Oculo-visual abnormalities in Parkinson's disease: Possible value as biomarkers

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Word count: 4674

Running title: Ocular markers in PD

Key words: Parkinson's disease, vision, retina, biomarkers, in vivo imaging

Conflict of Interest: The authors declare that they have no conflict of interest.

Acknowledgements: We acknowledge support from The Wellcome Trust (WT099729) for
MFC and Research Foundation Flanders (a personal fellowship) for LDG.

ABSTRACT

Parkinson's disease (PD) is one of the most common neurodegenerative disorders and the second leading cause of dementia worldwide. With an aging population, the prevalence of the disease has dramatically increased. Clinical management has advanced through recent developments in dopaminergic imaging and genetic risk profiling. However, early and accurate diagnosis of the disorder remains a big challenge, largely due to a lack of non-invasive and inexpensive reliable diagnostic tests. Besides the well-studied cerebral neurodegeneration that underlies the cardinal symptoms of PD (*i.e.*, bradykinesia, tremor, rigidity, and postural instability), ocular changes have also been described in PD, including visual dysfunction, pupil abnormality, lens opacity and retinal neuronal loss and dysfunction. These ocular pathological processes are related to α -synuclein deposition, and dopamine deficiency in the retina –mirroring the defining pathological features of PD in the brain. Together, these observations support the notion that the eye can serve as a 'window' to the brain, providing clinicians with non-invasive methods to visualise disease. This review focuses on recent advances in the characterization of ocular changes in PD and their promising use as biomarkers in the eye, which can be potentially used for aiding in early diagnosis, tracking disease progression, and for evaluating novel therapeutic strategies.

Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide, affecting 1% of the population aged above 65.¹ Abnormal accumulation of proteinaceous cytoplasmic inclusions, called Lewy bodies and neurites, and dopaminergic cell death in the substantia nigra are the defining neuropathological hallmarks. Dopaminergic cell loss also determines the cardinal symptoms of bradykinesia, tremor, rigidity, and postural instability. Although considerable progress has been made in understanding its pathophysiology, early and accurate diagnosis PD is still a formidable challenge.² There is currently no effective treatment available to slow down disease progression; and this is largely due to the lack of well-established biomarkers for early diagnosis and monitoring of progression. Typically, PD is asymptomatic until 50% of the dopaminergic neurons have been lost.^{3,4} Thus, treatment can only be initiated in the late phase of the disease.

In PD, Lewy bodies are also found in other central nervous system (CNS) regions, leading to non-motor symptoms such as depression, sleep disorders, constipation, olfactory dysfunction and visual symptoms.^{5,6} Growing evidence from clinical, neuropathological, and imaging studies indicates that these non-motor symptoms can be linked to the preclinical phase of PD.⁵ Disturbances of smell, sleep, mood, and gastrointestinal function may reflect the early involvement of peripheral and central nervous systems. In line with Braak's staging, these non-motor signs of PD appear as early as five years before the onset of the classic motor signs.^{5,6} Hence, novel diagnostic protocols have been proposed for the identification of high risk, asymptomatic individuals who could benefit from therapies that act to delay or prevent neurodegeneration.⁷

Recent studies have shown that the eye, particularly the retina, is also affected in PD. Given the unique optical properties and its accessibility for non-invasive approaches, the eye can be regarded as an optimal site for early detection of neurodegenerative events.⁸ This review aims to give an overview of the visual, ocular and retinal changes that have been documented in PD patients, and to discuss the use of ocular biomarkers for early diagnosis, follow-up of disease progression, and treatment efficacy. Although visual defects in PD are the combined result of changes at multiple levels of the visual pathway, this review primarily focusses on the eye and retina. Higher visual function effects have been comprehensively reviewed elsewhere.⁹ Functional and structural changes at this level are therefore described in detail, especially if they are objective, quantifiable measures that have potential in early diagnosis and follow-up of disease.

The retina and the brain

As the brain, the retina is part of the CNS, and both are derived from the neural tube. The retina connects with the brain through the optic nerve, which relays the electrical signals from the retina to the brain. There are five types of neurons in the mammalian retina, responsible for the transduction of light into electrical signals: photoreceptors in the outermost layer; bipolar, horizontal and amacrine cells in the middle layer; and retinal ganglion cells (RGCs) in the innermost layer. In the brain, the optic nerve fibres make synapses with their primary target cells in the lateral geniculate nucleus and the superior colliculus, from which the visual information is further relayed to the primary visual cortex (Figure 1).

As an integral part of the CNS, the retina displays striking similarities to the brain and spinal cord, including functionality, response to insult, and immunology. Furthermore, cellular and molecular mechanisms implicated in retinal neurodegenerative processes appear to be similar to those in the CNS, such as vascular abnormalities, inflammation, mitochondrial dysfunction, protein aggregation, and blood-brain/-retina barrier disruption,¹⁰⁻¹³ and visual disturbances are common in many neurodegenerative diseases, including PD.

Historically, the prime difficulty in the early detection of neurodegenerative diseases is the lack of sensitivity of available diagnostic tests and the inability to visualise single-cell changes or specific neuronal circuits. However, due to the transparent nature of the ocular media, the retina is easily accessible and can be visualized non-invasively. Advanced imaging technologies permit the direct observation of changes in the retina, such as optical coherence tomography (OCT) to measure thickness and remodelling of the retinal layers, confocal scanning laser ophthalmoscopy (cSLO) to detect changes in the optic nerve head, and novel fluorescent imaging techniques such as DARC (Detection of Apoptosing Retinal Cells) to identify and monitor retinal neuronal apoptosis.^{14,15} Furthermore, electrophysiology techniques such as electroretinography (ERG) and visual evoked potentials (VEP) enable assessment of selective retinal circuits and to determine dysfunction of specific retinal cell types. Altogether, ophthalmic diagnostic tools hold great potential in the search for biomarkers for early, low-cost and non-invasive detection of PD (Figure 2).

Abnormalities in oculo-visual functions

A variety of oculo-visual abnormalities have been reported in PD, including defects in

primary vision, such as visual acuity,¹⁶⁻¹⁹ spatial contrast sensitivity,²⁰⁻²² colour vision,²³⁻²⁶ and eye movement,^{27,28} as well as deficits in more complex visual tasks involving the perception of the spatial relationships between objects (visuospatial attention) (Table 1).²⁹⁻³³ While a body of evidence from psychophysical, electrophysiological and morphological tests indicates that retinal function and structure is affected in these patients, there is no doubt that defects in 'higher order' (sub)cortical visual processing are also contributing. Indeed, besides a 'bottom-up' disruption of information processing due to dopamine deficiency and progressive neurodegeneration in the retina, leading to de-afferentiation of the visual cortex; loss of dopaminergic neurons, in e.g., the lateral geniculate nucleus and visual cortex, also results in a 'top-down' component to the deterioration of visual perception in PD patients.³⁴ In fact, the visual defects in PD can be attributed to changes at any level of the visual pathway (Figure 1), as well as other sensory systems and motor function.^{35,36} In addition, sleep and circadian disturbances are a frequent complaint of PD patients associated with the eye, in particular the melanopsin-containing RGCs, which are believed to control the circadian rhythm.³⁷ In conclusion, visual complaints are common in PD patients, are likely to originate from a combination of retinal and (sub)cortical disease manifestations, and often affect activities of daily living (Table 1).

Visual abnormalities and daily living

Indeed, quality of life in PD is not only affected by motor symptoms but also by non-motor symptoms, including visual abnormalities. Objective assessments of visual symptoms in PD enable to predict visual and cognitive impairments, and to estimate their impact on the patient's activities of daily living (ADL).

PD patients show a range of visual perceptual deficits that may affect ADL, from basic abilities such as colour recognition^{29-32,66,60,62,71,72} and perception of planar motion and optic flow,³⁸ to higher-order abilities such as facial emotion recognition and facial scanning.³⁹ In addition, PD patients experience problems with higher-level visuospatial functioning, a skill necessary to perform everyday tasks such as preparing meals and selecting medications.³⁸⁻⁴¹ A feature of particular interest is contrast sensitivity, which is vital for many routine activities and a strong predictor of visual hallucinations. As such, it profoundly impacts ADL, including risk of falls, reading difficulties and driving performance.⁴²⁻⁴⁶ Indeed, a clear association between driving performance and contrast sensitivity has been found in PD, and drivers with

PD may be at risk for unsafe driving in low-contrast visibility conditions (e.g., fog, dusk, dim environments).⁴⁷⁻⁴⁹ Contrast sensitivity thus has been recommended to be taken into account when determining fitness to drive.^{50,51}

PD is described as a heterogeneous disorder and the initial symptoms can be subtyped into with and without resting tremor. These two types of motor symptoms likely arise from disturbances of different neural systems,⁵²⁻⁵⁴ and non-tremor onset patients experience faster disease progression and more difficulties with ADL in general. They are reported to experience greater impairment of visual functions and related ADL, including adjusting to lighting conditions (light/dark adaptation); seeing fine detail (visual acuity and spatial vision); appreciating the spatial relations between objects (depth perception); detecting and orienting to stimuli in the periphery (peripheral vision), and quickly processing visual information (visual processing speed).⁵⁵ Therefore, visual tests can serve as tools for assessment of ADL in PD. It also suggests that environmental enhancements, such as increasing room lighting and reducing visual clutter, may help to ameliorate visual ADL in PD patients.

Contrast sensitivity

Together with impaired colour discrimination, contrast dysfunction has been found to be one of the earliest signs of PD,⁵⁶ and perhaps is the most quantified and specific visual manifestation of PD.⁵⁷⁻⁵⁹ Reduced contrast sensitivity in PD patients was first reported by Regan and Neima in 1984, demonstrating low-contrast abnormality in patients with normal visual acuity.⁶⁰ The specific foveal contrast sensitivity loss in PD has been quantified using both temporal⁵⁷ and spatiotemporal⁵⁸ modulation of the visual patterns, and results indicated that loss in contrast sensitivity in PD affects the spatiotemporal combination.⁵⁹ Further studies have shown that loss of contrast sensitivity in PD patients occurs specifically high or intermediate spatial frequencies, and both foveal and peripheral locations are affected.^{21,26,61-}

⁶⁴

Changes in contrast sensitivity in PD have been associated with dopamine depletion in the retina, and L-DOPA administration has been found to improve contrast sensitivity.^{61,65} Disrupted retinal dopaminergic signalling does not seem to be the only mechanism, however, as these deficits in contrast sensitivity appear to be dependent on the orientation of the stimulus –a feature that is determined at higher visual centres.⁶⁶⁻⁶⁹

Several studies have suggested that the loss in contrast sensitivity in PD is progressive

and correlates with disease severity and/or cognitive changes, and that deterioration in contrast sensitivity could be used as a pre-motor biomarker to refine diagnosis.^{19,70-73} Recently, an application for consumer tablet computers has been developed to offer a quick screening tool to supplement formal visual testing in PD patients, making contrast sensitivity testing quicker and easier.⁷⁰ However, further validation will be needed for its use in clinical trials.

Colour vision

Colour vision dysfunction has been recognised as a specific non-motor characteristic of PD and has been found to correlate with the severity of clinical symptoms and disease progression.⁷⁴⁻⁷⁷ Clinical and psychophysical examinations have revealed reduced performance in several colour discrimination tasks,^{24,78-81} which were ameliorated by L-DOPA administration.⁸² Colour vision is associated with parvo-(red-green) and konio-cellular (blue-yellow) pathways, while achromatic information is transmitted via the magno-cellular pathway.⁸³ Changes in both chromatic and achromatic sensitivity have been reported in PD, with independent patterns of damage occurring within the three channels.^{68,84,85} Furthermore, a disease-specific impairment in the retina has been identified, which is distinct from normal ageing or age-related retinal diseases, such as glaucoma.^{68,84,85} Whether these abnormalities have a retinal or a (sub/extra)cortical component is still a matter of debate, because there is evidence that colour discrimination deficits in PD are related to cognitive impairment and white-matter alterations.^{86,87} On the other hand, alterations in chromatic and achromatic pattern ERG responses in PD patients suggest that intraretinal dopaminergic synaptic activity is altered.^{24,88} Defective colour vision has been suggested to be an early sign of dopamine dysfunction in PD and thus an early biomarker of PD^{89,90} –however, controversial results have been produced.⁹¹

The Farnsworth-Munsell 100 Hue and the D-15 tests are the most widely used clinical tests, with the best discriminatory power, to detect colour vision defects in PD.^{20,92} These tests have the potential to identify synucleinopathy-mediated neurodegenerative disease up to 5 years before the onset of the clinical signs.^{78,93,94} It appears that colour vision dysfunction is closely related to quality of life in PD patients,^{83,95,96} suggesting its assessment as a measurement of PD progression.^{24,92,93,96} Nonetheless, it should be mentioned that these tests are subjective, hence the test outcome could –at least in part– be related to cognitive

performance and cortical alterations.⁸⁶

Electrophysiology

Objective evaluation of changes in visual function can be achieved by electrophysiological examinations, *i.e.*, ERG and VEP (Table 1). Multifocal ERGs have revealed decreased electrical activity at the fovea of PD patients.^{97,98} Reduced amplitudes of the ERG a- and b-waves,⁹⁹⁻¹⁰² the scotopic oscillatory potentials OP2 and OP3, and the overall index (OP1+OP2+OP3) were seen in PD patients, with prolonged mean peak times in OP1, OP2, OP3, and OP4.^{22,100} In addition, the amplitude and latency of the pattern ERG P50 compound were reduced and delayed;^{34,62,88,99,103-106} and increased VEP latency (P100 and N70) has been reported in subsets of PD patients.^{57,72,101,104,107-110}

Several lines of evidence support that ERG and VEP abnormalities are closely related to impaired dopaminergic transmission. First, L-DOPA treatment alleviates ERG and VEP defects in PD patients,^{103,111} and secondly, administration of dopaminergic receptor antagonists in healthy subjects^{111,112} or local dopamine depletion/blockage in animals¹¹³⁻¹¹⁵ results in electrophysiological abnormalities mimicking those observed in PD patients. These observations are suggestive of biochemical and bioelectrical malfunctions in the PD retina and highlight that the reported ERG/VEP alterations are at least in part secondary to retinal manifestations. On a cellular level, ERG abnormalities can be related to dopamine-related mechanisms. Scotopic a-wave abnormalities might reflect a distorted coupling between rods and cones, resulting in a dysfunctional shift from night- to daytime vision.^{100,116-118} Oscillatory potentials, on the other hand, are believed to be a read-out for ON interactions of retinal interneurons, and can thus be linked to the dopaminergic A18 amacrine cells that are known to be involved in ON pathways.^{100,119-121} Also, the photopic b-wave amplitude appears to be modulated by amacrine cells, and abnormalities could correspond to impaired light adaptation –a process modulated by dopamine.^{100,122-124} Finally, abnormal pattern ERG responses might be the result of impaired dopamine signalling via D1 and D2 dopamine receptors, affecting the centre-surround receptive fields of RGCs.^{115,125}

Selecting the appropriate spatial, temporal and contrast stimuli appears to be essential to detect ERG/VEP changes in PD subjects –and is a likely explanation for the contradictory findings in early studies–,⁶⁸ and is also key to discriminate between PD and normal aging.¹²⁶ Together, ERG/VEP studies have yielded pivotal insights into retinal dopamine mechanisms

and pattern ERG has been put forward as a useful method to monitor dopamine therapy,¹²⁵ yet the diagnostic power of ERG/VEP for PD remains to be fully explored. Delayed VEPs were demonstrated to correlate with severity of motor symptoms and disease duration,^{34,127} while pattern ERG abnormalities correlated with clinical stage and disease duration and predicted reduced quality of life.^{34,99,126} This led Garcia-Martin and colleagues to conclude that pattern ERG may be used for detecting patients with a higher risk of progression. In addition, they and others have concluded that combining OCT and ERG/VEP biomarkers could increase diagnostic power and aid prediction of quality of life and disease severity.^{34,72}

Pupil

Several indications of abnormal pupil reactivity have been reported in PD patients. Pupil diameters have been observed to be larger, with unequal pupil sizes after light adaptation; light reflex latency was significantly increased, whilst amplitude, maximum constriction velocity and maximum acceleration were decreased in PD patients.¹²⁸⁻¹³² In addition, PD patients exhibit hypersensitivity to parasympathomimetic and sympathomimetic agents.^{133,134} The detailed pathophysiology of these pupillary abnormalities in PD is still not fully understood; however, a diminished autonomic response has been suggested –as in the case for most of the non-motor symptoms in PD– mainly involving the parasympathetic system.^{128,135}

Pupillary abnormalities are thought to be associated with visual symptoms, especially blurred vision,¹³⁴ and also correlate with other non-motor and motor symptoms, including olfactory dysfunction, orthostatic heart rate change, cognitive impairment and motor symptoms.¹³⁶⁻¹⁴⁰ In addition, pupillary abnormalities can present early in the disease course, even before motor symptoms occur.^{137,141} Because modern pupillometry is a fast, objective, non-invasive and low-cost technique, this makes pupillary abnormalities an attractive prospect as potential non-motor biomarkers for early detection and monitoring of disease progression in PD.^{129,134,137,139,140}

Lens

Cataract is common in PD patients in conjunction with other visual disturbances, yet few studies have addressed lens pathology.¹⁴² In a retrospective cohort study, a 26% increased risk of cataract patients developing PD was found.¹⁴³ *Vice versa*, a significantly

higher frequency of cataract was demonstrated in PD patients.¹⁴² Cataract in PD patients is mainly located in nuclear and posterior subcapsular lens regions.

Cataract is caused by protein accumulation, which in normal conditions is prevented by α -crystallins.¹⁴⁴ Intriguingly, α -crystallins have been found to co-localize with α -synuclein in Lewy bodies,¹⁴⁵ and overexpression of α -synuclein in transgenic mice induces cataract.¹⁴⁶ By analysing human lens samples collected from cataract surgery, it was found that α -synuclein tends to be more prominent in residual lens fragments in PD patients compared to control subjects.¹⁴⁷ Cataracts in PD could thus be associated with α -synuclein accumulation, but more studies are needed to confirm the role of α -synuclein. Furthermore, mitochondrial dysfunction and oxidative stress may also contribute to lens pathology in PD.

Abnormalities in retinal morphology

As mentioned above, functional examinations of visual functions remain subjective and can be affected by cognitive and cortical dysfunctions. However, along with electrophysiological assessments, structural imaging of the retina can produce objective parameters which could be more reliable in the evaluation of the disease. In this respect, the introduction of OCT in the early 90's has opened a new era for *in vivo* retinal imaging, allowing to perform accurate measurements of all retinal layers longitudinally and non-invasively.^{148,149}

In vivo imaging of the RNFL with OCT

In contrast to retinal diseases such as glaucoma, diabetic retinopathy and retinitis pigmentosa, no standard and validated OCT protocols are available to evaluate the retina in PD. Two scanning protocols have been used thus far: peripapillary retinal nerve fibre layer (RNFL) and macular volume scans. Numerous studies have demonstrated a significant reduction in RNFL thickness of PD patients.^{150,151} Several studies have also compared RNFL thickness of inferior, superior, temporal, and nasal quadrants in PD,^{98,152-157} showing that the temporal quadrant—which is typically affected in mitochondrial optic neuropathies—^{11,12,158} is most commonly affected.^{98,153,155,156,158,159} However, other studies have found no difference between healthy controls and PD subjects.¹⁶⁰⁻¹⁶³ These discrepancies have been attributed to differences in disease stage/severity, incomplete ophthalmological assessments of the

control groups, sensitivity differences between OCT equipment and analysis methods, and asymmetry in the retinas of PD patients.^{150,151,158,164,165}

In the retina, dopaminergic amacrine neurons are found at the inner plexiform-inner nuclear layer border and their processes in the inner plexiform layer predominantly innervate the avascular fovea.^{166,167} Foveal vision has been found to be affected in PD,^{20,31} and assessing macular volume/thickness might therefore have a higher diagnostic yield than RNFL thickness. Pathological thinning of the inner retinal layers (RGC, inner plexiform and inner nuclear layers) has been observed in PD patients, and is most evident in an annular zone 1-to-2mm from the foveola^{150,165,168-170} –this region corresponds to the distance from the foveola at which the inner retinal layers appear on the slope surface of the foveal pit. Notably, most studies examining the macular volume did not find significant differences in PD patients.^{160,162-164} However, considering that the inner plexiform layer only constitutes ~11% of the total macular volume, it could be challenging to find significant differences. By specifying the region of interest with dedicated segmentation software, significant thinning of the inner retinal layers in PD patients was found,^{34,157,160,164,165,168-171} and a success rate of 78% true-positives was reached.¹⁶⁹ In addition, developments in image analysis, e.g., specific protocols for the assessment of the inner nuclear layer at a defined perifoveolar distance,¹⁷¹ associated with mathematical modelling to quantify foveal symmetry, breadth and depth, continue to lead to novel insights.^{172,173}

Several lines of evidence corroborate the use of OCT parameters as biomarkers of PD, with good correlations of individual retinal layer thickness and macular volume with disease severity, duration and quality of life,^{34,157,159,164,171,174-178} although these results are somewhat controversial.^{97,156,158,168,179,180} Furthermore, the RNFL appeared to be thinner in patients with visual hallucinations –which is a strong outcome predictor for, e.g., nursing home placement and mortality.¹⁶⁸ In addition, macular thickness may be considered in the differential diagnosis between PD and Alzheimer’s and other neurodegenerative disorders (e.g., glaucoma).¹⁶⁴ Although many studies have assessed retinal changes in PD using OCT, to date, limited clinical trials on the use of OCT in PD that have been registered (Supplementary Table 1).

In vivo imaging of RGC apoptosis with DARC

Annexin-V has been widely used by cell biologists to monitor cell apoptosis, as it binds to exposed phosphatidylserine molecules that are translocated from the inner to the outer cell membrane during apoptosis.¹⁸¹ DARC (Detection of Apoptosing Retinal Cells) is a novel imaging technology that utilizes fluorescently labelled Annexin-V to identify retinal neuronal apoptosis.¹⁸² DARC has been applied in various animal models of retinal neurodegeneration where it has been shown to successfully detect RGC apoptosis.¹⁸³ A recent Phase 1 clinical trial has demonstrated DARC to visualize retinal neuronal apoptosis at single-cell resolution in the human retina (Figure 3).¹⁸⁴ Furthermore, the level of apoptosis was found to be significantly higher in glaucoma patients compared to healthy controls, and appeared predictive of disease progression, suggesting the potential of DARC as a surrogate for retinal neurodegenerative disease.¹⁸⁴ DARC is currently being used to assess dementia in Phase II trials (EudraCT 2016-002531-15, ISRCTN 10751859).

DARC has recently been applied to assessing retinal apoptosis in PD models. Using a rotenone-induced rat model, the Cordeiro group has demonstrated for the first time a significant increase in the number of apoptotic RGCs, compared to normal controls.¹⁸⁵ By imaging animals over time, significant RGC apoptosis was found to occur at the early stages of disease (10-20 days following PD induction) compared to later time points (30-60 days). Moreover, DARC imaging was successful at testing the neuroprotective effect of rosiglitazone on RGC apoptosis in the same model (Figure 3). Given that the characteristic histological neurodegenerative changes in the substantia nigra and striatum only occurred by day 60 in this model, the observations suggest that retinal changes may precede the pathological manifestations in the brain, which suggest that DARC and OCT could be potential surrogate biomarkers.

Histological assessment

Immunohistological studies have revealed α -synuclein to be present in *post mortem* retinas of PD patients. Lewy bodies were found in dispersed amacrine cells at the border of the inner nuclear layer and in the RGC layer; and diffuse α -synuclein depositions and Lewy neurites were seen in the inner plexiform layer and the RNFL.^{186,187} These observations correspond to the sites of retinal thinning observed with OCT, such as the RNFL, which contains the RGC axons; and the inner nuclear and inner plexiform layers, where the dopaminergic amacrine cells reside. Furthermore, these data are also in line with altered ERG responses in PD patients and the overall decrease in dopamine levels in PD retinas.^{188,189}

Interestingly, no signs of neurodegeneration or α -synuclein deposition have been found in the outer retina.^{160,162,168,170,171,186,187}

Genetics and ocular manifestations

The International Parkinson Disease and Movement Disorder Society has recently revised the definition and diagnostic criteria of PD, and developed research criteria for prodromal PD.¹⁹⁰⁻¹⁹² The discovery of α -synuclein, the advances in PD genetics and the novel insights into non-motor symptoms of PD have created awareness for the fact that PD is a heterogeneous disorder that can be staged into clinical, prodromal or preclinical PD. Amongst other things, future research should be directed at formal delineation of subtypes.

Our understanding of the genetic mutations that cause or predispose to PD, and their association with defined molecular pathways/pathophysiological mechanisms, has grown, and oculo-visual defects associated with certain mutations may identify particular disease mechanisms. For example, patients with *GBA* (glucocerebrosidase) and *SNCA* (α -synuclein) gene mutations –both linked to lysosomal dysfunction–, more often present with visual hallucinations, rapid eye movement (REM) sleep behaviour disorder and cognitive defects than idiopathic PD patients.^{8,193-197} *LRRK2* (leucine-rich repeat kinase 2) mutations, on the other hand, are associated with mitochondrial dysfunction, and patients typically have better colour discrimination and lower rates of visual hallucinations, REM sleep behaviour disorder and cognitive defects, compared to idiopathic PD.^{9,192,194,198-200} Finally, visual hallucinations are believed to only occur in patients with Lewy body pathology, and may therefore be helpful in discriminating PD from related parkinsonian syndromes.²⁰¹⁻²⁰³ Intriguingly, OCT examinations have revealed that the temporal quadrant of the retina seems to be more affected in PD,^{98,153,155,156,158,159} which is a disease feature that has also been described in Leber's hereditary optic neuropathy, the first human disease to be associated with mitochondrial DNA defects.^{11,12,158} The retina might thus provide an unprecedented window on the disease mechanisms underlying PD. Improved understanding of the genetic differences and the diverging visual performance in PD/parkinsonian syndromes, might lead to the identification of crucial biomarkers for disease stratification.

Outlook

To date, many studies investigating oculo-visual abnormalities in PD patients have focused on determining the prevalence and specificity of selected oculo-visual symptoms, and the validity of selected ophthalmological examinations for diagnosis and disease tracking. Despite a growing number of reports, it remains difficult to draw conclusions, due to the low numbers of patients, lack of meta-analyses, hiatuses in study design, differences in study protocols, *etc.* The potential of the eye/retina as a window to the Parkinsonian brain thus has not yet been fully explored, and there is an urgent need for (i) longitudinal studies, assessing the potential of retinal biomarkers for follow-up and prediction of disease progression; (ii) studies with head-to-head comparisons of PD *versus* other neurodegenerative diseases, evaluating the potential of ocular manifestations for differential diagnosis; (iii) novel approaches integrating multiple biomarkers and employing novel technologies to increase diagnostic yield.

First, the majority of studies assessing ocular biomarkers of PD have been cross-sectional studies. While they have advanced our knowledge about the occurrence and significance of oculo-visual abnormalities in PD patients, their design falls short in determining the potential use of ocular biomarkers for follow-up and/or prediction of disease progression. Longitudinal studies, assessing ocular biomarkers in combination with neurological and neuroimaging parameters, in large patient populations, are essential to uncover whether oculo-visual abnormalities can assist in predicting disease progression and quantifying response to treatment. In addition, given that visual deficits often present before clinical symptoms, novel insights from these studies could also aid the selection of ocular biomarkers that could be added to the criteria for prodromal PD. Indeed, the Movement Disorder Society has formulated a statistical approach to calculate probability of (prodromal) disease, based on weighted analysis of defined diagnostic markers. The method has been presented as a scaffold upon which new evidence-based diagnostic markers can be added.^{204,205} Of note, Diederich *et al.* showed that changes in colour discrimination and contrast sensitivity have a discriminatory power for early diagnosis that outweighs non-motor symptoms such as hyposmia and sleep disturbance.⁸ Finally, these future studies can also shed light on whether assessment of visual function and retinal imaging in PD holds promise for stratifying patients into enriched and more homogenous populations for clinical trials, for selection of treatment,⁹ and for evaluation of response to (experimental) treatment. Continued validation of approachable diagnostics such as OCT, DARC and ERG, furthermore, may open up the

possibility of population-wide screening for PD and lead to novel means for identifying patients at risk that need further neurological examinations.

Second, an outstanding question is to what extent ocular manifestations of PD can be differentiated from other parkinsonian syndromes, normal aging, and other neurodegenerative diseases. In a comparison of PD and MSA, corticobasal degeneration, progressive supranuclear palsy, and Lewy body dementia, R.A. Armstrong suggested predominantly differences in complex visual functions, such as visuospatial dysfunction, visual hallucinations, event-evoked potentials.^{29,206-210} Differences in the eye between PD and MSA have been reported, including RNFL thinning with preferential loss of M-type RGCs in the MSA retina, with preservation of visual acuity and colour vision in MSA compared to PD.^{207,211}

We and others do not believe that the retinal biomarkers discussed in this manuscript are unique to PD/parkinsonism. Indeed, visual dysfunction and retinal degeneration are inherent to aging and have been described in many neurological/neurodegenerative conditions.²¹²⁻²¹⁸ Nevertheless, few studies have addressed this question and, where available, results have been mentioned in this review. Briefly, ocular manifestations including progressive deterioration in visual acuity, contrast sensitivity, colour vision and dark adaptation are known to be caused by age-related ophthalmological disease.²¹⁹ This confounding factor, however, has been excluded in virtually all studies by using age-matched control subjects. Furthermore, clearly distinct effects of aging *versus* PD are seen for several ocular biomarkers: e.g., colour vision, which is particularly affected along the blue-yellow (tritan) axis in aging, yet along red-green (protan/deutan) axis in PD;^{68,84} spatiotemporal contrast sensitivity, where sensitivity is reduced in response to different patterns of moving gratings in aging *versus* PD;^{220,221} ERG, where a specific deficit in the medium-frequency range is seen in PD, in contrast to an overall amplitude reduction in aging.^{126,216} In relation to multiple sclerosis, Alzheimer's, psychiatric disorders (e.g., schizophrenia, bipolar disorder, autism spectrum disorder), and cerebrovascular disease (stroke), a wide range of overlapping ocular/visual manifestations has been reported (reviewed in ²¹⁶). For Alzheimer's disease, for example, common biomarkers with PD include reduced low-contrast visual acuity, affected colour vision, enhanced pupillary responses, increased latency and reduced amplitude of pattern ERG and VEP components, and affected complex visual functions such as visuospatial attention and visual hallucinations.^{215,222,223} The Alzheimer's retina also reveals RNFL thinning,

however, most prominent in the superior quadrant of the Alzheimer's retina, which is in contrast to the temporal retina in PD.²²⁴⁻²²⁸ To disentangle the clue of common retinal/visual abnormalities, large studies with head-to-head comparison of multiple neurodegenerative diseases are needed.

These commonalities between PD and other neurodegenerative diseases lead to the third major focus point that we want to suggest for the future, *i.e.*, the need for novel approaches integrating multiple (ocular) biomarkers and novel technologies to increase diagnostic yield. Cognisance that a single biomarker may provide insufficient information has led to increasingly combining multiple biomarkers in other fields and development of risk calculators. This could be an exciting opportunity with ocular biomarkers, *e.g.*, OCT and ERG parameters, in a diagnostic calculator for PD.^{157,180,229,230} Furthermore, novel data analysis approaches for retinal images have been revolutionizing the ophthalmology field since the landmark paper by Gulshan *et al.* in 2016, which described automated retinopathy detection based on deep learning.²³¹ Machine/deep learning approaches could unveil novel, high-dimensional, quantitative measures to diagnose and objectively assess disease progression.

Importantly, a major hiatus in the current status of biomarkers for PD is the lack of techniques to assess retinal α -synuclein burden. In this respect, potential novel applications for PD could be derived from studies in Alzheimer's patients. The eye-brain connection, and the development of novel techniques and biomarkers to assess ocular manifestations, have already been explored in greater depth in Alzheimer's disease. Indeed, besides more conclusive evidence for the use of OCT for early diagnosis,²³²⁻²³⁴ several additional techniques to monitor ocular manifestations of Alzheimer's have been/are being developed; including, assessing the neurovascular unit (oximetry, OCT-angiography, Doppler-OCT, dynamic retinal vessel analysis),²³³ amyloid aggregation status and phosphorylated tau (hyperspectral imaging, cSLO of autofluorescent or curcumin-labelled amyloid, fluorescent ligand eye scanning system, fluorescence lifetime imaging ophthalmoscopy), RGC apoptosis (DARC).^{235,236,237-242} Furthermore, we have only just entered an era of ground-breaking imaging techniques, with novel developments such as (wide-field) OCT, fluorescent ligand eye scanning system, fluorescence lifetime imaging ophthalmoscopy. More applications, *e.g.*, identifying specific cell types, are to be expected and to further revolutionize research in neurodegenerative disease.

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FIG. 1. A schematic diagram of Visual pathway. The retina processes neural signals when it detects light. There are five types of neurons in the mammalian retina, responsible for the transmission of visual signals to the brain, which are, from the outer to the inner retina, photoreceptors (rods and cones), bipolar cells, horizontal cells, amacrine cells and retinal ganglion cells (RGCs). Light enters the eye from the inner surface of the retina (light entrance), and photoreceptors detect the light and transduce the visual signals to RGCs (signal transmission), and then RGCs transmit the signals to the brain via the optic nerve. In the brain, the optic nerve fibres pass the information to the lateral geniculate nucleus in thalamus and the superior colliculus in the midbrain. The visual signals are further relayed to the primary visual cortex. RPE: retinal pigment epithelium.

FIG. 2. Oculo-visual abnormalities in PD patients. Patients with PD often have a range of visual abnormalities, of which impaired contrast sensitivity and colour vision, abnormal pupil reactivity, cataract, retinal thinning, neuronal apoptosis, and electrophysiological deficits (*green*) could potentially be used as biomarkers for early diagnosis and tracking of disease progression. In addition to autonomic dysfunction at the level of the pupil and protein accumulation (α -crystalline, α -synuclein) in the lens, these oculo-visual changes have been suggested to be the result of retinal neuronal loss, α -synuclein deposition, and dopamine deficiency in the retina, in addition to more classical processes also seen in the brain (*red*). Together, these observations support the notion that the eye can serve as a 'window' to the brain, providing clinicians with non-invasive methods (*green*) to visualise disease.

FIG. 3. DARC imaging of RGC apoptosis in human retina and in a rodent model of PD: A: The DARC image shows apoptosing cells (displayed as bright fluorescent spots) in a glaucoma patient. B-C: Rotenone induced a substantial apoptosis of RGCs (white spots) in rat retina (B), and rosiglitazone treatment significantly prevented RGC apoptosis (C). Furthermore, rosiglitazone prevented swelling of the retinal layers as shown below in the OCT images. RNFL: retinal nerve fibre layer, IPL: inner plexiform layer, ONL: outer nuclear layer, OPL: outer plexiform layer, ONL: outer nuclear layer, IS/OS: inner segment/outer segment of photoreceptor layer.

1198 Author's role:
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