doi:10.1093/brain/awp068 Brain 2009: 132; 1128–1145 | 1128

BRAIN
A JOURNAL OF NEUROLOGY

REVIEW ARTICLE

The retina in Parkinson's disease

Neil K. Archibald,[1] Michael P. Clarke,[2] Urs P. Mosimann[3] and David J. Burn[4]

1 Clinical Ageing Research Unit, Newcastle University, UK
2 Royal Victoria Infirmary, Newcastle upon Tyne, UK
3 Institute for Ageing and Health, Newcastle University, Campus for Ageing and Vitality Newcastle upon Tyne, UK
4 Clinical Ageing Research Unit, Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne, UK

Correspondence to: Dr. Neil Archibald,
Clinical Research Fellow,
Clinical Ageing Research Unit,
Newcastle University,
Campus for Ageing and Vitality,
Newcastle upon Tyne, NE4 5PL, UK.
E-mail: neil.archibald@ncl.ac.uk

As a more complete picture of the clinical phenotype of Parkinson's disease emerges, non-motor symptoms have become increasingly studied. Prominent among these non-motor phenomena are mood disturbance, cognitive decline and dementia, sleep disorders, hyposmia and autonomic failure. In addition, visual symptoms are common, ranging from complaints of dry eyes and reading difficulties, through to perceptual disturbances (feelings of presence and passage) and complex visual hallucinations. Such visual symptoms are a considerable cause of morbidity in Parkinson's disease and, with respect to visual hallucinations, are an important predictor of cognitive decline as well as institutional care and mortality. Evidence exists of visual dysfunction at several levels of the visual pathway in Parkinson's disease. This includes psychophysical, electrophysiological and morphological evidence of disruption of retinal structure and function, in addition to disorders of 'higher' (cortical) visual processing. In this review, we will draw together work from animal and human studies in an attempt to provide an insight into how Parkinson's disease affects the retina and how these changes might contribute to the visual symptoms experienced by patients.

Keywords: Parkinson's disease; visual hallucinations; visual perception; retina; dopamine

Abbreviations: DA = dopaminergic; ERG = electroretinogram; L-DOPA = levodopa; LGN = lateral geniculate nucleus; M-cells = magnocellular retinal ganglion cells; MMSE = mini-mental state examination; MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; P-cells = parvocellular retinal ganglion cells; PERG = pattern ERG; RNFL = retinal nerve fibre layer; UFOV = useful field of vision; V1 = primary visual cortex; VEP = visual evoked potential

Parkinson's disease is the second most common neurodegenerative disorder in the developed world, after Alzheimer's disease, with a prevalence of 0.3% and an estimated incidence of 8–18 per 100 000 person years (de Lau and Breteler, 2006). Both incidence and prevalence increase with age, with the latter estimated at 1% in the over 60s and 4% in the over 80s (de Rijk *et al*., 1995; Nussbaum and Ellis, 2003). In our ageing population, therefore, the clinical impact of Parkinson's disease is likely to increase steadily in future years.

James Parkinson's original description of 'the shaking palsy' in 1817 focussed on the motor features of the disorder—tremor, bradykinesia and rigidity (Parkinson, 2002; Kempster *et al*., 2007). Over time, a more complete picture of the clinical phenotype of Parkinson's disease has emerged, revealing it to be a true

Received September 8, 2008. Revised February 26, 2009. Accepted February 27, 2009. Advance Access publication March 31, 2009

multi-system disorder with a wide variety of motor and non-motor features. Prominent among the non-motor aspects of Parkinson's disease are mood disturbance (Cummings and Masterman, 1999; Lemke *et al*., 2004; Martinez-Martin *et al*., 2007), cognitive decline and dementia (Levy *et al*., 2002; Aarsland *et al*., 2003; Foltynie *et al*., 2004; Janvin *et al*., 2006*b*), sleep disorders (Comella, 2006), hyposmia (Bohnen *et al*., 2007) and autonomic failure (Allcock *et al*., 2006; Lucetti *et al*., 2006; Wullner *et al*., 2007).

In addition, visual symptoms are common, ranging from complaints of dry eyes and reading difficulties, through to perceptual disturbances (feelings of presence and passage) and complex visual hallucinations (Repka *et al*., 1996; Fenelon *et al*., 2000; Barnes and David, 2001; Holroyd *et al*., 2001; Biousse *et al*., 2004). Such visual symptoms are a considerable cause of morbidity in Parkinson's disease (Aarsland *et al*., 1999) and, with respect to visual hallucinations, are an important predictor of cognitive decline as well as institutional care and mortality (Goetz and Stebbins, 1993, 1995; Aarsland *et al*., 2000; Goetz *et al*., 2006). Evidence exists of visual dysfunction at several levels of the visual pathway in Parkinson's disease. This includes psychophysical, electrophysiological and morphological evidence of disruption of retinal structure and function, in addition to disorders of 'higher' (cortical) visual processing. In this review, we will draw together work from animal and human studies in an attempt to provide an insight into how Parkinson's disease affects the retina and how these changes might contribute to the visual symptoms experienced by patients.

Structure of the retina

In order to appreciate the impact Parkinson's disease has on the retina, we must first re-visit some of the basic anatomy described by Cajal in 1892. The organization of the retina, with the photoreceptors arranged abutting the retinal pigment epithelium (RPE), means that, with the exception of the fovea, light has to penetrate the cell bodies and unmyelinated fibres of more superficial structures before striking the light-sensitive photoreceptors. This may seem counterintuitive at first but is necessitated by the reliance of photoreceptors on the RPE for visual pigment regeneration as well as to facilitate absorption of light escaping the photoreceptor array, preventing back-scatter and subsequent image degradation. The human retina contains two types of photoreceptor—rods, present in both the parafoveal and peripheral retina and designed for low-light (scotopic) vision and cones, found predominantly in the macula and specialized for bright-light (photopic) colour vision (Curcio *et al*., 1990).

Retinal signalling occurs in two directions—vertically and horizontally. Vertical neurotransmission takes place predominantly from photoreceptor to bipolar cell to retinal ganglion cell and it is the retinal ganglion cell which acts as the final common pathway in the flow of visual information to the optic nerve. Photoreceptors synapse with bipolar cells in the outer plexiform layer and bipolar cell to retinal ganglion cell neurotransmission occurs in the synaptic zones of the inner plexiform layer. The principal neurotransmitter of the vertical system is glutamate, in general terms, acting via excitatory ionotropic and inhibitory metabotropic glutamate receptors.

In addition, there are cells mediating horizontal neurotransmission in both the outer and inner plexiform layers, and these are vital in shaping the temporal and spatial qualities of scotopic and photopic vision. Horizontal cells synapse in the outer plexiform layer, affecting photoreceptor/bipolar cell interactions, while amacrine cells perform a similar role in the inner plexiform layer for bipolar to ganglion cell transmission (Fig. 1). This horizontal transmission is mediated primarily by the inhibitory transmitters, GABA and glycine in addition to electrical gap junctions. Signal transmission occurs on a one-to-one basis for cone-to-midget bipolar cell-to-midget ganglion cell in the central fovea, facilitating high acuity colour vision. In contrast, there is considerable convergence in the rod-to-rod-driven ganglion cell pathway, allowing this part of the retina to detect low intensity signals but at the cost of much lower spatial resolution.

Retinal ganglion cell axons become myelinated at the optic nerve head and the majority carry information to the lateral geniculate nucleus (LGN) of the thalamus. Larger RGCs, more prominent in the peripheral retina, and known as magnocellular RGCs (M-cells) carry information on movement and contrast, whereas parvocellular RGCs (P-cells) most prominent in the central retina, signal fine feature and colour information to higher visual centres (Maunsell *et al*., 1990; Ferrera *et al*., 1992, 1994; Nealey and Maunsell, 1994; Tobimatsu *et al*., 1995; Malpeli *et al*., 1996). It is beyond the scope of this article to cover in detail the retinal mechanisms of colour opponency involved in generating colour vision. However, it should be noted that, although the central retina is traditionally described as the seat of colour vision, considerable processing of colour vision occurs in the peripheral retina as well, albeit with a different pattern of colour opponency, larger receptive fields and altered sensitivity to temporal-frequency modulation (Martin *et al*., 2001; Solomon *et al*., 2005; Solomon and Lennie, 2007).

Aside from the LGN, other sub-cortical targets for these retinal efferents are the superior colliculus (SC), the pulvinar complex of the dorsal thalamus and the mid-brain tectum. It is the axons of LGN neurons which project to visual (striate) cortex in a retinotopic fashion, initially terminating in area V1 of the visual cortex and from here, visual information passes into the extra-striate visual areas (V2–V5). From the striate and early extra-striate regions visual information flows into the parietal lobes in the form of a 'dorsal stream' and the temporal lobes in the form of a 'ventral stream'. The dorsal stream seems particularly specialized for movement and spatial perception, whereas the ventral stream is responsible for perception of object form (Ungerleider and Mishkin, 1982; Goodale and Milner, 1992; Ungerleider and Haxby, 1994; Goodale and Westwood, 2004). In a similar fashion, visual information from the SC and retina is integrated with information from the visual cortex in the pulvinar, projecting extensively both back to the striate and extra-striate cortices as well as to parietal and temporal lobes (Yeterian and Pandya, 1997; Grieve *et al*., 2000; Kaas and Lyon, 2007). In addition to its inputs to the pulvinar, the SC is also responsible for integrating response to visual, auditory and somatosensory stimuli.

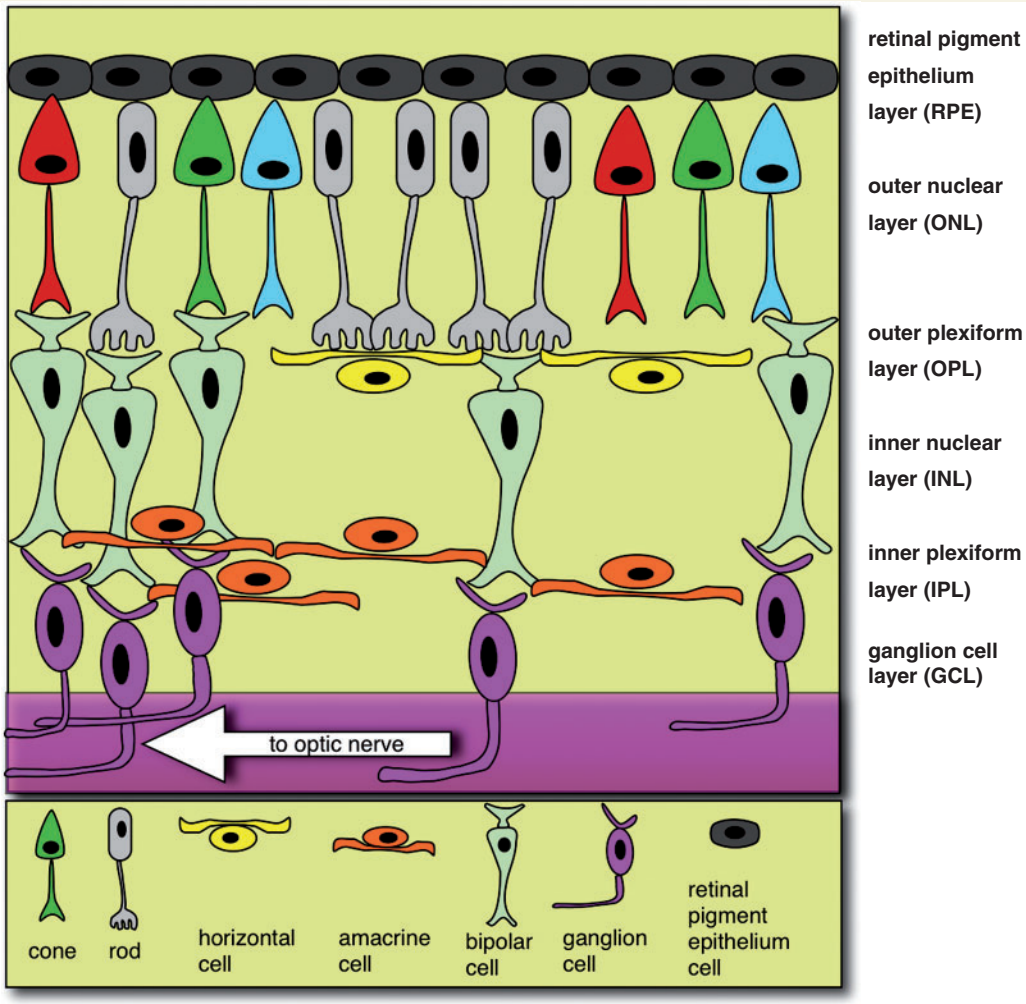

Figure 1 Cross-section of the retina demonstrating the principal cell types involved in retinal signalling.

Whilst our description is an over-simplification of the structural organization of the visual system, it serves to illustrate the hierarchical nature of the visual system from retina to cortex. Although the focus of this article is the retina it must be borne in mind that the 'anterior' visual system does not exist in isolation and many abnormalities of visual function can be attributed to 'central' as well as retinal dysfunction.

Retinal physiology

Photoreceptors exist in a depolarized state in the dark, constantly releasing glutamate and hyperpolarize when stimulated by light. Unlike most other neurons, they do not produce action potentials but instead respond to changing light stimuli with graded alterations in membrane potential. When light excites a photoreceptor, glutamate release from the hyperpolarized cell is reduced. Because bipolar cells express either ionotropic or metabotropic glutamate receptors, the reduction in photoreceptor glutamate release results in either inhibition or disinhibition in different subtypes of bipolar cell. Bipolar cells that are disinhibited are called 'ON' bipolar cells and they, in turn, stimulate 'ON' retinal ganglion cells in the inner plexiform layer, through either direct (cone ON bipolar) or indirect circuitry (rod bipolar) (Bloomfield and Dacheux, 2001). Conversely, 'OFF' bipolar cells contact 'OFF' RGCs and it is this passage of photosensitive information that allows the RGCs to vary action potential firing frequency dependent on light intensity and contrast (Hartline, 1938; Nelson *et al*., 1978; Peichl and Wassle, 1981; Amthor *et al*., 1989).

Each retinal ganglion cell is influenced by light falling on a discrete area of the retina. This is known as the receptive field of the retinal ganglion cell and its size and photosensitive properties are dependent on the extent of synaptic contact made in the outer plexiform layer and inner plexiform layer, and the degree of convergence of photoreceptors onto bipolar cells. This means that receptive fields in the peripheral retina, where sometimes hundreds of rods converge on a single bipolar cell, are consequently much larger than those in the macula.

An important functional component of the receptive field is that, under photopic conditions, any given cone photoreceptor is excited (or inhibited) from a small central circular stimulus and oppositely affected by stimulation of a broader peripheral zone. Hence a further layer of complexity is added to the light response, with a 'centre and surround' component to retinal ganglion cell

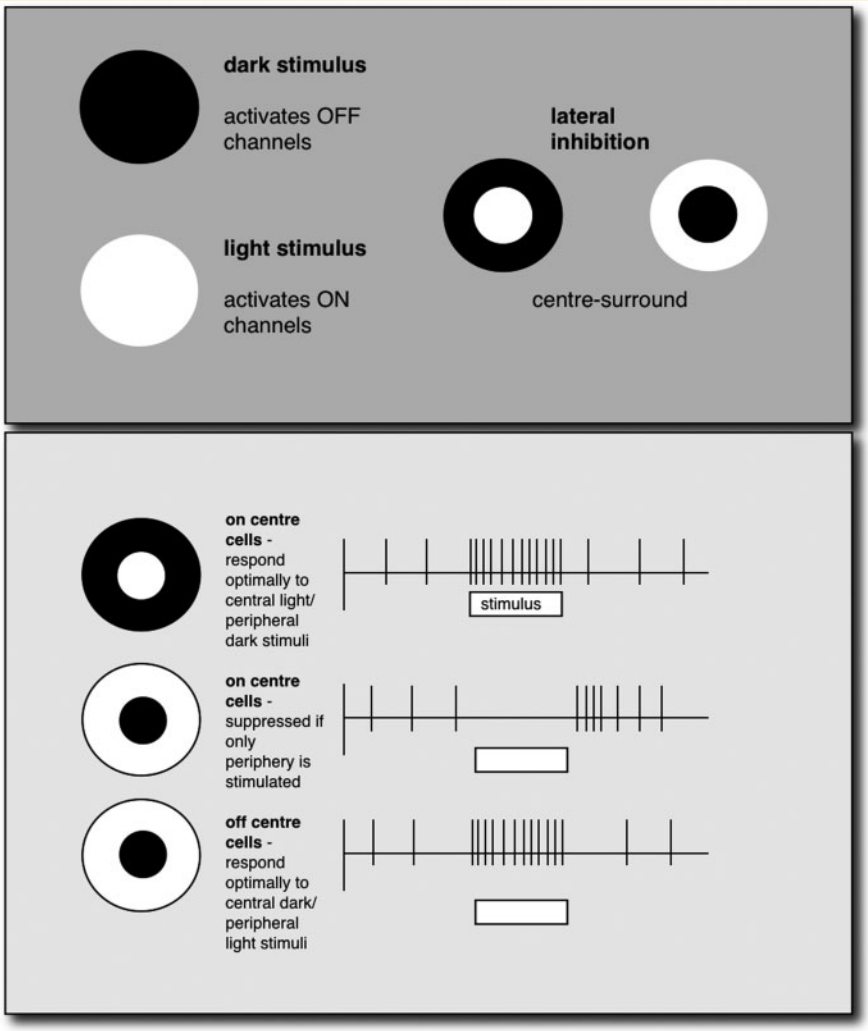

Figure 2 Diagrammatic representation of the centre-surround concept of lateral inhibition in retinal ganglion cell receptive fields. Note the opposing responses of on centre and off centre ganglion cells. Based on Kuffler (1953).

receptive fields and both ON-centre and OFF-centre ganglion cell responses to light. This means that RGCs give information on contrast rather than absolute light intensity, enabling us to distinguish contours and forms (Fig. 2) (Hartline, 1940; Werblin and Dowling, 1969; Baylor *et al*., 1971; Shapley and Perry, 1986; Werblin, 1991).

In reality, there are numerous subtypes of bipolar cells, RGCs, amacrine and horizontal cells, utilizing different neurotransmitter systems and making synaptic contact in specific sub-layers of the inner and outer plexiform layers. It is beyond the scope of this article to cover these in detail, but those with potential relevance to Parkinson's disease will be discussed later. One of the key concepts of early retinal processing is that, with such considerable cellular interactions, both vertically and horizontally, and due to the exquisite sensitivity of the retina for colour, contrast and movement, extensive modification of visual information has occurred long before it reaches the visual cortex (Baccus and Meister, 2002; Solomon *et al*., 2004). The retina is not the only part of the visual pathway involved in contrast processing, however, with contrast adaptation also taking place centrally in the striate cortex (V1) as well as extra-striate regions V2, V3 and human V4 (Ohzawa *et al*., 1985; Kohn and Movshon, 2003; Gardner *et al*., 2005). Appreciation of the multiple sites of, for instance, contrast modulation is vital if we are to localize Parkinson's disease-specific alterations in such processing to the anterior or posterior visual system.

Dopaminergic neurons in the retina

Observations from Malmfors in 1963 first highlighted the role catecholamines might play in rat retinal function (Malmfors, 1963). It was noted that rats, pharmacologically depleted of catecholamines using reserpine, showed marked photosensitivity despite their small pupil size. Study of the rabbit retina demonstrated dopaminergic (DA) neurons (Haeggendal and Malmfors, 1963) which have subsequently been identified in the INL of the human retina (Frederick *et al*., 1982). The principal

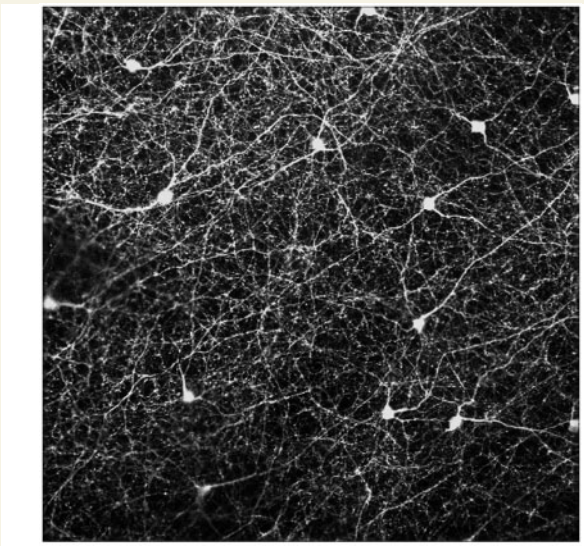

Figure 3 Dopaminergic cells in the rat retina visualized by immunocytochemical staining with an antibody against tyrosine hydroxylase. Courtesy of Paul Witkovsky.

DA cell in the retina is an amacrine subtype called A18 although a second, less well-defined DA cell has also been identified in primate and rodent retinas (Mariani, 1990, 1991; Kolb *et al*., 1992; Witkovsky *et al*., 2005). The density of A18 neurons is low but their widespread dendritic arborization and long fine axons ensure overlap with neighbouring DA cells as well as other amacrine cells and bipolar cells (Fig. 3) (Pourcho, 1982; Voigt and Wassle, 1987; Dacey, 1990; Kolb *et al*., 1990). The inputs to DA amacrine cells are still not precisely defined anatomically and although A18 cells receive input predominantly from rod bipolar cells (Kolb *et al*., 1990) they may also receive input from a type of cone bipolar cell called the giant bistratified cell (Hokoc and Mariani, 1987). From a functional standpoint it is clear that DA neurons are depolarized by light onset and this occurs under both scotopic and photopic conditions, implying input from depolarizing bipolars of both rod and cone varieties (Zhang *et al*., 2007).

DA neurons contact two other types of amacrine cell belonging to the rod pathway—the AII and the A17 amacrine cell (Bloomfield and Dacheux, 2001). The AII amacrine cells receive input from rod and cone bipolar cells and pass this information forward to ON and OFF RGCs (Famiglietti and Kolb, 1975; Dacheux and Raviola, 1986). AII cells are coupled to cone ON bipolars by gap junctions allowing rod signals to flow into the ON cone pathway (Xia and Mills, 2004). They also make glycinergic synapses onto OFF RGCs, inhibiting them under scotopic conditions. Thus, not only are the AII amacrine cells involved in the so-called 'horizontal' processing of retinal signalling but also play a pivotal role in channelling visual information 'vertically' through the retina in low light states. In addition, AII cells, via gap junctions, contact other AII amacrine cells forming a functional syncytium across the retina (Strettoi *et al*., 1992). A17 cells receive input from large numbers of rod bipolar cells but feed this back to the same cell types, presumably modulating the scotopic threshold of the retina (Nelson and Kolb, 1985).

AII cells express D1-subtype dopamine receptors and gamma-aminobutyric acid type-A ($GABA_A$) receptors, activation of the former leading to 'excitation' (Veruki and Wassle, 1996; Veruki, 1997; Contini and Raviola, 2003). Given that DA cells also contain GABA, this suggests that both neurotransmitters are involved in modulating amacrine function (Wulle and Wagner, 1990). In return, DA cells receive 'excitatory' (glutamatergic) bipolar cell and 'inhibitory' (GABAergic and glycinergic) amacrine cell inputs which alter the action potential firing rate and hence DA release (Gustincich *et al*., 1997, 1999; Feigenspan *et al*., 1998). As well as direct synaptic effects on amacrine and bipolar cells, diffusion of dopamine in the retinal extracellular matrix exerts a paracrine effect, obviating the need for direct synaptic contact, and extending the range of action over many microns (Witkovsky *et al*., 1993). Knowledge of these anatomical connections demonstrates that dopaminergic A18 cells, via their complex interactions with rod and cone bipolars, AII and A17 cells have a pivotal role in modulating the flow of rod-driven visual information through the retina.

Dopamine acts through G-protein coupled receptors, which regulate production of cyclic AMP. Dopamine receptor subtypes D1 and D5, often collectively referred to as the D1-receptor family, increase cAMP levels and, in this context, are excitatory, whereas subtypes D2, 3 and 4, part of the D2-receptor family, act in an opposing fashion. Rod and cone photoreceptors are inhibited by activation of D2 family receptors whereas bipolar, horizontal, RGCs and amacrine cells are excited by D1 receptors. Dopaminergic cells themselves utilize an autoreceptor of the D2 family to modulate their own DA release (Muresan and Besharse, 1993; Nguyen-Legros *et al*., 1997; Veruki, 1997). Dopamine has direct affects on gap junction permeability both at the level of rod and cone interactions with horizontal cells (Nelson, 1977; Xin and Bloomfield, 1999; He *et al*., 2000) and at the level of AII:AII and AII:cone bipolar cell communication (Xia and Mills, 2004). The net effect is a reduction in gap junction permeability with rising dopamine concentrations and a resultant reduction in receptive field size (Ribelayga *et al*., 2008).

In addition to this highly variable excitatory and inhibitory feedback system, there is a more 'tonic' diurnal variation in retinal dopamine concentration, with low levels at night and higher levels during the day. This circadian rhythm is in counterphase with the retinal concentrations of melatonin, and indeed, DA and melatonin have mutually inhibitory effects on each other's production—acting as a 'biological clock' for the retina (Doyle *et al*., 2002*a*). Because of this light-sensitive variation in DA concentration it has been postulated that DA plays a role in the transition from a dark- to light-adapted state (Cahill, 1996; Tosini and Menaker, 1996; Doyle *et al*., 2002*b*; Ribelayga *et al*., 2008).

DA therefore acts in the outer and inner retina at multiple levels, producing alterations to the flow of visual information in a complex fashion. Experimental evidence in mammalian and sub-mammalian retinas points to dopaminergic regulation of the 'centre-surround' field size as well as promoting diminution of signals from rod photoreceptors through effects on amacrine cells (Jensen and Daw, 1984; Witkovsky *et al*., 1988; Jensen, 1989; Hampson *et al*., 1992; Deans *et al*., 2002). In other words, dopamine is a chemical messenger for light adaptation,

promoting the flow of information through cone circuits while diminishing that through rod circuits.

Testing visual function

In order to accurately interpret the results of research in this field some understanding of the tools used to probe retinal function is necessary. These range from simple high contrast tests of visual acuity through to retinal electrophysiology and complex psychophysical measures of contrast sensitivity.

Visual acuity is usually measured with high contrast target recognition tasks, such as the Snellen, LogMAR or Illiterate E charts. Test objects here are large enough that stimulus detection is not the limiting factor, but rather acuity measures are dependent on the eye's ability to resolve the critical detail of the stimulus i.e. the width of the letter strokes and the adjacent gaps. In Fig. 4A, the letter 'E' falls on a specific area of the retina, measured in degrees and minutes of visual arc (one degree = 60 min). The area of retina exposed to the stimulus depends on the size of the letter and the distance from the eye. Hence, Snellen visual acuity is defined by the distance at which the chart is read and the size of the letters discriminated. 'Normal' Snellen visual acuity (6/6 or 20/20) describes the ability to discern a letter presented at 6 m (20 feet) when it subtends 5 min of visual arc on the retina (Snellen line 6).

Measures of visual acuity can also be defined in terms of the spatial frequency of the stimulus discriminated and this can best be understood by picturing a high-contrast black and white grating. The grating has a spatial frequency dependent on the width of the bars and their spacing—high spatial frequency gratings having narrow bars, close together. The grating alternates between high- and low-contrast and therefore spatial frequency is measured in cycles per degree (cpd). For instance, 6/6 Snellen acuity would equate to a spatial frequency of 30 cycles per degree (Fig. 4B, C).

Despite its familiarity to patients and clinicians as well as the ease of use, the Snellen chart is not without practical limitations. The unequal number of letters on each line and lack of a constant ratio of letter heights between adjacent lines makes precise

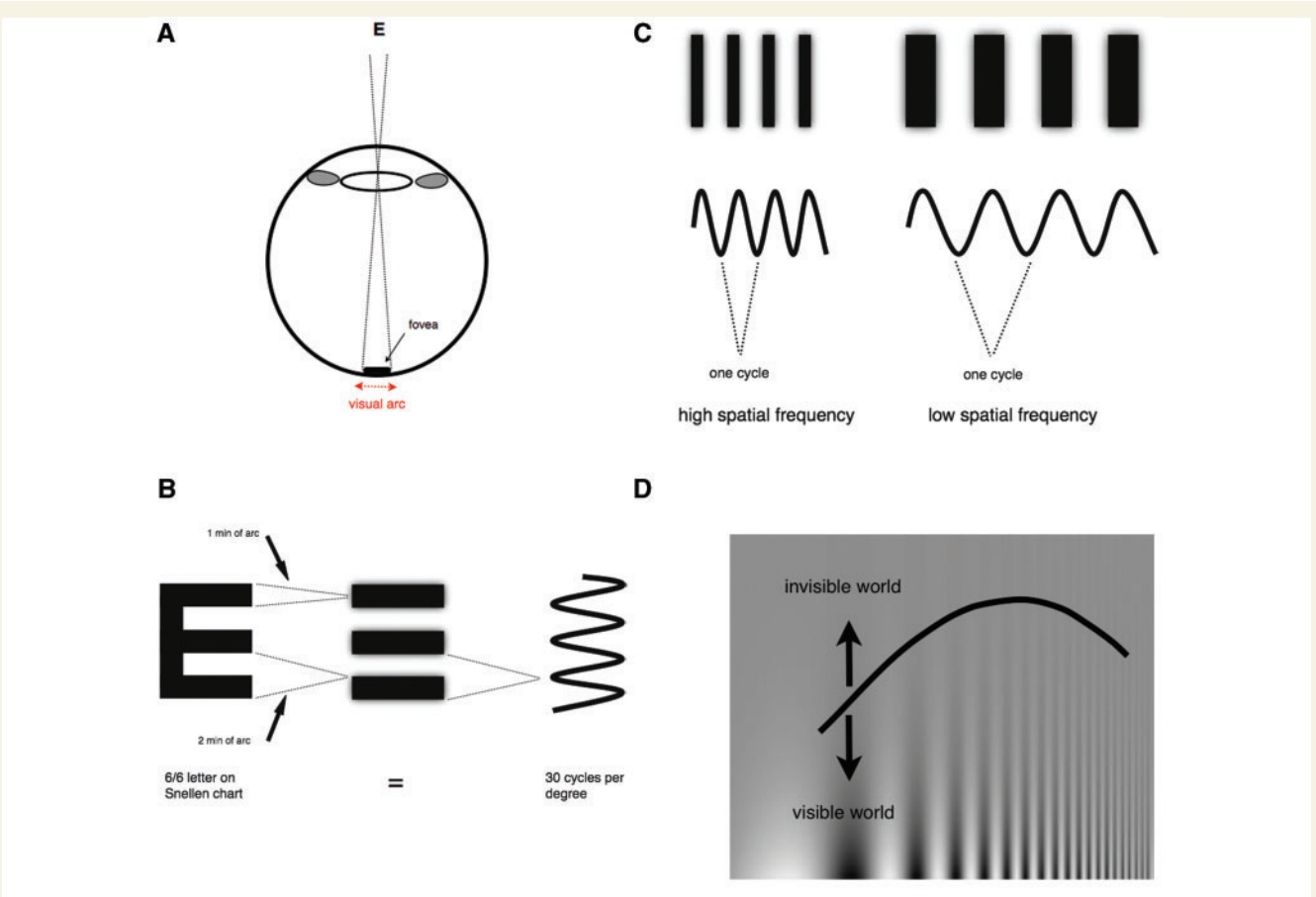

Figure 4 (**A**) Note the letter 'E' falling on the retina and subtending a visual arc measured in degrees and minutes (60 min = 1 deg). (**B**) Below, the conversion from Snellen nomenclature (i.e. 6/6) to spatial frequency in cycles per degree (cpd). At 6/6 acuity, the visual stimulus (letter, grating) must subtend a visual angle of 5 min, with each component of the stimulus taking up 1 min. A full 'cycle'from black–white–black therefore takes 2 min of arc and 30 cycles could therefore fit in 1 full degree. (**C**) narrower bars with tighter spacing have increased spatial frequency. (**D**) the Campbell–Robson grating demonstrates our ability to discern gratings at mid-spatial frequency better than those of low- or high-spatial frequency.

measurement of visual acuity difficult, particularly at lower levels of acuity. These problems have led to the increasing use of the LogMAR system for measuring visual acuity. Here, each line contains five letter optotypes, each assigned an individual logarithmic value according to the angle of resolution at the retinal level. This allows conversion of a geometric letter sequence to a linear scale, providing a more statistically robust measure of visual acuity.

The retina is designed to report on contrast, allowing the discrimination and identification of objects across a variety of illumination levels. This contrast detection of the retina is typically explored using visual stimuli such as gratings, although checkerboard patterns or simple letter optotypes can also be utilized. All tests of contrast are dependent on the luminance of the stimulus and grating patterns have the advantage of allowing contrast to be varied in a sinusoidal fashion without affecting the average stimulus luminance and allowing isolation of specific channels of retinal neurons that respond optimally to that given spatial frequency. Contrast can be lowered until grating detection is impossible, a fact best illustrated by the Campbell–Robson grating shown in (Fig. 4D). Here, spatial frequency increases from left to right with decreasing contrast from bottom to top. It will be evident when viewing the grating that both very low and very high spatial frequencies are more difficult to discern as the contrast drops. The point at which grating detection is lost for a given spatial frequency is known as the contrast threshold and it is the reciprocal of this value that identifies the contrast sensitivity. Plotting contrast sensitivity against spatial frequency gives an inverted 'bell-shaped curve' called the contrast sensitivity function—allowing us to define the point of transition from the 'visible' to the 'invisible' world. The experimental use of sinusoidal gratings in this fashion has been key to the development of our understanding of retinal function both at the level of the retinal ganglion cell response to contrast (Enroth-Cugell and Robson, 1966) and in generating a working hypothesis for the role of dopamine in the retina and the subsequent changes seen in Parkinson's disease.

In addition to using static gratings with different spatial frequencies, one can also employ gratings which drift or flicker, introducing a temporal frequency modulation, another important concept in visual science. Variations in temporal frequency are described in reversals per sec (rev/sec) or complete cycles per second (Hz). As gratings are made up of alternating high and low contrast components, one completed cycle per second, from high-low-high contrast, requires two reversals per second. As temporal frequency increases, contrast becomes more difficult to perceive, resulting in flicker fusion, the point at which the stimulus appears not to change at all.

Given the layout of the retina, with specific rod and cone distributions and different populations of bipolar and RGCs it will be obvious that the spatial and temporal qualities of the retina are not uniform but rather depend on which parts are stimulated and under what conditions. Hence, at least from a retinal perspective, visual acuity and contrast sensitivity will depend not just on 'optical' factors such as refractive error and pupil size but also on 'neural' factors such as photoreceptor density, stimulus contrast and luminance and the region of the retina being stimulated (Perry and Cowey, 1985; Thibos *et al*., 1987; Dacey and Petersen, 1992; Altpeter *et al*., 2000; Silva *et al*., 2008).

Retinal involvement in Parkinson's disease

There can be little doubt that dopamine plays an important role in retinal function but precisely how dopaminergic deficiency, as seen in Parkinson's disease, might affect the retina, is less clear. The hypothesis that the retina is a site of functional and structural change in Parkinson's disease raises a number of questions. Firstly, given that Parkinson's disease prevalence increases with age, if there is evidence of retinal dysfunction in Parkinson's disease the proportion due to Parkinson's disease-specific as opposed to age-related change needs to be clarified. If there is a disease-specific effect, could this be due to dopaminergic deficiency at a retinal level, to central deficits in the LGN or visual cortex, or to both? If there is a local dopaminergic deficiency in the Parkinsonian retina, does this interfere with signal transmission and hence cause functional limitations in vision? And finally, to what extent does dysfunction of the retina contribute to the generation of the more striking visual symptoms seen in Parkinson's disease such as visual hallucinations? Work over the past 40 years has addressed many of these issues and, where answers are available, these will be highlighted in the course of the article.

The ageing retina

Visual function changes as we age, in part due to age-related diseases of the eye such as cataract, age-related macular degeneration, diabetic retinopathy and glaucoma (Klein *et al*., 1992; Mangione *et al*., 1994; Owsley *et al*., 2000, 2001; Johnson, 2001). Even in the absence of such overt pathology, however, visual function declines with age. Such changes include reduction in the focal power of the lens, leading to presbyopia, and a reduction in pupil size often referred to as 'senile miosis'. The former limits the focusing ability of the eye and the latter, in extreme situations, may reduce retinal illumination. Retinal degeneration also occurs leading to reductions in rod and cone numbers and the loss of RGCs (Pitts, 1982; Weale, 1987; Curcio, 2001). These changes will ultimately define and limit the 'neural' function of the ageing retina. Age-related ophthalmological disease, often in combination with such factors, contributes to the deterioration in visual acuity, contrast sensitivity, colour vision and dark adaptation evident as we age. In addition, central dysfunction due to visual cortex pathology and co-existing cognitive decline may confound studies of vision in the ageing population (Table 1).

Snellen charts provide a measure of visual acuity under conditions not routinely encountered in the 'real-world'. In essence, Snellen acuity measures the ability to read a chart under static, high-contrast conditions. In reality, visual stimuli fall on the retina with highly variable levels of contrast and luminance. In addition, both stimulus and recipient are frequently in motion, requiring constant corrective eye movements and attentional selection of

Table 1 Summary of age-related alterations in visual function

Ageing changes	Functional impact
Age-related ophthalmological disease	
Cataract	Reduction in retinal illumination
	Changes in visual acuity and contrast sensitivity
	Alteration in lens focal power
Age-related macular degeneration (AMD)	Reduction in visual acuity
	Reduction in dark adaptation
Diabetic retinopathy	Reduction in visual acuity
Glaucoma	Restricted visual fields
	Reduction in visual acuity
	Reduction in colour vision
Age-related ophthalmological changes	
Reduction in lens focal power (presbyopia)	Changes in visual acuity and contrast sensitivity
Senile miosis	Reduction in retinal illumination
Retinal degeneration	Limitation of 'neural' function of retina
	Impaired dark adaptation
	Reduced static and dynamic visual acuity
	Reduced contrast sensitivity
	Impaired colour vision
'Central' visual impairment	
Primary visual cortex	Visuo-perceptual impairment
Secondary visual cortical areas	Reductions in visual acuity
	Reduced contrast sensitivity
	Impaired motion perception

relevant stimulus components if the image is to be maintained on the optimal part of the retina.

In that regard, there is also a marked effect of ageing on visual processing of moving objects. Early studies examining so-called dynamic visual acuity have demonstrated specific dynamic impairments in the elderly. Dynamic visual acuity is required for important 'real-world' tasks such as walking and driving and is a better marker of driving ability in the elderly than static visual acuity (Burg and Hulbert, 1961; Brown, 1972*a, b*). This is because, whilst static visual acuity sets the maximum achievable dynamic visual acuity, there is a fall off in dynamic acuity caused by 'retinal slip' of the image as eye tracking becomes more inaccurate at higher target velocities. Measurement of dynamic visual acuity is more difficult and time-consuming than assessing static visual acuity and there exists no standardized technique in routine clinical practice, perhaps explaining the lack of recent clinical data in the field. More recently, it has been demonstrated that older subjects show greater impairment on sinusoidal grating and dot cinematogram tests of motion perception (Willis and Anderson, 2000; Billino *et al*., 2008; Conlon and Herkes, 2008). Such tasks assess motion perception processing in retinal, subcortical and cortical visual areas although the relative contribution low-level, retinal deficits make to such changes remains unclear.

In addition, contrast sensitivity declines as we age, particularly at intermediate and high spatial frequencies. This contrast sensitivity loss is caused, in part, by 'optical' factors such as lens opacity and senile miosis in combination with retinal 'neural' factors such as photoreceptor and ganglion cell degeneration (Owsley and Sloane, 1987; Sloane *et al*., 1988*a, b*; Burton *et al*., 1993; Schefrin *et al*., 1999). Such alterations in the spatial and temporal qualities of the retina could potentially confound studies of vision in Parkinson's disease unless control groups appropriately matched for age are also assessed.

Colour vision relies on the cone photoreceptor population and is therefore largely confined to the central retina. Because there is a segregation of colour-specific information at the retinal level into blue-yellow (BY) and red-green (RG) pathways, it is possible to use colour discrimination tasks to assess cone and retinal ganglion cell subpopulations. Colour (photopic) vision is affected by the ageing process particularly along the BY (tritan) axis, possibly due to cone dysfunction and opacified lens absorption of short wavelength light (Knoblauch *et al*., 1987; Nguyen-Tri *et al*., 2003). However, scotopic vision is more vulnerable to the ageing affect and rod photoreceptors are particularly at risk (Curcio *et al*., 1993; Jackson and Owsley, 2000; Jackson *et al*., 2002). This has implications for dark adaptation in the elderly eye, a potential additional problem in the dopamine-deficient retina.

Retinal dopamine in Parkinson's disease

Neurochemical evidence for dopaminergic deficiency in the human retina was first advanced with reports of reduced tyrosine hydroxylase immunoreactivity of dopaminergic cells in five patients with Parkinson's disease (Nguyen-Legros, 1988). Tyrosine hydroxylase (TH) is the rate-limiting enzyme in the synthesis of dopamine and hence identifies DA-containing cells in the retina. Harnois and Di Paolo, examining parkinsonian patients at post-mortem, found that subjects not receiving L-DOPA therapy at the time of death had significantly lower retinal dopamine concentrations than controls or those whose death occurred less than 15 h after their last dose (Harnois and Di Paolo, 1990). Such post-mortem studies in human tissue are rare, with small numbers of patients involved and, as such, one must interpret these findings with a degree of caution. Treatment of monkeys with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxin which destroys dopaminergic cells, causes a dose-dependent, but reversible, reduction in TH immunoreactivity in amacrine cells (Tatton *et al*., 1990). Dopaminergic depletion of the cat retina leads to enhancement of intraretinal scotopic electrophysiological responses (scotopic threshold and PII responses), an effect reversed by the addition of dopamine and consistent with dopaminergic modulation of amacrine function (Naarendorp *et al*., 1993). These studies, despite their limitations, provided a tantalizing link between previously documented electrophysiological and psychophysical evidence of retinal dysfunction in Parkinson's disease and the hypothesis that it was dopaminergic deficiency itself that mediated these changes.

Evidence of visual dysfunction in Parkinson's disease

Visual acuity

Reports of impaired visual acuity in Parkinson's disease patients first emerged in the early 1990s in a small cross-sectional study (Jones *et al*., 1992) (Table 2). Small absolute changes in Snellen and computer-generated tests of acuity were found in Parkinson's disease. Surprisingly, given the broad range of visual complaints reported, few studies have looked specifically at visual acuity in the Parkinson's disease population. The clinical significance of diminished visual acuity is highlighted by the finding of visual loss as a risk factor for visual hallucinations in Parkinson's disease (Holroyd *et al*., 2001; Matsui *et al*., 2006) and in Alzheimer's disease (McShane *et al*., 1995; Chapman *et al*., 1999). A potential confounder is the impact cognitive impairment has on the ability of patients to perform tests of vision. However, Matsui *et al*. studied Parkinson's disease patients with and without visual hallucinations, and despite a reduction in visual acuity in the Parkinson's disease group, no significant difference in mini-mental state examination (MMSE) scores between groups was reported (Matsui *et al*., 2006).

Diminished visual acuity is a well-established risk factor for visual hallucinations in patients with ocular pathology—the Charles Bonnet syndrome. In this condition, patients experience a variety of visual phenomena from simple visual disturbances (flashes of light) through to well-formed, complex visual hallucinations (Teunisse, 1997; Teunisse *et al*., 1999; Santhouse *et al*., 2000). Functional MRI images in actively hallucinating Charles Bonnet syndrome patients have implicated the inferior occipito-temporal cortex, fusiform face area and posterior fusiform gyrus in the genesis of specific hallucinatory experiences (Ffytche *et al*., 1998). There are many differences in the clinical context in which visual hallucinations occur in Charles Bonnet syndrome and Parkinson's disease. Visual acuity is classically significantly impaired in Charles Bonnet syndrome in contrast to the alterations in acuity seen in Parkinson's disease with the commonest ocular pathology being macular degeneration (Teunisse *et al*., 1996). In addition, although complex visual hallucinations are described, simple visual disturbances are most common (ffytche and Howard, 1999). Nevertheless, the concept of 'de-afferentation' of the visual cortex by ocular disease (Cogan, 1973; Burke, 2002) priming the system for visual hallucination-generation is an attractive hypothesis in Parkinson's disease given the changes in visual acuity.

Table 2 Summary of evidence for visual dysfunction in Parkinson's disease

Visual modality affected
Visual acuity
Contrast sensitivity
Colour vision
Motion perception
Retinal structure
Electroretinogram recordings
Visual evoked potential recordings

Contrast sensitivity

The first clinical reports of abnormal contrast sensitivity in Parkinson's disease came from Regan and Neima (1984) when they investigated the vision of 10 patients using letter charts similar to Snellen cards, but with varying contrast levels. Half of the Parkinson's disease patients tested demonstrated abnormalities on low contrast letter tests despite many having normal Snellen acuities. Further studies using vertical gratings with a sinusoidal luminance profile have consistently shown contrast sensitivity loss at a variety of spatial frequencies (Bulens *et al*., 1986; Harris *et al*., 1992; Delalande *et al*., 1996; Langheinrich *et al*., 2000). Bodis-Wollner and Yahr reported that the spatial frequency loss in Parkinson's disease was most marked at 4.8 cpd, the normal peak contrast sensitivity region in controls (Bodis-Wollner *et al*., 1987). Such modification of the contrast sensitivity curve in Parkinson's disease was exaggerated when temporal variation was introduced at the 4–8 Hz range (Bodis-Wollner *et al*., 1987; Regan and Maxner, 1987). In addition, spatiotemporal contrast sensitivity to moving gratings was diminished in Parkinson's disease in a different pattern to the reductions seen in age-matched controls, suggesting a disease-specific 'motion blur' in contrast perception (Mestre *et al*., 1990; Masson *et al*., 1993).

That these alterations are driven by dopaminergic deficiencies in the retina is supported by the findings that contrast sensitivity improves after the administration of L-DOPA (Bulens *et al*., 1987; Hutton *et al*., 1993) and that similar alterations occur in drug-induced parkinsonism (Bulens *et al*., 1989). In addition, Parkinson's disease patients with marked motor fluctuations between their 'on' and 'off' state, show a mid-spatial frequency decrease in contrast sensitivity similar to that observed in stable parkinsonian patients. When tested in their 'on' condition, the contrast sensitivity curves more closely resembled age-matched controls (Bodis-Wollner and Onofrj, 1987). These psychophysical tests of presumed retinal function are, however, relatively complex tasks drawing on attentional and cognitive abilities in addition to retinal properties (Crucian and Okun, 2003; Geldmacher, 2003). Given that few studies have controlled for these potential confounders, it is difficult to know how much of the contrast sensitivity change can be truly attributed to retinal dysfunction. Contrast sensitivity losses have been identified as orientation-specific in some cases (Regan and Maxner, 1987; Bulens *et al*., 1988) arguing for a degree of cortical influence as orientation specificity is not determined at a retinal level (Hubel and Freeman, 1977; Hubel *et al*., 1977, 1978; Regan and Maxner, 1987). It seems likely that the abnormality in contrast sensitivity has a strong retinal component however as, despite abnormal contrast sensitivity findings in Parkinson's disease patients, cortical adaptation to changing stimuli remains intact (Tebartz van Elst *et al*., 1997).

Static measures of contrast sensitivity are attractive due to their ease of application in a clinical setting, as well as their intuitive

familiarity to patients, but they cover a relatively narrow range of spatial frequencies and have been criticized for their lack of test-retest reliability (Reeves *et al*., 1991). Contrast charts used vary from study-to-study but include static gratings as well as contrast charts with letter optotypes of diminishing contrast. Several studies, using static charts, have demonstrated disturbances of contrast sensitivity (Price *et al*., 1992; Buttner *et al*., 1996; Pieri *et al*., 2000; Uc *et al*., 2005) with evident progression in one longitudinal follow-up study over 20 months (Diederich *et al*., 1998, 2002).

Contrast sensitivity is vital for a range of day-to-day activities and diminished contrast sensitivity has been implicated in falls, difficulties in reading and driving performance, as well as with activities of daily living in elderly patients (Owsley and Sloane, 1987; Ivers *et al*., 1998; West *et al*., 2002; de Boer *et al*., 2004; Kooijman and Cornelissen, 2005; Lord, 2006; Worringham *et al*., 2006). The functional significance of contrast sensitivity changes in Parkinson's disease specifically is less clear. A similar change in contrast sensitivity is seen when the retina makes the transition from high- to low-luminance levels (Wink and Harris, 2000). It is tempting to infer from this that dopamine is, at least in part, responsible for preparing the retina for photopic vision and that a deficiency state leads to an inappropriately dark-adapted retina. In addition, despite equivalent cognitive scores on MMSE, Diederich showed that Parkinson's disease patients with visual hallucinations had significantly worse contrast sensitivity than those without hallucinations, suggesting a putative role for retinal dysfunction in the development of visual complications in Parkinson's disease (Diederich *et al*., 1998).

Colour vision

Deficits in colour vision in Parkinson's disease are also well documented and suggest involvement of different colour-opponent pathways in the disease process. In general, colour vision is cone-mediated via specific, segregated visual pathways—parvocellular, mediated by small RGCs (P cells) and terminating in the parvocellular layers of the LGN and koniocellular, mediated by bistratified RGCs and synapsing in the interlaminar layers of the LGN. In contrast, achromatic information is transmitted by large RGCs (M cells) in the magnocellular pathway. Clinical, psychophysical and electrophysiological tests of colour vision have all been applied to the Parkinson's disease population, although each has potential drawbacks. The Farnsworth-Munsell 100 Hue test (FM) and the D-15 Lanthony test (D-15) are the most widely used clinical tests, requiring participants to arrange coloured discs into a smoothly graduated colour sequence. Even allowing for the limited quantification power and the variability in test-retest scores (Birch *et al*., 1998), Parkinson's disease patients demonstrate significantly higher error rates on the FM test than age-matched controls (Price *et al*., 1992; Pieri *et al*., 2000). Less dramatic, but statistically significant, deficits are also seen in colour discrimination tasks devoid of the 'motor' requirements of the FM and D-15 tasks (Haug *et al*., 1994, 1995; Regan *et al*., 1998). Silva *et al*. (2005) probed chromatic and achromatic contrast sensitivity changes in Parkinson's disease using complex psychophysical measures designed to isolate parvocellular, koniocellular and magnocellular pathways. Significant impairment in all three pathways was found, more marked along the protan/deutan (RG) axis than the tritan (BY). This pattern contrasts with that typically seen in ageing—predominant tritan axis deficiency—or in retinal disease states such as glaucoma in which all colour axes are involved with particular emphasis on the tritan axis or Best Macular dystrophy where colour axis involvement depends on the stage of the disease itself (Castelo-Branco *et al*., 2004, Campos *et al*., 2005). Such comparisons suggest a disease-specific pattern of retinal impairment in Parkinson's disease distinct from 'normal ageing' or the commoner age-related ophthalmological diseases. Evidence that these abnormalities have a retinal component comes from the finding of amplitude reductions in chromatic and achromatic PERG responses in Parkinson's disease when compared to controls and subjects with Multiple System Atrophy (MSA) (Sartucci *et al*., 2006).

Motion perception

In addition to changes in visual acuity and contrast sensitivity, perception of motion is also affected in Parkinson's disease and Parkinson's disease dementia (Trick *et al*., 1994; Mosimann *et al*., 2004). Uc *et al*. (2005) studied visual attention and motion perception in Parkinson's disease patients and age-matched controls using the useful field of vision (UFOV) test and random dot cinematograms. The UFOV test assesses speed of visual processing and selective and divided visual attention when visual stimuli (car silhouettes) are presented individually and simultaneously in the central and peripheral visual field. Random dot cinematograms are used to present a motion signal amid spatially random background noise. Parkinson's disease patients demonstrated impairments of visual attention, spatial and motion detection compared to controls. These group differences became non-significant when contrast sensitivity and visual acuity were controlled for—suggesting a retinal contribution to this impaired motion perception. However, group differences persisted for measures of visual speed of processing and alternative measures of visual attention, supporting a cortical contribution to such perceptual disturbances as well. The correlation between impaired visual perception and cognition backs up this hypothesis, arguing in favour of both 'bottom up' (retinal) and 'top down' (cortical) components to the breakdown in visual perception in Parkinson's disease.

One recent approach that sheds further light on this area involved the use of a range of hierarchical stimuli designed to bias responses from low-level (magnocellular), intermediate-level and higher-level (dorsal stream) visual pathways and study their inter-dependence (Castelo-Branco *et al*., 2008). Parkinson's disease patients, screened for ophthalmological disorders and matched for cognition by MMSE, demonstrated preferential impairment in motion discrimination tasks requiring perceptual integration of moving surfaces. Despite abnormalities of low-level magnocellular pathways, there was no correlation between these and motion integration impairments in the Parkinson's

disease group. This recent work, demonstrating a dissociation between low- and high-level visual processing in Parkinson's disease, suggests that motion perception in the higher visual centres of the cortex is affected in Parkinson's disease and that not all such perceptual impairments can be explained by abnormalities in the early magnocellular pathway from retina to sub-cortical, striate and extra-striate regions. The studies by Castelo-Branco *et al*. and Uc *et al*. also highlight the link between impairments of motion perception and motor function, with impaired performance on simple and complex finger-tapping tasks correlating with motion perception measures in the former and severity of postural instability and gait disorders correlating with impairments in visual speed of processing in the latter.

Structural changes in the retina

These changes in visual function might suggest structural alterations at a microscopic or macroscopic level in the retina. In light of the increasing evidence that cortical and sub-cortical visual pathology also plays a role in these abnormalities, development of tools to probe the retina in isolation become increasingly important. One solution to these methodological issues is to focus on retinal structure in Parkinson's disease and other Lewy body disorders. One such post-mortem study has suggested swelling of photoreceptors and RGCs as well as pale intracellular inclusions in the outer plexiform layer in the retina in patients with dementia with Lewy bodies. All sixteen patients studied at post-mortem suffered visual hallucinations and demonstrated ante-mortem abnormalities on flash-ERG (Devos *et al*., 2005). It is difficult to generalize from this small study in dementia with Lewy bodies to the Parkinson's disease population, however, and further studies are required.

Non-invasive techniques are now available to probe retinal structure. Optical coherence tomography provides high-resolution cross-sectional data on the retina by measuring time delays and backscatter from a pulsed laser source. It is possible to assess peripapillary retinal nerve fibre layer (RNFL) thickness using this technique, thereby providing an estimation of retinal ganglion cell nerve fibre integrity. Optical coherence tomography has been shown to be accurate, with an axial resolution of 3–5 microns on newer machines, and reproducible in the assessment of glaucoma and ageing (Blumenthal *et al*., 2000; Paunescu *et al*., 2004; Budenz *et al*., 2005) provided signal strength is adequate (Cheung *et al*., 2008). Factors such as age, ethnicity, axial length and optic disc size all influence RNFL thickness as measured by optical coherence tomography and should be taken in to account when interpreting results obtained by this method (Budenz *et al*., 2007). In addition, optical coherence tomography demonstrates morphological changes in retinal structure in multiple sclerosis, Alzheimer's disease and glaucoma (Parisi *et al*., 1999; Kanamori *et al*., 2003; Iseri *et al*., 2006). Retinal nerve fibre thinning has been found in Parkinson's disease, albeit in relatively small numbers of patients (Inzelberg *et al*., 2004; Altintas *et al*., 2007). Such studies require repetition in larger cohorts to ensure reproducibility and, to date, the functional implications of this structural change are unknown.

VEP and ERG

Retinal responses to visual stimuli generate electrical activity in the eye, as does the transmission of these responses to the primary visual cortex. Measurement of the amplitude and latency of such electrical responses provides information on the functional integrity of the visual pathway and both electroretinograms (ERG) and visual-evoked potentials (VEP) have been extensively studied in Parkinson's disease. Early work from Bodis-Wollner and Yahr (1978) demonstrated a delay in the VEP latency to sinusoidal gratings at a mid-spatial frequency and these findings have been replicated in a number of subsequent studies using a variety of spatial and temporal stimulus parameters (Regan and Neima, 1984; Marx *et al*., 1986; Nightingale *et al*., 1986; Tartaglione *et al*., 1987; Ikeda *et al*., 1994). Such VEP latency changes can be reversed with the administration of L-DOPA therapy and, in the healthy retina, treatment with dopaminergic blockers, such as haloperidol, results in an increment of VEP latency at identical spatial frequencies to those used in the Parkinson's disease patient group (Onofrj *et al*., 1986). It is possible to obtain both normal and abnormal results in the same patients depending on the characteristics of the pattern stimulus and this helps to explain the often contradictory neurophysiological findings in early work (Tartaglione *et al*., 1987).

Pattern ERG (PERG), by stimulating the retina at an even mean luminance, measures the electrical contribution from cells of the inner retina—predominantly the retinal ganglion cells (Maffei *et al*., 1985). As with other measures, the response is highly dependent on the spatial, temporal and contrast characteristics of the gratings or checkerboards used. Studies have consistently shown alterations in both PERG latencies and amplitudes in Parkinson's disease (Nightingale *et al*., 1986; Gottlob *et al*., 1987; Stanzione *et al*., 1990; Peppe *et al*., 1992, 1998; Langheinrich *et al*., 2000; Sartucci *et al*., 2006). In contrast to a 'global' reduction in amplitude of PERG response, to a variety of sinusoidal grating spatial frequencies, in age-matched controls compared to young controls, Parkinson's disease patients show a specific medium-frequency deficit (Tagliati *et al*., 1996). These changes respond to administration of L-DOPA (Peppe *et al*., 1995, 1998) and may be progressive (Ikeda *et al*., 1994). Administration of the selective D2 receptor antagonist *l*-sulpiride to normal controls mimics the mid-spatial frequency abnormalities seen in Parkinson's disease (Stanzione *et al*., 1995), unlike the PERG response to haloperidol, a dopamine receptor antagonist with affinity for both D1 and D2 receptors (Stanzione *et al*., 1999). Identical changes in the PERG response are also seen in the monkey retina using *l*-sulpiride (Tagliati *et al*., 1994) and these important findings in the human and primate suggest a pivotal role for the D2 receptor-dependent action of dopamine in 'tuning' the PERG response to stimuli of different spatial frequencies.

Animal studies, particularly in the primate, have also proven extremely useful in advancing a coherent hypothesis for dopaminergic actions at a retinal level. Ghilardi *et al*. (1989) administered MPTP systemically to monkeys, inducing a parkinsonian syndrome in all cases. Such measures have been shown to reduce primate

retinal dopamine levels at post-mortem assessment (Ghilardi *et al*., 1988*b*). Subsequent measurement of pattern VEP and ERG demonstrated reductions in amplitude and prolongation of latency in both measures compared to pre-administration results. Treatment with L-DOPA produced transient recovery both in parkinsonian signs and PVEP and PERG measurements (Ghilardi *et al*., 1988*a*). Administering 6-hydroxydopamine (6-OHDA) intraocularly to locally destroy dopaminergic function in monkeys also results in spatial frequency-dependent losses in PERG amplitude, which improve after L-DOPA administration (Ghilardi *et al*., 1989; Bodis-Wollner and Tzelepi, 1998). In addition, by measuring ERG response to flash and pattern stimuli after administration of a variety dopaminergic antagonists (*l*-sulpiride, haloperidol) and a D1 receptor agonist, Bodis-Wollner and Tzelepi (1998) postulated that dopamine, acting via both D1 and D2 receptors pre- and post-synaptically modulates the balance of centre-surround receptive fields of retinal ganglion cells, tuning the overall retinal response to spatial frequency in a 'push–pull' manner (Bodis-Wollner and Tzelepi, 1998).

Functional implications

What are the functional implications of these findings? That dopamine is vital to retinal function is now beyond doubt but the precise nature of its actions in the human retina are only now becoming clearer. The complexity of the connections of dopaminergic amacrine cells suggests multiple roles, not least in suppressing the transmission of rod-driven visual information from the peripheral retina in low-light, but not fully dark, conditions (mesopic). The use of alternating sinusoidal gratings both to stimulate individual ganglion cells, such as in the seminal work of Enroth-Cugell and Robson (1966), and in exciting a massed central retinal ganglion cell response, such as in the PERG, has provided the link necessary to better define the role of dopamine in normal retinal function. This bridge between cellular retinal structure and individual and summative retinal ganglion cell function implicates dopamine heavily in organizing the receptive field of these output cells of the retina. Thus the spatiotemporal contrast sensitivity abnormalities in Parkinson's disease, particularly at the point where the normal peak of contrast sensitivity occurs, are a measure of dopaminergic influences on the 'centre-surround' receptive fields of RGCs. The striking similarity between the contrast sensitivity function curves of dark-adapted normal retina and light-adapted Parkinson's disease retina implicate DA in the transition from scotopic to photopic vision (Harris *et al*., 1992; Wink and Harris, 2000). The finding of a diurnal variation in dopamine concentration, dependent on melatonin release, would support the dopaminergic mediation of dark–light transitions. In other words, dopamine activity favours cone-mediated, high-contrast vision and the parkinsonian retina may therefore exist in an inappropriately dark-adapted state. This, in turn, may lead to larger retinal ganglion cell receptive fields and lower spatial and temporal resolving potential and an ultimate impact on visual acuity, contrast sensitivity and colour perception.

ERG and VEP data consistently demonstrate functional disruption of the transfer of visual information out of the retina, particularly the magnocellular and parvocellular pathways. Magnocellular neurons are vital for integrating rod-driven signals and this pathway, from retina to visual cortex via LGN, is particularly sensitive to motion and low luminance contrast detection. The reliance on information from the rod system also means that the magnocellular pathway dominates in the peripheral retina. The cone contribution to this pathway is reflected in its important diurnal pattern of activity. Disruption of this M-pathway may deprive particularly the dorsal visual stream of vital cues for accurate motion perception. Parvocellular pathways, relaying colour and acuity data also breakdown in Parkinson's disease, possibly contributing to ventral stream failure of object-form perception.

In addition to this 'bottom up' disruption of information processing, there are also likely to be both sub-cortical and cortical components to visual symptomatology in Parkinson's disease and Parkinson's disease dementia. Visuocognitive and visuoperceptual impairments are most striking in Parkinson's disease dementia, where visual hallucinations are particularly prominent (Mosimann *et al*., 2004). Cognitive impairment is common in Parkinson's disease, even in incident cohorts with mild or early disease and simple screening tools for cognitive dysfunction such as the MMSE will miss many Parkinson's disease patients with mild cognitive impairment—a potential confounder in tests of visual function (Foltynie *et al*., 2004). New clinical diagnostic criteria for identifying patients with Parkinson's disease dementia, in conjunction with a better appreciation of mild cognitive impairment as a precursor to more marked decline (Janvin *et al*., 2006*a*; Williams-Gray *et al*., 2007), should allow separation of these patients from cognitively intact Parkinson's disease patients—a vital step if we are to integrate both 'bottom up' and 'top down' approaches to vision research in Parkinson's disease and Parkinson's disease dementia (Emre *et al*., 2007).

'De-afferentation' of the visual cortex from accurate retinal input can be seen in Charles Bonnet Syndrome as a potent risk factor for visual hallucinations. Hallucinations as a cortical release phenomenon have long been postulated in Charles Bonnet syndrome and a similar pathogenic mechanism may occur in Parkinson's disease and Parkinson's disease dementia. Impaired visual acuity and contrast sensitivity are risk factors for hallucinations in Parkinson's disease but it seems unlikely that the subtle changes seen in Parkinson's disease are the entire explanation. Further work is needed to explore the interactions between dysfunction of the retina and the central breakdown of visual processing both at the primary visual cortex and beyond. It seems likely that retinal changes contribute to the multitude of other visual symptoms encountered in Parkinson's disease (blurred vision, difficulty reading) although data is currently lacking to support this notion. Visuomotor problems such as gait disorders, freezing, postural instability and falls are a huge source of anxiety and morbidity in patients with Parkinson's disease. Evidence is now emerging that visual dysfunction directly contributes to these more traditional 'motor' complications, although the relative contributions of retina and visual cortex to the vast array of motor symptoms remain unclear (Uc *et al*., 2005; Castelo-Branco *et al*., 2008).

Structural degeneration of the retina has been reported in Parkinson's disease, but how this changes with disease progression

and whether it contributes to symptoms such as visual hallucinations is currently unknown. With the emergence of better non-invasive techniques for studying retinal function we now have the opportunity to embark on longitudinal studies to address this question. Combining this approach with post-mortem retinal work may also help to clarify the potential trophic role of dopamine in maintaining retinal structure and function. The counterphase balance between dopamine and melatonin may also be important, not just in pupillary function and retinal dark-light adaptation, but in the development of alterations in sleep–wake cycle or even REM-sleep behaviour disorder, prominent non-motor features of Parkinson's disease.

The inclusion of appropriate age-matched controls in many studies has highlighted the marked difference between normal ageing and Parkinson's disease in terms of retinal function. However, we do not have an answer to the question of how Parkinson's disease may interact with age-related ophthalmological diseases such as cataract and AMD as almost all studies to date have excluded patients with significantly diminished visual acuity or identifiable ocular pathology. Whilst this has helped to clarify the role of dopamine in retinal function and disease-specific disruption of visual processing in Parkinson's disease, it is not the 'real world' that we inhabit as clinicians. A better appreciation of how structural disease of the eye contributes to disability in Parkinson's disease is overdue, particularly as effective treatments exist for many of the concomitant ocular disorders that may contribute to visual symptoms in Parkinson's disease. Successful intervention therefore offers the prospect of improvements in the quality of life of Parkinson's disease patients and their carers. It also seems likely that we need to move beyond traditional static methods of assessing visual adequacy as detailed assessment of some of the more subtle changes in visual function may allow earlier identification of those patients at risk of developing visual, motor and cognitive complications of Parkinson's disease. In addition, understanding neurodegeneration within the retina, both at a microscopic and macroscopic level, may provide a clearer window through which to view the disease process itself and its influence, not just on the eye, but also on visuoperceptual, visuocognitive and visuomotor performance as well.

Acknowledgements

The authors would like to thank Profs Paul Witkovsky and Cynthia Owsley for their contributions and helpful suggestions and Prof. Patrick Chinnery and Mr Phil Griffiths for reviewing the manuscript prior to submission.

References

Aarsland D, Larsen JP, Karlsen K, Lim NG, Tandberg E. Mental symptoms in Parkinson's disease are important contributors to caregiver distress. Int J Geriatr Psychiatry 1999; 14: 866–74.

Aarsland D, Larsen JP, Tandberg E, Laake K. Predictors of nursing home placement in Parkinson's disease: a population-based, prospective study. J Am Geriat Soc 2000; 48: 938–42.

Aarsland D, Litvan I, Salmon D, Galasko D, Wentzel-Larsen T, Larsen JP. Performance on the dementia rating scale in Parkinson's disease with dementia and dementia with Lewy bodies: comparison with progressive supranuclear palsy and Alzheimer's disease. J Neurol Neurosurg Psychiatry 2003; 74: 1215–20.

Allcock LM, Kenny RA, Burn DJ. Clinical phenotype of subjects with Parkinson's disease and orthostatic hypotension: autonomic symptom and demographic comparison. Mov Disord 2006; 21: 1851–5.

Altintas O, Iseri PK, Ozkan B, Caglar Y. Correlation between retinal morphological and functional findings and clinical severity in Parkinson's disease. Doc Ophthalmol 2007; 116: 137–46.

Altpeter E, Mackeben M, Trauzettel-Klosinski S. The importance of sustained attention for patients with maculopathies. Vision Res 2000; 40: 1539–47.

Amthor FR, Takahashi ES, Oyster CW. Morphologies of rabbit retinal ganglion cells with concentric receptive fields. J Comp Neurol 1989; 280: 72–96.

Baccus SA, Meister M. Fast and slow contrast adaptation in retinal circuitry. Neuron 2002; 36: 909–19.

Barnes J, David AS. Visual hallucinations in Parkinson's disease: a review and phenomenological survey. J Neurol Neurosurg Psychiatry 2001; 70: 727–33.

Baylor DA, Fuortes MGF, O'Bryan PM. Receptive fields of the cones in the retina of the turtle. J Physiol (Lond.) 1971; 214: 265–94.

Billino J, Bremmer F, Gegenfurtner KR. Differential aging of motion processing mechansims: evidence against general pereceptual decline. Vision Res 2008; 48: 1254–61.

Biousse V, Skibell BC, Watts RL, Loupe DN, Drews-Botsch C, Newman NJ. Ophthalmologic features of Parkinson's disease [see comment]. Neurology 2004; 62: 177–80.

Birch J, Kolle RU, Kunkel M, Paulus W, Upadhyay P. Acquired colour deficiency in patients with Parkinson's disease. Vision Res 1998; 38: 3421–6.

Bloomfield SA, Dacheux R. Rod vision: pathways and processing in the mammalin retina. Prog Ret Eye Res 2001; 20: 351–84.

Blumenthal EZ, Williams JM, Weinreb RN, Girkin CA, Berry CC, Zangwill IM. Reproducibility of nerve fibre thickness measurements by use of optical coherence tomography. Ophthalmology 2000; 107: 2278–82.

Bodis-Wollner I, Marx M, Mitra S, Bobak P, Mylin L, Yahr M. Visual dysfunction in Parkinson's disease. Brain 1987; 110: 1675–98.

Bodis-Wollner I, Onofrj M. The visual system in Parkinson's disease. Adv Neurol 1987; 45: 323–7.

Bodis-Wollner I, Tzelepi A. The push-pull action of dopamine on spatial tuning of the monkey retina: the effects of dopaminergic deficiency and selective D1 and D2 receptor ligands on the pattern electroretinogram. Vision Res 1998; 38: 1479–87.

Bodis-Wollner I, Yahr MD. Measurements of visual evoked potentials in Parkinson's disease. Brain 1978; 101: 661–71.

Bohnen NI, Gedela S, Kuwabara H, Constantine GM, Mathis CA, Studenski SA, et al. Selective hyposmia and nigrostriatal dopaminergic denervation in Parkinson's disease. J Neurol 2007; 254: 84–90.

Brown B. Dynamic visual acuity, eye movements and peripheral acuity for moving targets. Vision Res 1972a; 12: 305–21.

Brown B. The effect of target contrast variation on dynamic visual acuity and eye movements. Vision Res. 1972b; 12: 1213–24.

Budenz DL, Anderson DR, Varma R, Schuman J, Cantor L, Savell J, et al. Determinants of normal retinal nerve fiber layer thickness measured by Stratus OCT. Ophthalmology 2007; 114: 1046–52.

Budenz DL, Chang RT, Huang X, Knighton RW, Tielsch JM. Reproducibility of retinal nerve fibre thickness measurements using the Stratus OCT in normal and glaucomatous eyes. Invest Ophthalmol Vis Sci 2005; 46: 2440–3.

Bulens C, Meerwaldt JD, Van der Wildt GJ. Effect of stimulus orientation on contrast sensitivity in Parkinson's disease. Neurology 1987; 38: 76–81.

Bulens C, Meerwaldt JD, Van der Wildt GJ. Effect of stimulus orientation on contrast sensitivity in Parkinson's disease. Neurology 1988; 38: 76–81.

Bulens C, Meerwaldt JD, van der Wildt GJ, Keemink CJ. Contrast sensitivity in Parkinson's disease. Neurology 1986; 36: 1121–5.

Bulens C, Meerwaldt JD, van der Wildt GJ, Keemink CJ. Visual contrast sensitivity in drug-induced Parkinsonism. J Neurol Neurosurg Psychiatry 1989; 52: 341–5.

Burg A, Hulbert SF. Dynamic visual acuity as related to age, sex and static acuity. J Appl Psychol 1961; 45: 111–6.

Burke W. The neural basis of Charles Bonnet hallucinations: a hypothesis [see comment]. J Neurol Neurosurg Psychiatry 2002; 73: 535–41.

Burton KB, Owsley C, Sloane ME. Aging and neural spatial contrast sensitivity: photopic vision. Vision Res 1993; 33: 939–46.

Buttner T, Kuhn W, Muller T, Heinze T, Puhl C, Przuntek H. Chromatic and achromatic visual evoked potentials in Parkinson's disease. Electroencephalogr Clin Neurophysiol 1996; 100: 443–7.

Cahill GM. Circadian regulation of melatonin production in cultured zebrafish pineal and retina. Brain Res 1996; 708: 177–81.

Campos SH, Forjaz V, Kozak LR, Silva E, Castelo-Branco M. Quantitative phenotyping of chromati dysfunction in best macular dystrophy. Arch Ophthalmol 2005; 123: 944–9.

Castelo-Branco M, Faria P, Forjaz V, Kozak LR, Azevedo H. Simultaneous comparison of relative damage to chromatic pathways in ocular hypertension and glaucoma: correlation with clinical measures. Invest Ophthalmol Vis Sci 2004; 45: 499–505.

Castelo-Branco M, Mendes M, Silva F, Massano J, Januario G, Januario C, *et al*. Motion integration deficits are independent of magnocelluar impairment in Parkinson's disease. Neuropsychologia 2008; Advance Access published on 3 September 2008, doi:10.1016/j.neuropsychologia.

Chapman FM, Dickinson J, McKeith I, Ballard C. Association among visual hallucinations, visual acuity, and specific eye pathologies in Alzheimer's disease: treatment implications [see comment]. Am J Psychiatry 1999; 156: 1983–5.

Cheung CYL, Leung CKS, Lin D, Pang C, Lam DSC. Relationship between retinal nerce fiber layer measurement and signal strength in optical coherence tomography. Ophthalmology 2008; 115: 1347–51.

Cogan DG. Visual hallucinations as release phenomena. Albrecht Von Graefes Arch Klin Exp Ophthalmol 1973; 188: 139–50.

Comella CL. Sleep disturbances and excessive daytime sleepiness in Parkinson disease: an overview. J Neural Transm 2006; 70 (Suppl): 349–55.

Conlon E, Herkes K. Spatial and temporal processing in healthy aging: implications for perceptions of driving skills. Neuropsychol Dev Cogn Sec B Aging Neuropsychol Cogn 2008; 15: 446–70.

Contini M, Raviola E. GABAergic synapses made by a retinal dopaminergic neuron. Proc Natl Acad Sci USA 2003; 100: 1358–63.

Crucian GP, Okun MS. Visual-spatial ability in Parkinson's disease. Front Biosci 2003; 8: s992–7.

Cummings JL, Masterman DL. Depression in patients with Parkinson's disease. Int J Geriatr Psychiatry 1999; 14: 711–8.

Curcio CA. Photoreceptor topography in ageing and age-related maculopathy. Eye 2001; 15: 376–83.

Curcio CA, Millican CL, Allen KA, Kalina RE. Aging of the human photoreceptor mosaic: evidence for selective vulnerability of rods in central retina [see comment]. Invest Ophthalmol Vis Sci 1993; 34: 3278–96.

Curcio CA, Sloan KR, Kalina RE, Hendrickson AE. Human photoreceptor topography. J Comp Neurol 1990; 292: 497–523.

Dacey DM. The dopaminergic amacrine cell. J Comp Neurol 1990; 301: 461–89.

Dacey DM, Petersen MR. Dendritic field size and morphology of midget and parasol ganglion cells of the human retina. Proc Natl Acad Sci USA 1992; 89: 9666–70.

Dacheux RF, Raviola E. The rod pathway in the rabbit retina: a depolarizing bipolar and amacrine cell. J Neurosci 1986; 6: 331–45.

de Boer MR, Pluijm SMF, Lips P, Moll AC, Volker-Dieben HJ, Deeg DJH, et al. Different aspects of visual impairment as risk factors for falls and fractures in older men and women [see comment]. J Bone Miner Res 2004; 19: 1539–47.

de Lau LM, Breteler MM. Epidemiology of Parkinson's disease. Lancet Neurol 2006; 5: 525–35.

de Rijk MC, Breteler MM, Graveland GA, Ott A, Grobbee DE, van der Meche FG, et al. Prevalence of Parkinson's disease in the elderly: the Rotterdam study. Neurology 1995; 45: 2143–6.

Deans MR, Volgyi B, Goodenough DA, Bloomfield SA, Paul DL. Connexin36 is essential for transmission of rod-mediated visual signals in the mammalian retina [see comment]. Neuron 2002; 36: 703–12.

Delalande I, Destee A, Hache JC, Forzy G, Bughin M, Benhadjali J. Visual evoked potentials and spatiotemporal contrast sensitivity changes in idiopathic Parkinson's disease and multiple system atrophy. Adv Neurol 1996; 69: 319–25.

Devos D, Tir M, Maurage CA, Waucquier N, Defebvre L, Defoort-Dhellemmes S, et al. ERG and anatomical abnormalities suggesting retinopathy in dementia with Lewy bodies. Neurology 2005; 65: 1107–10.

Diederich NJ, Goetz CG, Raman R, Pappert EJ, Leurgans S, Piery V. Poor visual discrimination and visual hallucinations in Parkinson's disease. Clin Neuropharmacol 1998; 21: 289–95.

Diederich NJ, Raman R, Leurgans S, Goetz CG. Progressive worsening of spatial and chromatic processing deficits in Parkinson disease [see comment]. Arch Neurol 2002; 59: 1249–52.

Doyle SE, Grace MS, McIvor W, Menaker M. Circadian rhythms of dopamine in mouse retina: the role of melatonin. Vis Neurosci 2002a; 19: 593–601.

Doyle SE, McIvor W, Menaker M. Circadian rhythmicity in dopamine content of mammalian retina: role of the photoreceptors. J Neurochem 2002b; 83: 211–9.

Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord 2007; 22: 1689–707, quiz 1837.

Enroth-Cugell C, Robson JG. The contrast sensitivity of retinal ganglion cells of the cat. J Physiol (Lond) 1966; 187: 517–52.

Famiglietti EV Jr, Kolb H. A bistratified amacrine cell and synaptic cirucitry in the inner plexiform layer of the retina. Brain Res 1975; 84: 293–300.

Feigenspan A, Gustincich S, Bean BP, Raviola E. Spontaneous activity of solitary dopaminergic cells of the retina. J Neurosci 1998; 18: 6776–89.

Fenelon G, Mahieux F, Huon R, Ziegler M. Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. Brain 2000; 123: 733–45.

Ferrera VP, Nealey TA, Maunsell JH. Mixed parvocellular and magnocellular geniculate signals in visual area V4. Nature 1992; 358: 756–61.

Ferrera VP, Nealey TA, Maunsell JH. Responses in macaque visual area V4 following inactivation of the parvocellular and magnocellular LGN pathways. J Neurosci 1994; 14: 2080–8.

ffytche DH, Howard RJ. The perceptual consequences of visual loss: 'positive' pathologies of vision. Brain 1999; 122: 1247–60.

Ffytche DH, Howard RJ, Brammer MJ, David A, Woodruff P, Williams S. The anatomy of conscious vision: an fMRI study of visual hallucinations. Nat Neurosci 1998; 1: 738–42.

Foltynie T, Brayne CEG, Robbins TW, Barker RA. The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. Brain 2004; 127: 550–60.

Frederick JM, Rayborn ME, Laties AM, Lam DM, Hollyfield JG. Dopaminergic neurons in the human retina. J Comp Neurol 1982; 210: 65–79.

Gardner JL, Sun P, Allen Waggoner J, Ueno K, Tanaka K, Cheng K. Contrast adaptation and representation in human early visual cortex. Neuron 2005; 47: 607–20.

Geldmacher DS. Visuospatial dysfunction in the neurodegenerative diseases. Front Biosci 2003; 8: e428–36.

Ghilardi MF, Bodis-Wollner I, Onofrj MC, Marx MS, Glover AA. Spatial frequency-dependent abnormalities of the pattern electroretinogram and visual evoked potentials in a parkinsonian monkey model. Brain 1988a; 111: 131–49.

Ghilardi MF, Chung E, Bodis-Wollner I, Dvorzniak M, Glover A, Onofrj M. Systemic. 1-methyl,4-phenyl,1-2-3-6-tetrahydropyridine (MPTP) administration decreases retinal dopamine content in primates. Life Sci 1988b; 43: 255–62.

Ghilardi MF, Marx MS, Bodis-Wollner I, Camras CB, Glover AA. The effect of intraocular 6-hydroxydopamine on retinal processing of primates. Ann Neurol 1989; 25: 357–64.

Goetz CG, Fan W, Leurgans S, Bernard B, Stebbins GT. The malignant course of 'benign hallucinations' in Parkinson disease. Arch Neurol 2006; 63: 713–6.

Goetz CG, Stebbins GT. Risk factors for nursing home placement in advanced Parkinson's disease. Neurology 1993; 43: 2227–9.

Goetz CG, Stebbins GT. Mortality and hallucinations in nursing home patients with advanced Parkinson's disease. Neurology 1995; 45: 669–71.

Goodale MA, Milner AD. Separate visual pathways for perception and action. TINS 1992; 15: 20–5.

Goodale MA, Westwood DA. An evolving view of duplex vision: separate but interacting cortical pathways for perception and action. Curr Opin Neurobiol 2004; 14: 203–11.

Gottlob I, Schneider E, Heider W, Skrandies W. Alteration of visual evoked potentials and electroretinograms in Parkinson's disease. Electroencephalogr Clin Neurophysiol 1987; 66: 349–57.

Grieve KL, Acuna C, Cudeiro J. The primate pulvinar nuclei: vision and action. Trends Neurosci 2000; 23: 35–9.

Gustincich S, Feigenspan A, Sieghart W, Raviola E. Composition of theGABAa receptors of retinal dopaminergic neurons. J. Neurosci 1999; 19: 7812–22.

Gustincich S, Feigenspan A, Wu DK, Koopman LJ, Raviola E. Control of dopamine release in the retina: a transgenic approach to neural networks. Neuron 1997; 18: 723–36.

Haeggendal J, Malmfors T. Evidence of dopamine-containing neurons in the retina of rabbits. Acta Physiol Scand 1963; 59: 295–6.

Hampson EC, Vaney DI, Weiler R. Dopaminergic modulation of gap junction permeability between amacrine cells in mammalian retina. J Neurosci 1992; 12: 4911–22.

Harnois C, Di Paolo T. Decreased dopamine in the retinas of patients with Parkinson's disease. Invest Ophthalmol Vis Sci 1990; 31: 2473–5.

Harris JP, Calvert JE, Phillipson OT. Processing of spatial contrast in peripheral vision in Parkinson's disease. Brain 1992; 115: 1447–57.

Hartline HK. The response of single optic nerve fibers of the vertebrate eye to illumination of the retina. Am J Physiol 1938; 121: 400–15.

Hartline HK. The receptive fields of optic nerve fibers. Am J Physiol 1940; 130: 690–9.

Haug BA, Kolle R, Trenkwalder C, Oertel WH, Paulus W. Predominant affection of the blue cone pathway in Parkinson's disease. Brain 1995; 118: 771–8.

Haug BA, Trenkwalder C, Arden GB, Oertel WH, Paulus W. Visual thresholds to low-contrast pattern displacement, colour contrast, and luminance contrast stimuli in Parkinson's disease. Mov Disord 1994; 9: 563–70.

He S, Weiler R, Vaney DI. Endogenous dopaminergic regulation of horizontal cell coupling in the mammalian retina. J Comp Neurol 2000; 428: 33–40.

Hokoc JN, Mariani AP. Tyrosine hydroxylase immunoreactivity in the rhesus monkey retina reveals synapses from bipolar cells to dopaminergic amacrine cells. J Neurosci 1987; 7: 2785–93.

Holroyd S, Currie L, Wooten GF. Prospective study of hallucinations and delusions in Parkinson's disease. J Neurol Neurosurg Psychiatry 2001; 70: 734–8.

Hubel DH, Freeman DC. Projection into the visual field of ocular dominance columns in macaque monkey. Brain Res 1977; 122: 336–43.

Hubel DH, Wiesel TN, Stryker MP. Orientation columns in macaque monkey visual cortex demonstrated by the 2-deoxyglucose autoradiographic technique. Nature 1977; 269: 328–30.

Hubel DH, Wiesel TN, Stryker MP. Anatomical demonstration of orientation columns in macaque monkey. J Comp Neurol 1978; 177: 361–80.

Hutton JT, Morris JL, Elias JW. Levodopa improves spatial contrast sensitivity in Parkinson's disease. Arch Neurol 1993; 50: 721–4.

Ikeda H, Head GM, Ellis CJ. Electrophysiological signs of retinal dopamine deficiency in recently diagnosed Parkinson's disease and a follow up study. Vision Res 1994; 34: 2629–38.

Inzelberg R, Ramirez JA, Nisipeanu P, Ophir A. Retinal nerve fiber layer thinning in Parkinson disease. Vision Res 2004; 44: 2793–7.

Iseri PK, Altinas O, Tokay T, Yuksel N. Relationship between cognitive impairment and retinal morphological and visual functional abnormalities in Alzheimer disease. J Neuroophthalmol 2006; 26: 18–24.

Ivers RQ, Cumming RG, Mitchell P, Attebo K. Visual impairment and falls in older adults: the Blue Mountains eye study. J Am Geriatr Soc 1998; 46: 58–64.

Jackson GR, Owsley C. Scotopic sensitivity during adulthood. Vision Res 2000; 40: 2467–73.

Jackson GR, Owsley C, Curcio CA. Photoreceptor degeneration and dysfunction in aging and age-related maculopathy. Ageing Res Rev 2002; 1: 381–96.

Janvin CC, Larsen JP, Aarsland D, Hugdahl K. Subtypes of mild cognitive impairment in Parkinson's disease: progression to dementia. Mov Disord 2006a; 21: 1343–9.

Janvin CC, Larsen JP, Salmon DP, Galasko D, Hugdahl K, Aarsland D. Cognitive profiles of individual patients with Parkinson's disease and dementia: comparison with dementia with lewy bodies and Alzheimer's disease. Mov Disord 2006b; 21: 337–42.

Jensen RJ. Mechanism and site of action of a dopamine D1 antagonist in the rabbit retina. Vis Neurosci 1989; 3: 573–85.

Jensen RJ, Daw NW. Effects of dopamine antagonists on receptive fields of brisk cells and directionally selective cells in the rabbit retina. J Neurosci 1984; 4: 2972–85.

Johnson CA. Psychophysical measurement of glaucomatous damage. Surv Ophthalmol 2001; 45: S313–8.

Jones RD, Donaldson IM, Timmings PL. Impairment of high-contrast visual acuity in Parkinson's disease. Mov Disord 1992; 7: 232–8.

Kaas JH, Lyon DC. Pulvinar contribution to the dorsal and ventral streams of visual processing in primates. Brain Res Rev 2007; 55: 285–96.

Kanamori A, Nakamura M, Escano MFT, Seya R, Maeda H, Negi A. Evaluation of the glaucomatous damage on retinal nerve fiber layer thickness measured by optical coherence tomography. Am J Ophthalmol 2003; 135: 513–20.

Kempster PA, Hurwitz B, Lees AJ. A new look at James Parkinson's essay on the shaking palsy. Neurology 2007; 69: 482–5.

Klein BEK, Klein R, Linton KLP. Prevalence of age-related lens opacities in a population: the Beaver Dam eye study. Ophthalmology 1992; 99: 546–52.

Knoblauch K, Saunders F, Kusuda M. Age and illuminance effects in the Farnsworth-Munsell 100-hue test. Appl Optics 1987; 26: 1441–8.

Kohn A, Movshon JA. Neuronal adaptation to visual motion in area MT of the macaque. Neuron 2003; 39: 681–91.

Kolb H, Cuenca N, Wang HH, Dekorver L. The synaptic organization of the dopaminergic amacrine cell in the cat retina. J Neurocytol 1990; 19: 343–66.

Kolb H, Linberg KA, Fisher SK. Neurons of the human retina: a Golgi study. J Comp Neurol 1992; 318: 147–87.

Kooijman AC, Cornelissen FW. Better lighting to reduce falls and fracture? A comment on de Boer *et al*. (2004): different aspects of visual impairment as risk factors for falls and fractures in older men and women [comment]. J Bone Miner Res 2005; 20: 2061–2; author reply 2063.

Kuffler SW. Discharge patterns and functional organization of mammalian retina. J Neurophysiol 1953; 16: 37–68.

Langheinrich T, Tebartz van Elst L, Lagreze WA, Bach M, Lucking CH, Greenlee MW. Visual contrast response functions in Parkinson's disease: evidence from electroretinograms, visually evoked potentials and psychophysics. Clin Neurophysiol 2000; 111: 66–74.

Lemke MR, Fuchs G, Gemende I, Herting B, Oehlwein C, Reichmann H, et al. Depression and Parkinson's disease. J Neurol 2004; 251 (Suppl 6): VI/24–7.
Levy G, Jacobs DM, Tang M-X, Cote LJ, Louis ED, Alfaro B, et al. Memory and executive function impairment predict dementia in Parkinson's disease. Mov Disord 2002; 17: 1221–6.
Lord SR. Visual risk factors for falls in older people. Age Ageing 2006; 35 (Suppl 2): ii42–5.
Lucetti C, Gambaccini G, Del Dotto P, Ceravolo R, Logi C, Rossi G, et al. Long-term clinical evaluation in patients with Parkinson's disease and early autonomic involvement. Parkinsonism Relat Disord 2006; 12: 279–83.
Maffei L, Fiorentini A, Bisti S, Hollander H. Pattern ERG in the monkey after section of the optic nerve. Exp Brain Res 1985; 59: 423–5.
Malmfors T. Evidence of adrenergic neurons with synaptic terminals in the retina of rat demonstrated with fluorescence and electron microscopy. Acta Physiol Scand 1963; 58: 99–100.
Malpeli JG, Lee D, Baker FH. Laminar and retinotopic organization of the macaque lateral geniculate nucleus: magnocellular and parvocellular magnification functions. J Comp Neurol 1996; 375: 363–77.
Mangione CM, Phillips RS, Lawrence MG, Seddon JM, Orav EJ, Goldman L. Improved visual function and attenuation of declines in health-related quality of life after cataract extraction. Arch Ophthalmol 1994; 112: 1419–25.
Mariani AP. Amacrine cells of the rhesus monkey retina. J Comp Neurol 1990; 301: 382–400.
Mariani AP. Synaptic organization of type 2 catecholamine amacrine cells in the rhesus monkey retina. J Neurocytol 1991; 20: 332–42.
Martin PR, Lee BB, White AJ, Solomon SG, Ruttiger L. Chromatic sensitivity of ganglion cells in the peripheral primate retina [see comment]. Nature 2001; 410: 933–6.
Martinez-Martin P, Schapira AHV, Stocchi F, Sethi K, Odin P, MacPhee G, et al. Prevalence of nonmotor symptoms in Parkinson's disease in an international setting; study using nonmotor symptoms questionnaire in 545 patients. Mov Disord 2007; 22: 1623–9.
Marx M, Bodis-Wollner I, Bobak P, Harnois C, Mylin L, Yahr M. Temporal frequency-dependent VEP changes in Parkinson's disease. Vision Res 1986; 26: 185–93.
Masson G, Mestre D, Blin O. Dopaminergic modulation of visual sensitivity in man. Fundam Clin Pharmacol 1993; 7: 449–63.
Matsui H, Udaka F, Tamura A, Oda M, Kubori T, Nishinaka K, et al. Impaired visual acuity as a risk factor for visual hallucinations in Parkinson's disease. J Geriatr Psychiatry Neurol 2006; 19: 36–40.
Maunsell JH, Nealey TA, DePriest DD. Magnocellular and parvocellular contributions to responses in the middle temporal visual area (MT) of the macaque monkey. J Neurosci 1990; 10: 3323–34.
McShane R, Gedling K, Reading M, McDonald B, Esiri MM, Hope T. Prospective study of relations between cortical Lewy bodies, poor eyesight, and hallucinations in Alzheimer's disease. J Neurol Neurosurg Psychiatry 1995; 59: 185–8.
Mestre D, Blin O, Serratrice G, Pailhous J. Spatiotemporal contrast sensitivity differs in normal aging and Parkinson's disease. Neurology 1990; 40: 1710–4.
Mosimann UP, Mather G, Wesnes KA, O'Brien JT, Burn DJ, McKeith IG. Visual perception in Parkinson disease dementia and dementia with Lewy bodies. Neurology 2004; 63: 2091–6.
Muresan Z, Besharse JC. D2-like dopamine receptors in amphibian retina: localization with fluorescent ligands. J Comp Neurol 1993; 331: 149–60.
Naarendorp F, Hitchock PF, Sieving PA. Dopaminergic modulation of rod pathway signals does not affect the scotopic ERG of cat at dark-adapted threshold. J Neurophysiol 1993; 70: 1681–91.
Nealey TA, Maunsell JH. Magnocellular and parvocellular contributions to the responses of neurons in macaque striate cortex. J Neurosci 1994; 14: 2069–79.
Nelson R. Cat cones have rod input: a comparison of the response properties of cones and horizontal cell bodies in the retina of the cat. J Comp Neurol 1977; 172: 109–35.
Nelson R, Famiglietti EV Jr, Kolb H. Intracellular staining reveals different levels of stratification for on- and off-centre ganglion cells in cat retina. J Neurophysiol 1978; 41: 472–83.
Nelson R, Kolb H. A17: a broad-field amacrine cell in the rod system of the cat retina. J Neurophysiol 1985; 54: 592–614.
Nguyen-Legros J. Functional neuroarchitecture of the retina: hypothesis on the dysfunction of retinal dopaminergic circuitry in Parkinson's disease. Surg Radiol Anat 1988; 10: 137–44.
Nguyen-Legros J, Simon A, Caille I, Bloch B. Immunocytochemical localization of dopamine D1 receptors in the retina of mammals. Vis Neurosci 1997; 14: 545–51.
Nguyen-Tri D, Overbury O, Faubert J. The role of lenticular senescence in age-related color vision changes. Invest Ophthalmol Vis Sci 2003; 44: 3698–704.
Nightingale S, Mitchell KW, Howe JW. Visual evoked cortical potentials and pattern electroretinograms in Parkinson's disease and control subjects. J Neurol Neurosurg Psychiatry 1986; 49: 1280–7.
Nussbaum RL, Ellis CE. Alzheimer's disease and Parkinson's disease [see comment][erratum appears in N Engl J Med 2003; 348: 2588]. N Engl J Med 2003; 348: 1356–64.
Ohzawa I, Sclar G, Freeman RD. Contrast gain control in the cat's visual system. J Neurophysiol 1985; 54: 651–67.
Onofrj M, Ghilardi MF, Basciani M, Gambi D. Visual evoked potentials in parkinsonism and dopamine blockade reveal a stimulus-dependent dopamine function in humans. J Neurol Neurosurg Psychiatry 1986; 49: 1150–9.
Owsley C, Jackson GR, Cideciyan AV, Huang Y, Fine SL, Ho AC, et al. Psychophysical evidence for rod vulnerability in age-related macular degeneration. Invest Ophthalmol Vis Sci 2000; 41: 267–73.
Owsley C, Jackson GR, White M, Feist R, Edwards D. Delays in rod-mediated dark adaptation in early age-related maculopathy. Ophthalmology 2001; 108: 1196–202.
Owsley C, Sloane ME. Contrast sensitivity, acuity, and the perception of 'real-world' targets. Br J Ophthalmol 1987; 71: 791–6.
Parisi V, Manni G, Spadaro M, Colacino G, Restuccia R, Marchi S, et al. Correlation between morphological and functional retinal impairment in multiple sclerosis patients. Invest Ophthalmol Vis Sci 1999; 40: 2520–7.
Parkinson J. An essay on the shaking palsy. 1817. J Neuropsychiatry Clin Neurosci 2002; 14: 223–36; discussion 222.
Paunescu LA, Schuman JS, Price LL, Stark PC, Beaton S, Ishikawa H, et al. Reproducibility of nerve fiber thickness, macular thickness, and optic nerve head measurements using StratusOCT. Invest Ophthalmol Vis Sci 2004; 45: 1716–24.
Peichl L, Wassle H. Morphological identification of on- and off-centre brisk transient (Y) cells in cat retina. Proc R Soc Lond 1981; 212: 139–56.
Peppe A, Stanzione P, Pierantozzi M, Semprini R, Bassi A, Santilli AM, et al. Does pattern electroretinogram spatial tuning alteration in Parkinson's disease depend on motor disturbances or retinal dopaminergic loss? lElectroencephalogr Clin Neurophysiol 1998; 106: 374–82.
Peppe A, Stanzione P, Pierelli F, De Angelis D, Pierantozzi M, Bernardi G. Visual alterations in de novo Parkinson's disease: pattern electroretinogram latencies are more delayed and more reversible by levodopa than are visual evoked potentials. Neurology 1995; 45: 1144–8.
Peppe A, Stanzione P, Pierelli F, Stefano E, Rizzo PA, Tagliati M, et al. Low contrast stimuli enhance PERG sensitivity to the visual dysfunction in Parkinson's disease. Electroencephalogr Clin Neurophysiol 1992; 82: 453–7.
Perry VH, Cowey A. The ganglion cell and cone distributions in the monkey's retina: implications for central magnification factors. Vision Res 1985; 25: 1795–810.

Pieri V, Diederich NJ, Raman R, Goetz CG. Decreased colour discrimination and contrast sensitivity in Parkinson's disease. J Neurol Sci 2000; 172: 7–11.

Pitts DG. The effects of aging on selected visual functions: dark adaptation, visual acuity, stereopsis, and brightness contrast. In: Sekuler R, Kline DW, Dismukes K, editors. Aging and human visual function. New York: Alan R. Liss; 1982. p. 131–59.

Pourcho RG. Dopaminergic amacrine cells in the cat retina. Brain Res 1982; 252: 101–9.

Price MJ, Feldman RG, Adelberg D, Kayne H. Abnormalities in color vision and contrast sensitivity in Parkinson's disease. Neurology 1992; 42: 887–90.

Reeves BC, Wood JM, Hill AR. Vistech VCTS 6500 charts—within- and between-session reliability. Optom Vis Sci 1991; 68: 728–37.

Regan BC, Freudenthaler N, Kolle R, Mollon JD, Paulus W. Colour discrimination thresholds in Parkinson's disease: results obtained with a rapid computer-controlled colour vision test. Vision Res 1998; 38: 3427–31.

Regan D, Maxner C. Orientation-selective visual loss in patient's with Parkinson's disease. Brain 1987; 110: 415–32.

Regan D, Neima D. Visual fatigue and visual evoked potentials in multiple sclerosis, glaucoma, ocular hypertension and Parkinson's disease. J Neurol Neurosurg Psychiatry 1984; 47: 673–8.

Repka MX, Claro MC, Loupe DN, Reich SG. Ocular motility in Parkinson's disease. J Pediatr Ophthalmol Strabismus 1996; 33: 144–7.

Ribelayga C, Cao Y, Mangel SC. The circadian clock in the retina controls rod-cone coupling. Neuron 2008; 59: 790–801.

Santhouse AM, Howard RJ, ffytche DH. Visual hallucinatory syndromes and the anatomy of the visual brain. Brain 2000; 123: 2055–64.

Sartucci F, Orlandi G, Bonuccelli U, Borghetti D, Murri L, Orsini C, et al. Chromatic pattern-reversal electroretinograms (ChPERGs) are spared in multiple system atrophy compared with Parkinson's disease. Neurol Sci 2006; 26: 395–401.

Schefrin BE, Tregear SJ, Harvey LO Jr, Werner JS. Senescent changes in scotopic contrast sensitivity. Vision Res 1999; 39: 3728–36.

Shapley R, Perry VH. Cat and monkey retinal ganglion cells and their visual functional roles. Trends Neurosci 1986; 9: 229–35.

Silva MF, Faria P, Regateiro FS, Forjaz V, Januario C, Freire A, et al. Independent patterns of damage within magno-, parvo- and koniocellular pathways in Parkinson's disease [see comment]. Brain 2005; 128: 2260–71.

Silva MF, Maia-Lopes S, Mateus C, Guerreiro M, Sampaio J, Faria P, et al. Retinal and cortical patterns of spatial anisotropy in contrast sensitivity tasks. Vision Res 2008; 48: 127–35.

Sloane ME, Owsley C, Alvarez SL. Aging, senile miosis and spatial contrast sensitivity at low luminance. Vision Res 1988a; 28: 1235–46.

Sloane ME, Owsley C, Jackson CA. Aging and luminance-adaptation effects on spatial contrast sensitivity. J Opt Soc Am [A] 1988b; 5: 2181–90.

Solomon SG, Lee BB, White AJR, Ruttiger L, Martin PR. Chromatic organization of ganglion cell receptive fields in the peripheral retina. J Neurosci 2005; 25: 4527–39.

Solomon SG, Lennie P. The machinery of colour vision. Nat Rev Neurosci 2007; 8: 276–86.

Solomon SG, Peirce JW, Dhruv NT, Lennie P. Profound contrast adaptation early in the viusal pathway. Neuron 2004; 42: 155–62.

Stanzione P, Bodis-Wollner I, Pierantozzi M, Semprini R, Tagliati M, Peppe A, et al. A mixed D1 and D2 antagonist does not replay pattern electroretinogram alterations observed with a selective D2 antagonist in normal humans: relationship with Parkinson's disease pattern electroretinogram alterations. Clin Neurophysiol 1999; 110: 82–5.

Stanzione P, Fattapposta F, Tagliati M, D'Alessio C, Marciani MG, Foti A, et al. Dopaminergic pharmacological manipulations in normal humans confirm the specificity of the visual (PERG-VEP) and cognitive (P300) electrophysiological alterations in Parkinson's disease. Electroencephal Clin Neurophysiol Suppl 1990; 41: 216–20.

Stanzione P, Pierantozzi M, Semprini R, Tagliati M, Traversa R, Peppe A, et al. Increasing doses of l-sulpiride reveal dose- and spatial frequency-dependent effects of D2 selective blockade in the human electroretinogram. Vision Res 1995; 35: 2659–64.

Strettoi E, Raviola E, Dacheux RF. Synaptic connections of the narrow-field, bistratified rod amacrine cell (AII) in the rabbit retina. J Comp Neurol 1992; 325: 152–68.

Tagliati M, Bodis-Wollner I, Kovanecz I, Stanzione P. Spatial frequency tuning of the monkey pattern ERG depends on D2 receptor-linked action of dopamine. Vision Res 1994; 34: 2051–7.

Tagliati M, Bodis-Wollner I, Yahr M. The pattern electroretinogram in Parkinson's disease reveals lack of retinal spatial tuning. Electroencephalogr Clin Neurophysiol 1996; 100: 1–11.

Tartaglione A, Oneto A, Bandini F, Favale E. Visual evoked potentials and pattern electroretinograms in Parkinson's disease and control subjects. J Neurol Neurosurg Psychiatry 1987; 50: 1243–4.

Tatton WG, Kwan MM, Verrier MC, Seniuk NA, Theriault E. MPTP produces reversible disappearance of tyrosine hydroxylase-containing retinal amacrine cells. Brain Res 1990; 527: 21–31.

Tebartz van Elst L, Greenlee MW, Foley JM, Lucking CH. Contrast detection, discrimination and adaptation in patients with Parkinson's disease and multiple system atrophy. Brain 1997; 120: 2219–28.

Teunisse RJ. Charles Bonnet syndrome, insight and cognitive impairment [comment]. J Am Geriatr Soc 1997; 45: 892–3.

Teunisse RJ, Cruysberg JR, Hoefnagels WH, Kuin Y, Verbeek AL, Zitman FG. Social and psychological characteristics of elderly visually handicapped patients with the Charles Bonnet syndrome. Compr Psychiatry 1999; 40: 315–9.

Teunisse RJ, Cruysberg JR, Hoefnagels WH, Verbeek AL, Zitman FG. Visual hallucinations in psychologically normal people: Charles Bonnet's syndrome [see comment]. Lancet 1996; 347: 794–7.

Thibos LN, Cheney FE, Walsh DJ. Retinal limits to the detection and resolution of gratings. J Opt Soc Am A 1987; 4: 1524–9.

Tobimatsu S, Tomoda H, Kato M. Parvocellular and magnocellular contributions to visual evoked potentials in humans: stimulation with chromatic and achromatic gratings and apparent motion. J Neurol Sci 1995; 134: 73–82.

Tosini G, Menaker M. Circadian rhythms in cultured mammalian retina. Science 1996; 272: 419–21.

Trick GL, Kaskie B, Steinman SB. Visual impairment in Parkinson's disease: deficits in orientation and motion discrimination. Optom Vis Sci 1994; 71: 242–5.

Uc EY, Rizzo M, Anderson SW, Qian S, Rodnitzky RL, Dawson JD. Visual dysfunction in Parkinson disease without dementia. Neurology 2005; 65: 1907–13.

Ungerleider LG, Haxby JV. What and where in the human brain. Curr Opin Neurobiol 1994; 4: 157–65.

Ungerleider LG, Mishkin M. Two cortical visual systems. Analysis of visual behaviour. Cambridge: MIT Press; 1982. p. 549.

Veruki ML. Dopaminergic neurons in the rat retina express dopamine D2/3 receptors. Eur J Neurosci 1997; 9: 1096–100.

Veruki ML, Wassle H. Immunohistochemical localization of dopamine D1 receptors in rat retina. Eur J Neurosci 1996; 8: 2286–97.

Voigt T, Wassle H. Dopaminergic innervation of A II amacrine cells in mammalian retina. J Neurosci 1987; 7: 4115–28.

Weale RA. Senescent vision: is it all the fault of the lens? lEye 1987; 1: 217–21.

Werblin FS. Synaptic connections, receptive fields, and patterns of activity in the tiger salamander retina. Invest Ophthalmol Vis Sci 1991; 32: 459–83.

Werblin FS, Dowling JE. Organization of the retina of the mudpuppy, *Necturus maculosus*. II Intracellular recording. J Neurophysiol 1969; 32: 339–55.

West SK, Rubin GS, Broman AT, Munoz B, Bandeen-Roche K, Turano K. How does visual impairment affect performance on tasks of everyday life? The SEE Project. Salisbury Eye Evaluation. Arch Ophthalmol 2002; 120: 774–80.

Williams-Gray CH, Foltynie T, Brayne CEG, Robbins TW, Barker RA. Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. Brain 2007; 130: 1787–98.

Willis A, Anderson SJ. Effects of glaucoma and aging on photopic and scotopic motion perception. Invest Ophthalmol Vis Sci 2000; 41: 325–35.

Wink B, Harris J. A model of the Parkinsonian visual system: support for the dark adaptation hypothesis. Vision Res 2000; 40: 1937–46.

Witkovsky P, Arango-Gonzalez B, Haycock JW, Kohler K. Rat retinal dopaminergic neurons: differential maturation of somatodendritic and axonal compartments. J Comp Neurol 2005; 481: 352–62.

Witkovsky P, Nicholson C, Rice ME, Bohmaker K, Meller E. Extracellular dopamine concentration in the retina of the clawed frog, *Xenopus laevis*. Proc Natl Acad Sci USA 1993; 90: 5667–71.

Witkovsky P, Stone S, Besharse JC. Dopamine modifies the balance of rod and cone inputs to horizontal cells of the *Xenopus* retina. Brain Res 1988; 449: 332–6.

Worringham CJ, Wood JM, Kerr GK, Silburn PA. Predictors of driving assessment outcome in Parkinson's disease. Mov Disord 2006; 21: 230–5.

Wulle I, Wagner H-J. GABA and tyrosine hydroxylase immunocytochemistry reveal different patterns of colocalization in retinal neurons of various vertebrates. J Comp Neurol 1990; 296: 173–8.

Wullner U, Schmitz-Hubsch T, Antony G, Fimmers R, Spottke A, Oertel WH, et al. Autonomic dysfunction in 3414 Parkinson's disease patients enrolled in the German Network on Parkinson's disease (KNP e.V.): the effect of ageing. Eur J Neurol 2007; 14: 1405–8.

Xia X, Mills SL. Gap junction regulatory mechanisms in the AII amacrine cell of the rabbit retina. Vis Neurosci 2004; 21: 791–805.

Xin DY, Bloomfield SA. Dark- and light-induced changes in coupling between horizontal cells in mammalian retina. J Comp Neurol 1999; 405: 75–87.

Yeterian EH, Pandya DN. Corticothalamic connections of extrastriate visual areas in rhesus monkeys. J Comp Neurol 1997; 378: 562–585.

Zhang D-Q, Zhou T-R, McMahon DG. Functional heterogeneity of retinal dopaminergic neurons underlying their multiple roles in vision. J Neurosci 2007; 27: 692–9.