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
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 (Cummins and Masterman, 1999; Lemke et al., 2004; Martinez-Martín et al., 2007), cognitive decline and dementia (Levy et al., 2001; Aarsland et al., 2003; Foltynie et al., 2004; Janvin et al., 2006), sleep disorders (Comella, 2006), hyposmia (Bohnen et al., 2007) and autonomic failure (Alcock 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; Bloussé 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 photoceptor/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 afferents 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 cortical 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; Greive 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.
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
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
Dopaminergic cells in the rat retina visualized by immunocytochemical staining with an antibody against tyrosine hydroxylase. Courtesy of Paul Witkovsky.

Figure 3

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). All 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).

All cells express D1-subtype dopamine receptors and gamma-aminobutyric acid type-A (GABA_A) receptors, activation of the former leading to ‘excituation’ (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, A11 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 All:AII and All: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., 2002a). 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., 2002b; 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

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**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
The retina in Parkinson’s disease

Table 1 Summary of age-related alterations in visual function

<table>
<thead>
<tr>
<th>Ageing changes</th>
<th>Functional impact</th>
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<tr>
<td><strong>Age-related ophthalmological disease</strong></td>
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<td>Cataract</td>
<td>Reduction in retinal illumination Changes in visual acuity and contrast sensitivity</td>
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<tr>
<td>Age-related macular degeneration (AMD)</td>
<td>Reduction in visual acuity Reduction in dark adaptation</td>
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<td>Diabetic retinopathy</td>
<td>Reduction in visual acuity Restricted visual fields</td>
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<td>Glaucoma</td>
<td>Reduction in visual acuity</td>
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<td>Reduction in colour vision</td>
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<td><strong>Age-related ophthalmological changes</strong></td>
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<td>Reduction in lens focal power (presbyopia)</td>
<td>Changes in visual acuity and contrast sensitivity</td>
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<tr>
<td>Senile miosis</td>
<td>Reduction in retinal illumination</td>
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<td>Retinal degeneration</td>
<td>Limitation of ‘neural’ function of retina</td>
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<td></td>
<td>Impaired dark adaptation</td>
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<td>Reduced static and dynamic visual acuity</td>
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<td>Reduced contrast sensitivity</td>
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<td>Impaired colour vision</td>
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<td><strong>‘Central’ visual impairment</strong></td>
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<td>Primary visual cortex</td>
<td>Visuo-perceptual impairment</td>
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<td>Secondary visual cortical areas</td>
<td>Reductions in visual acuity</td>
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<td>Reduced contrast sensitivity</td>
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<td></td>
<td>Impaired motion perception</td>
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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 psycho-histological 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 minimal 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.

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 Onofri, 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

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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; Worthingham 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 proton/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 nonsignificant 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 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., 1988b). 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., 1988a). 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, is 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., 2006a; 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 visuo-perceptual, visuocognitive and visuomotor performance as well.

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