J Comp Neurol* 1990; 301: 55-64.
219. Armstrong RA. Neuropathological differences between areas B17 and B18: Implications for visual evoked responses in Alzheimer's disease. *Dementia* 1994; 5: 247-251.
220. Congdon N, Vingerling JR, Klein BE *et al.* Eye Diseases Prevalence Research Group. *Arch Ophthalmol* 2004;122:487-494.
221. Klein BEK, Howard KP, Lee KE, Klein R. Changing incidence of lens extraction over 20 years. The Beaver Dam Eye Study. *Ophthalmology* 2014;121:5-9.

222. Javitt JC, Brenner MH, Curbow B, Legro MW & Street DA. Outcomes of cataract surgery. Improvement in visual acuity and subjective visual function after surgery in the first, second, and both eyes. *Arch Ophthalmol* 1993;111:686-691.
223. Mangione CM, Phillips RS, Lawrence MG *et al.* Improved visual function and attenuation of declines in health-related quality of life after cataract extraction. *Arch Ophthalmol* 1994;112:1419-1425.
224. Mönestam E, Wachmeister L. Impact of cataract surgery on the visual ability of the very old. *Am J Ophthalmol* 2004;137:145-155.
225. Lundstrom M, Steveni U, Thorburn W. Cataract surgery in the very elderly. *J Cataract Refract Surg* 2000;26:408-414.
226. Greenberg PB, Liu J, Wu WC *et al.* Predictors of mortality within 90 days of cataract surgery. *Ophthalmology* 2010;117:1894-1899.
227. Jefferis JM, Taylor JP, Clarke MP. Does cognitive impairment influence outcomes from cataract surgery? Results from a 1-year follow-up cohort study. *Br J Ophthalmol* 2015;99:412-417.
228. Tielsch JM, Javitt JC, Coleman A, Katz J & Sommer A. The prevalence of blindness and visual impairment among nursing home residents in Baltimore. *N Engl J Med* 1995;332:1205-1209.
229. Mitchell P, Hayes P, Wang JJ. Visual impairment in nursing home residents: the Blue Mountains eye study. *MJA* 1997;166:73-76.
230. Friedman DS, Munoz B, Roche KB *et al.* Poor uptake of cataract surgery in nursing home residents. The Salisbury eye evaluation in nursing home groups study. *Arch Ophthalmol* 2005;123:1581-1587.
231. Owsley C, McGwin G, Scilley K *et al.* Impact of cataract surgery on health-related quality of life in nursing home residents. *Br J Ophthalmol* 2007;91:1359-1363
232. Bédard E, Kergoat H, Kergoat M-J & Leclerc B-S. Systematic review of vision-related quality of life questionnaires for older institutionalised seniors with dementia. Ophthalmic Physiol Opt 2015. doi: 10.1111/opo.12215
233. Clinical Practice Guideline Expert Committee. Canadian Ophthalmological Society evidence-based clinical practice guidelines for the periodic eye examination in adults in Canada. *Can J Ophthalmol* 2007;42:39-45,158-63.

234. Robinson BE, Stolee P, Mairs K, Santi S & Glenny C. Review of the Canadian Association of Optometrists. Frequency of eye examinations guideline - Summary. An evidence-based approach. *Can J Optom* 2011;73:15-16.
235. Ordre des optométristes du Québec. Guide d'exercice. http://www.ooq.org/. Updated April 2014. Accessed on April 06, 2015.
236. http://www.aoa.org/documents/optometrists/CPG.pdf. Accessed April 06, 2015
237. Kergoat H, Boisjoly H, Freeman EE *et al.* The perceived needs and availability of eye care services for older adults in Quebec long-term care facilities. *Can Geriatr J* 2014;17:108-113.
238. Retooling for an aging America: Building the health care workforce. http://www.nap.edu/catalog/12089/retooling-for-an-aging-america-building-the-health-care-workforce Accessed May 17, 2015.
239. Mankin LaMascus A, Bernard MA, *et al.* Bridging the workforce gap for our aging society: How to increase and improve knowledge and training. Report of an expert panel. *J Am Geriatr Soc.* 2005;53:343-347.
240. Teresi J, Morse AR, Holmes D *et al.* Impact of a vision intervention on the functional status of nursing home residents. *J Vis Impair Blind* 2005; 99: 96-108.
241. Owsley C, McGwin Jr G, Scilley K *et al.* Effect of refractive error correction on health-related quality of life and depression in older nursing home residents. *Arch Ophthalmol* 2007;125:1471-1477.
242. Coleman Al, Yu F, Keeler E, Mangione CM. Treatment of uncorrected refractive error improves vision-specific quality of life. *J Am Geriatr Soc* 2006;54:883-890.
243. Brannan S, Dewar C, Sen J, *et al.* A prospective study of the rate of falls before and after cataract surgery. *Br J Ophthalmol* 2003;87:560-562.
244. De Coster C, Dik N, Bellan L. Health care utilization for injury in cataract surgery patients. *Can J Ophthalmol* 2007;42:567-572.
245. Carabellese C, Appollonio I, Rozzini R, *et al.* Sensory impairment and quality of life in a community elderly population. *J Am Geriatr Soc* 1993;41:401-407.
246. Horowitz A. The relationship between vision impairment and the assessment of disruptive behaviors among nursing home residents. *The Gerontologist* 1997; 37:620-628.

247. Knudtson MD, Klein BEK, Klein R. Biomarkers of aging and falling: The BeaverDam eye study. *Arch Gerontol Geriatr* 2009;49:22-26.
248. The Importance of Vision in Preventing Falls. Guidelines produced by the College of Optometrists and the British Geriatrics Society and endorsed by Age UK and the Royal College of General Practitioners. 2011
249. O'Loughlin JL, Robitaille Y, Boivin JF, *et al.* Incidence of and risk factors for falls and injurious falls among the community-dwelling elderly. *Am J Epidemiol* 1993; 137:342-354.
250. Formiga F, Ferrer A, Duaso E, *et al.* Falls in nonagenarians living in their own homes: The NonaSantfeliu study. *J Nutr Health Aging* 2008;12:273-276
251. Guideline for the prevention of falls in older persons. American Geriatrics Society, British Geriatrics Society, and American Academy of Orthopaedic Surgeons Panel on Falls Prevention. *J Am Geriatr Soc* 2001;49:664-672.
252. King MB, Tinetti ME. Falls in community-dwelling older persons. *J Am Geriatr Soc* 1995;43:1146-1154.
253. Ministère de la santé et des services sociaux: Cadre normatif du système Med-Écho (Maintenance et exploitation des données pour l'étude de la clientèle hospitalière). Québec: Ministère de la santé et des services sociaux; 2009.
254. Jack CI, Smith T, Neoh C, Lye M, *et al.* Prevalence of low vision in elderly patients admitted to an acute geriatric unit in Liverpool: Elderly people who fall are more likely to have low vision. *Gerontology* 1995;41:280-285.
255. Boutin T, Kergoat MJ, Latour J, *et al.* Vision in the global evaluation of older individuals hospitalized following a fall. *J Am Med Dir Assoc* 2012;13:187.e15-19.
256. Elliott DB. The Glenn A. Fry Award Lecture 2013: Blurred vision, spectacle correction, and falls in older adults. Optom Vis Sci 2014;91:595-601.
257. Kergoat H, Chriqui E, Hafez A. Les problèmes visuels en soins de longue durée. In: Guide médical en soins de longue durée. Montréal: L'Institut universitaire de gériatrie de Montréal; 2015.

258. Lawrence V, Murray J, ffytche D & Banerjee S. "Out of sight, out of mind": a qualitative study of visual impairment and dementia from three perspectives. Intern Psychogeriatrics 2009;21:511-518.
259. Moyle W, Mcallister M, Venturato L & Adams T. Quality of life and dementia. The voice of the person with dementia. *Dementia* 2008;6:175-191.
http://www.bgs.org.uk/index.php/nursepublications/nursefalls/1455-visionfalls Accessed May 14, 2015.
260. Statistics Canada. The Canadian population in 2011: Age and sex. Catalogue no. 98-311-X2011001.
261. United States Census Bureau, U.S. Population Projections. Projected population by single year of age, sex, race, and Hispanic origin for the United States: July 1, 2000 to July 1, 2050. 2008. Available at:
http://www.census.gov/population/www/projections/downloadablefiles.html. Accessed March 5, 2015.
262. Prince M, Bryce R, Ferri C. Alzheimer's disease international. World Alzheimer report 2011. The benefits of early diagnosis and intervention. 2011;72 p.
263. Lee AG, Beaver HA, Jogerst G & Daly JM. Screening elderly patients in an outpatient ophthalmology clinic for dementia, depression, and functional impairment. *Ophthalmology* 2003;110:651-657.
264. Cogan DG. Visual disturbances with focal progressive dementing disease. *Am J Ophthalmol* 1985;100:68-72.
265. Mendez MF, Mendez MA, Martin R, Smyth KA & Whitehouse PJ. Complex visual disturbances in Alzheimer's disease. *Neurology* 1990;40:439-443.
266. Cedazo-Minguez A, Winblad B. Biomarkers for Alzheimer's disease and other forms of dementia: Clinical needs, limitations and future aspcts. *Exp Gerontol* 2010;45:5-14.
267. Schipper HM. Biological markers and Alzheimer disease: A Canadian perspective. *Int J Alzheimers Dis* 2010 Aug 8;2010. pii: 978182. doi: 10.4061/2010/978182.
268. Prvulovic D, Hampel H. Ethical considerations of biomarker use in neurodegenerative diseases-A case study of Alzheimer's disease. *Progress Neurobiol* 2011;95:517-519.

269. Sinha N, Firbank M, O'Brien JT. Biomarkers in dementia with Lewy bodies: a review. *Int J Geriatr Psychiatry* 2012;27:443-453.
270. Fiandaca MS, Mapstone ME, Cheema AK & Federoff HJ. The critical need for defining preclinical bioarkers in Alzheimer's disease. *Alzheimer's & Dementia* 2014;10:S196-S212.
271. Raji MA, Tang RA, Heyn PC *et al.* Screening cognitive impairment in older adults attending an eye clinic. *J Natl Med Assoc* 2005;97:808-814.
272. Holroyd S, Shepherd ML. Alzheimer's disease: A review for the ophthalmologist. *Surv* Ophthalmol 2001;45:516-524.
273. Owsley C, McGwin G, Scilley K *et al.* The visual status of older persons residing in nursing homes. *Arch Ophthalmol* 2007;125:925-930.
274. Gonzalez DS. The Charles Bonnet syndrome: a case report and a brief review. *Acta Espanolas de Psiquiatria* 2003;31:48-52.
275. Kergoat H, Kergoat MJ, Clerc D. Syndrome de Charles Bonnet. *Rev Can Optom* 2008;70:19-22.

Table 1. A classification of the dementias

Group	Definition	Examples
A	Neurodegenerative disorders, aetiology uncertain	Alzheimer's disease Dementia with Lewy bodies Parkinson's disease dementia Fronto-temporal dementia Progressive supranuclear palsy Corticobasal degeneration
B	Dementia associated with systemic disease	Infection (syphilis, tuberculosis, inclusion body encephalitis, Infective endocarditis); Vascular dementia (cerebral arteriosclerosis, arteritis); Intoxication (sedatives, alcohol, narcotics); Metabolic disorders (uremia, chronic hepatic insufficiency, hypoglycemia, hypothyroidism, pernicious anaemia, pellagra); Neoplasms
C	Dementia associated with viruses or prions	Progressive multifocal leucoencephalopathy, Subacute sclerosing panencephalitis, Creutzfeldt-Jacob disease
D	Dementia with miscellaneous causes	Brain abscess, Trauma, Hydrocephalus, Chronic meningitis

Table 2. Overview of visual dysfunction in various dementias

Visual feature	Dysfunction
Visual acuity	Normal in early stages of AD, may deteriorate in avanced disease.[40,43,45,62] Limited data on other dementias.
Colour vision	Controversial but likely to be affected in AD, DLB and PDD.[47-53]
Stereoacuity	Impaired in AD and VD.[41,54-56]
Contrast sensitivity	Impaired in AD and VD.[59-62]
Motion detection	Higher thresholds necessary for detecting a moving stimulus in AD.[69,70]
CFFF	Controversial, can be impaired[72] or normal in AD.[41]
Visual masking	Significantly affected by a backward patterned mask stimulus in AD.[58,78,79]
Visual fields	Limited data but evidence for defects in AD.[82] rCBF measurements indicate potential for visual field deficits in DLB.[85-87]
Pupillary function	Controversial. Significant response to mydriatics in AD.[89-96]
Eye movements	Most significant in PDD and DLB. Defects in fixation, decline in saccadic latency, undershooting of target in AD.

	Saccadic latency prolonged in FTD. Abnormal saccadic and smooth pursuit eye movements and convergence in DLB.[48,98-103,106,117]
EEG	Increase in slow activity and a smaller decrease in fast activity in AD; no increase in slow activity but an increase in fast activity in FTD[118]. Reduction in synchrony of the slow frequency bands in VD.[119] Changes also in DLB.[120]
ERG	Controversial in AD.[123-128,212] Defects likely in DLB.[129]
VEP	Controversial in AD but flash response could be delayed and pattern response normal.[131-136]
Visual event EP	Greater response in DLB than AD but greater in AD than FTD.[138,139]
Complex functions	Defects in reading[140], visuospatial function[48,141,142], and object identification in AD.[47] AD and VD have similar deficits.[147] Visuospatial function affected in DLB but less so in AD.[155] Relative preservation of visuospatial function in FTD.[156]
Visual hallucinations	Common in DLB and PDD and less frequent in AD and FTD.[129,130,159-176]

Abbreviations: *Disorders*: AD = Alzheimer's disease, FTD = Frontotemporal dementia, VD = Vascular dementia, PDD = Parkinson's disease dementia, DLB = Dementia with Lewy bodies; *Visual features*: CFFF = Critical flicker fusion frequency, EEG = electroencephalogram, ERG = Electroretinogram, VEP = Visual evoked potential, Visual event EP = Visual event-related potentials

Legend to Figure

Fig 1. Factors involved in visual hallucinations in dementia with Lewy bodies (DLB). Abbreviations: LB = Lewy bodies, CAT = Choline acetyltransferase