Visual Symptoms in Parkinson's disease and Parkinson's disease dementia

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Abstract

Non-motor symptoms such as dementia and visual hallucinations are key determinants of long-term outcome and quality of life in Parkinson's disease (PD). Attempting to understand these issues better was the motivation behind this thesis.

A *major aim* of the study was to characterise the visual symptoms experienced by patients with PD and PD dementia, focussing not just on complex visual hallucinations, whose prognostic implications are already well-described, but also on a range of other visual symptoms including illusory misperceptions, sensations of passage and presence and double vision. A *major objective* was to define key measures of visual exploration strategy during visuocognitive assessment and examine the link between strategy, cognition and visual and motor symptoms. We also set out to examine the utility of retina-specific visual assessment techniques to define the potential role of retinal dysfunction in visual impairment and symptomatology.

A *major finding* of this study was that not all visual symptoms share a common pathophysiological basis. Our results argue in favour of splitting hallucinations into separate phenomenological groups in order to better define causation and predictive value in future longitudinal studies. In addition, exploration strategy on a variety of visual tasks was demonstrated to be significantly less efficient in subjects with perceptual difficulties, providing insight into the interaction between cognition and eye movements in PD. Retinal structure, as assessed by optical coherence tomography, was not significantly altered in PD and our results would caution against the use of this technique as a disease biomarker until more is known about the limitations of this method. Finally, our neurophysiological assessment hints at the retina as the site of diminished visual acuity in PD despite there being no striking differences in central and peripheral retinal responses between control and PD subjects.

For my father

"The larger the searchlight, the greater the circumference of the unknown"

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Statement of work undertaken

The study design was a collaborative effort, with input from my supervisors - David Burn, Urs Mosimann and MIke Clarke (MC). All patient and carer interviews were undertaken by me, as was the data entry and subsequent statistical analysis. The ophthalmological assessments would not have been possible without the training I received from MC during the course of the project. In addition, MC performed a large number of the cataract and retinal examinations. Retinal photography and scanning was performed by the medical photography department of the Royal Victoria Infirmary, although subsequent data collection and analysis was undertaken by me.

Karen Bradshaw (KB), and staff within the Medical Physics Department, helped me to develop the protocols for electroretinogram and visual evoked potential recordings and programmed the necessary software. KB also set up each recording session and trained me to run the equipment and collect the raw data. Subsequent data analysis was done by KB and statistical analysis by me. The eye tracking protocol was designed in collaboration with Urs Mosimann and Sam Hutton, the latter providing technical assistance when required. Programming of the the eye tracker and all experimental assessments were done by me. Preliminary data analysis was achieved with input from Sam Hutton, although all subsequent analysis was my own work.

Abbreviations

AD = Alzheimer's disease

ADL = Activities of daily living

AEMSS = Age and education adjusted MOANS sub-scale score

ATT = Attention

BAPVA = "Best at presentation" VA

BDI = Beck depression inventory

BY = Tritan

CBS = Charles Bonnet Syndrome

CDT = Clock drawing test

COMT = Catechol-O-methyl transferase inhibitor

CONCEPT = Conceptualization

CONST = Construction

CS = Contrast sensitivity

CVH = Complex visual hallucination

DA = Dopaminergic

DLB = Dementia with Lewy bodies

DLPFC = Dorsolateral prefrontal cortex

DRS-2 = Mattis dementia rating scale

EDS = Excessive daytime somnolence

ERG = Electroretinogram

ESS = Epworth sleepiness scale

FEF = Frontal eye field

fMRI = functional magnetic resonance imaging

FOG = Freezing of Gait

HC = Healthy control

IOP = Intraocular pressure

IP = Initiation/perseveration

IPL = Inner plexiform layer

IPS = Intraparietal sulcus

L-DOPA = Levodopa

LED = Levodopa equivalent dose

LGN = Lateral geniculate nucleus

LOC = Lateral occipital cortex

M-cells = Magnocellular RGCs

MCI = Mild cognitive impairment

MEM = Memory

MMSE = Mini-mental state examination

MSA = Multiple System Atrophy

MSQ = Mayo sleep questionnaire

NEVHI = North East hallucination inventory

NPI = Neuropsychiatric inventory

OCT = Optical coherence tomography

OPL = Outer plexiform layer

P-cells = Parvocellular RGCs

PBN = Premotor burst neuron

PD = Parkinson’s disease

PD-CNL = Cognitively normal PD

PD-pMCI = PD with possible mild cognitive impairment

PDD = Parkinson’s disease dementia

PDQ-8 = Parkinson’s disease quality of life questionnaire – 8 item scale

PEF = Parietal eye field

PERG = Pattern electroretinogram

PFC = Prefrontal cortex

PPC = Posterior parietal cortex

PSP = Progressive Supranuclear Palsy

PVEP = Pattern visual evoked potential

RBD = Rapid eye movement (REM) sleep behaviour disorder

RG = Protan/deutan

RGC = Retinal ganglion cell

RNFL = Retinal nerve fibre layer

SC = Superior colliculus

SN = Substantia nigra

SPECT = Single photon emission computed tomography

TMS = Transcranial magnetic stimulation

UCVA = Uncorrected VA

UPDRS = Unified Parkinson’s disease rating scale

VA = Visual acuity

VEP = Visual evoked potential

1. Overview

1.1 Background

Parkinson's disease (PD), the second commonest neurodegenerative disorder in the UK, has an ever widening clinical phenotype encompassing a range of motor and non-motor symptoms. Dementia and visual hallucinations are key non-motor determinants of long-term outcome and quality of life, and a better understanding of these symptoms is central to improvements in care (*Lo et al.,* 2009*, McKinlay et al*., 2008). In addition to complex visual hallucinations (CVH), other visual symptoms reported in PD include illusory misperception, feelings of presence and passage in the visual periphery and double vision (diplopia).

The link between CVH and cognitive decline is clearly defined and CVH remain strong predictors of nursing home placement and mortality (*Aarsland et al.,* 2000*, de Maindreville et al*., 2005*, Goetz and Stebbin*s, 1993*, Goetz and Stebbin*s, 1995*, Goetz et al*., 2006). Although illusions, passage and presence often co-occur with CVH, they also exist in isolation and may not have the same predictive value in terms of the development of PD dementia (PDD) (*Llebaria et al.,* 2010). The association between cognition and visual phenomena such as illusions, presence and passage has not been specifically addressed.

The pathophysiology of hallucinosis in PD remains a subject for debate, but interactions between impaired visual input (*Santhouse et al.,* 2000*, Teunisse*, 1997*, Teunisse et al*., 1999), brainstem and higher cognitive dysfunction (*Benke,* 2006*, Manford and Andermann*, 1998*, Ohayo*n, 2000*, Manni et al*., 2002*, Onofrj et al*., 2002*, Pacchetti et al*., 2005), particularly impaired attention and executive function, have all been implicated (Collerton et al., 2005, Diederich et al., 2005). Prior to this study, presence, passage and illusions have often been collectively defined as "visual hallucinations", an approach that implicitly, and perhaps inaccurately, assumes a common aetiological basis.

Whilst some of the visual symptoms common in PD are likely to stem from "central", or more accurately "cortical" visual processing deficits, others may be related to lower level disturbances of visual function. Visual acuity (VA) (*Matsui et al.,* 2006), contrast sensitivity (CS) (*Bodis-Wollner et al.,* 1987*, Uc et al*., 2005), colour perception (*Pieri et al.,* 2000*, Price et al*., 1992) and motion perception (*Castelo-Branco et al.,* 2008) are all impaired in PD, with retinal dysfunction advanced as one possible explanation for these findings.

Non-invasive imaging techniques such as optical coherence tomography (OCT) have demonstrated changes in retinal structure in PD, albeit in relatively small numbers of carefully selected, younger patients (*Altintas et al.,* 2007*, Inzelberg et al*., 2004*, Moschos et al*., 2010*, Cubo et al*., 2010*, Hajee et al*., 2009). In addition, the amplitude and latency of the pattern electroretinogram (PERG) response is altered in PD, providing further evidence that the disease process in PD targets the retina (*Langheinrich et al.,* 2000*, Sartucci et al*., 2006a). The functional implication of these findings, in terms of visual symptoms, has not been addressed in any studies to date. It has also been argued that OCT might prove a useful biomarker for assessing disease progression in PD. However, to be considered as a viable potential biomarker, altered retinal morphology in PD would need to be a robust and repeatable finding in larger cohorts, preferably with longitudinal follow-up, and be applicable to a typical cohort of elderly PD patients with a variety of co-morbidities.

Dopamine plays an important role in retinal signalling by modulating the flow of rod-driven visual information (*Dacey,* 1990*, Kolb et al*., 1990*, Pourcho*, 1982*, Voigt and Wassle*, 1987*, Bloomfield and Dacheu*x, 2001*, Witkovsky et al*., 1993) and mediates the retinal transition from a dark-adapted to light-adapted state (*Cahill,* 1996*, Doyle et al*., 2002b*, Ribelayga et al*., 2008*, Tosini and Menake*r, 1996). Electrical responses to pattern stimuli can be measured both at the retinal (PERG) and visual cortical level (visual evoked potential (VEP)) and separate visual pathways can be preferentially activated by manipulating the spatial and temporal characteristics of the stimuli used. The response of a dopamine-deficient,

dark-adapted retina may be tipped in favour of reporting rod-driven responses, ultimately manifesting as fleeting, peripheral sensations of visual passage (*Harris et al.,* 1992*, Wink and Harri*s, 2000). Techniques such as OCT and the PERG potentially provide a way of distinguishing the retinal contribution to visual impairment in PD from more cortically-mediated deficits.

Selection of visual information in a complex scene is achieved by deploying sequences of fixations interspersed with rapid eye movements (saccades) (*Henderson and Hollingworth,* 1999). Cortical control of eye movements is achieved through the coordinated actions of the frontal and parietal eye fields (*Rivaud et al.,* 1994*, Pierrot-Deseilligny et al*., 1995*, Pierrot-Deseilligny et al*., 1991b*, Muri et al*., 1996) in conjunction with the prefrontal and posterior parietal cortex (*Pierrot-Deseilligny et al.,* 1995*, Pierrot-Deseilligny et al*., 2005). These areas project, via the superior colliculus, thalamus and basal ganglia to brainstem structures concerned with saccadic eye movements (*Hikosaka et al.,* 2000).

Eye movement abnormalities are well recognised in patients with PD but evidence for disease-specific disruption of saccades in PD is contradictory. Whereas some studies have demonstrated increases in saccadic latency, reductions in amplitude and increased error rates (*Rascol et al.,* 1989*, Kennard and Luec*k, 1989*, Briand et al*., 1999*, Hood et al*., 2007, *MacAskill et al*., 2002*, van Stockum et* al., 2008), others have not replicated these findings (*Vidailhet et al.,* 1994*, Briand et al*., 1999*, Briand et al*., 2001*, Lueck et al*., 1990*, Vidailhet et al*., 1999*, Mosimann et al*., 2005). Both the properties of the stimulus used, medication effects and cognitive heterogeneity of study cohorts are important determinants of saccadic metrics and may help explain some of the inconsistencies in the literature (*Chambers and Prescott,* 2010*, Michell et al*., 2006*, Hood et al*., 2007*, Hodgson et al*., 1999*, Mosimann et al*., 2005). Aside from the absolute metrics of saccades and fixations, visual exploration strategies can be used to provide insights into the cognitive processes required for more “real-world” tasks such as emotion recognition, text- and clock-reading (*Hodgson et al.,* 2002*, Mosimann et al*., 2004a*, Lueck et al*., 2000*,*

Ogrocki et al., 2000). Taken together, the characteristics of saccades, fixations and exploration strategies may help to illustrate the complex interplay between cognitive sub-domains in PD and provide a precise and objective measure of cognition for future interventional studies. Visual exploration strategies during a variety of tasks may also offer clinical insights into motor and non-motor symptoms such as CVH and visually-induced gait freezing. For example, PD patients with visual hallucinations perform less well on visuoperceptual tasks than non-hallucinators, suggesting an association between the "perceptual" impairment and the development of visual symptoms such as hallucinations (*Mosimann et al*., 2004b, *Koerts et al.,* 2010*, Meppelink et al*., 2008). In a similar fashion, impairment in the processing of "spatial" visual information may be associated with motor complications such gait freezing and postural instability, although evidence is lacking to support this hypothesis.

The four main studies in this thesis approached the visual system in a systematic fashion, beginning with a detailed characterisation of visual symptoms in PD across cognitive groups, followed by an examination of the evidence for retinal dysfunction in PD and its potential functional implications. The final chapter of the thesis describes the visual exploration strategies of PD subjects, with and without cognitive impairment, to examine, first, the role such measures might play in predicting visual and motor disability, and second, what insights are provided into cognitive impairment in PD.

1.2 Outline of study aims and hypotheses

- To characterise the range of visual symptoms seen in a cohort of patients with PD and PDD and assess their correlations with ocular pathology and cognition, exploring the following hypotheses:
    - ✦ complex visual hallucinations, illusory misperception, sensations of presence and passage do not share a common pathophysiology and will have different clinical predictors.

- cognitive impairment contributes to the reduced visual acuity and contrast sensitivity seen in PD by interfering with test performance.

- To compare retinal structure in a PD and healthy age-matched control cohort for evidence of retinal nerve fibre or macular thinning in the PD group and assess the utility of this approach as a potential biomarker for disease progression in PD.
    - PD patients will demonstrate thinning of the peri-papillary retinal nerve fibre layer and macula compared to healthy controls.
    - the role of Optical Coherence Tomography as a potential biomarker may be limited by the co-occurrence of retinal disease (macular degeneration, glaucoma) and tolerability of the procedure in a representative PD sample.
- To examine the magnocellular and parvocellular responses of the retina (PERG) and early visual cortex (VEP) in PD and correlate these with visual symptoms.
    - magnocellular (peripheral retina) responses in the PD group will differ from controls and correlate with the presence of “passage” symptoms, whereas parvocellular (central retina) responses will be equivalent in both groups.
- To examine visual exploration strategies in patients with PD and PDD with the following hypotheses:
    - visual exploration is impaired in patients with PD compared to HC and this impairment is more marked as overall cognitive function declines.
    - impairment of visual exploration, reflecting the interaction between visuoperceptual abilities, attentional and executive function, will be predictive of poorer performance on the eye tracking battery.
    - impaired exploration strategies on visuospatial tasks will be predictive of freezing of gait, whereas exploration strategies on visuoperceptual tasks will predict the presence of complex visual hallucinations.

2. General Introduction

2.1 Parkinson's disease

Parkinson's disease (PD) is the second commonest neurodegenerative disorder in the UK after Alzheimer's disease. Although traditionally thought of as a movement disorder, the broad clinical phenotype of PD, embracing a range of both motor and non-motor symptoms, would suggest it is better thought of as a multi-system neurodegenerative disorder.

2.1.1 Clinical features

James Parkinson's original description of "the shaking palsy" in 1817 focused on the motor features of the disorder – tremor, bradykinesia and rigidity (*Kempster et al.,* 2007*, Parkinso*n, 2002). Between patients, there is considerable variation in the presentation of motor features (*Foltynie et al.,* 2002). For example, tremor is not a universal feature of PD, although patients presenting with a tremor-dominant phenotype, or in whom this phenotype dominates over time, may have a more favourable prognosis and slower disease progression (*Ebmeier et al.,* 1990*, Hershey et al*., 1991). Conversely, postural instability and gait difficulty (PIGD) is much more common in PD patients with dementia (PDD) and transition from a tremor-dominant to PIGD phenotype is associated with an increased risk of dementia (*Burn et al.,* 2003*, Alves et al*., 2006). There is a reduction in life expectancy associated with the diagnosis of PD, with mortality hazard ratios varying between 1.3 and 4.1 (*Herlofson et al.,* 2004*, Marras et al*., 2005). Independent predictors of mortality include age at diagnosis, disease severity at presentation, early visual hallucinations and development of balance disorders and dementia, indicating that it is a combination of motor and non-motor problems that contributes to increased mortality rates in PD (*Lo et al.,* 2009).

As part of the evolving clinical phenotype of PD, non-motor aspects of the disease are increasingly recognized. These include neuropsychiatric disturbances such as anxiety, depression, delusions and visual

hallucinations (*Cummings and Masterman,* 1999*, Lemke et al*., 2004*, Martinez-Martin et al*., 2007), cognitive decline and dementia (*Aarsland et al.,* 2003*, Foltynie et al*., 2004*, Hely et al*., 2008), sleep disorders such as rapid eye movement (REM) sleep behaviour disorder (*Comella,* 2006), hyposmia (*Bohnen et al.,* 2007) and autonomic failure (*Allcock et al.,* 2006*, Lucetti et al*., 2006*, Wullner et al*., 2007). As the disease progresses, these non-motor symptoms become increasingly important determinants of quality of life in people with PD (*Chaudhuri et al.,* 2006*, Martinez-Martin et al*., 2007).

2.1.2 Visual symptoms in PD

Visual symptoms are common in PD and include blurred vision and difficulty reading (*Hutton and Morris,* 2001), dry eyes and diplopia (*Biousse et al.,* 2004*, Chaudhuri et al*., 2006), feelings of presence and passage in the visual periphery and CVH (*Aarsland et al.,* 1999*, Fenelon et al*., 2000*, Mosimann et al*., 2006). Whilst some of these symptoms are likely to stem from cortical visual processing deficits, others may be related to lower level disturbances of visual function. Symptoms such as perceptual disturbances and CVH will be covered in more detail later in the introduction.

Biousse et al. (2004) studied the ophthalmic features of a group of 30 PD participants and found complaints of dry, gritty eyes were present in over 60% of the PD cohort, with objective evidence of increased tear film break up time in over 50% of the group (compared with 22% of healthy controls). Clinically apparent oculomotor abnormalities are also evident in PD with reductions in the amplitude of vergence eye movements, reduced blink frequency and convergence insufficiency all significantly more common in PD than age-matched HCs (*Biousse et al.,* 2004*, Repka et al*., 1996). Although complaints of double vision were uncommon in the Biousse and Repka studies, diplopia has been reported in 22% of a much larger cohort (n = 123) of patients in a questionnaire study of non-motor symptoms in PD (cf. 4% of a control group) (*Chaudhuri et al.,* 2006). The cause of diplopia in PD is unclear. Whilst convergence insufficiency is a possible

explanation, this is a common feature in older adults and is likely to cause diplopia only for near visual tasks. An alternative explanation would be oculomotor abnormalities resulting in ocular misalignment, although no studies have specifically looked at this possibility.

2.1.3 Diagnosis

There are no serological or cerebrospinal biomarkers with robust sensitivity and specificity for identifying PD and despite advances in structural and functional brain imaging, the diagnosis of the disorder remains largely clinical. Central to this clinical process is the demonstration of “parkinsonism”, manifest by slowness and poverty of movement (bradykinesia/akinesia), in conjunction with other key features such as a (coarse) resting tremor, rigidity of muscle tone and postural instability. Together, these cardinal “motor” features are the cornerstone of the UK Brain Bank criteria for PD diagnosis **(Table 1)** (*Hughes et al.,* 1992). Such a diagnosis must be supported by clinical features typical of idiopathic PD and an absence of findings that might point to an alternative explanation for the parkinsonism.

Nevertheless, diagnostic inaccuracy remains problematic. In community studies of patients with suspected PD, misdiagnosis rates vary from 5 to 15%, with conditions such as vascular parkinsonism and essential tremor being most frequently misclassified as PD (*Newman et al.,* 2009*, Schrag et al*., 2002). The clinical features of dystonic tremor can also closely resemble those of PD, often requiring functional dopamine imaging to differentiate the two conditions (*Schneider et al.,* 2007). Even in patients with advanced disease, examined at specialist centres, neuropathological studies suggest an incorrect diagnosis in around 10% of cases, with other extrapyramidal conditions such as Multiple System Atrophy (MSA) and Progressive Supranuclear Palsy (PSP) making up the bulk of erroneous diagnoses (*Hughes et al.,* 2001).

Table 1. UK Brain Bank Criteria for a Diagnosis of Parkinson's Disease (Hughes et al., 1992).

UK Brain Bank Diagnostic Criteria for PD

Step 1 – Diagnosis of Parkinsonian syndrome

Bradykinesia plus at least one of the following:

- Rest tremor
- Rigidity
- Postural instability

Step 2 – Exclusion criteria including:

Presence of atypical features (such as):

- early falls
- supranuclear gaze palsy
- ataxia and cerebellar features
- early autonomic features
- early cognitive decline
- poor L-DOPA response

OR History of:

- repeated strokes
- neuroleptic medication use
- head injury
- definite encephalitis

Step 3 – Supportive prospective criteria (at least three required):

- Unilateral onset
- Rest tremor present
- Evidence of progression
- Persistent asymmetry
- Excellent response to L-dopa
- L-dopa-induced dyskinesias
- L-dopa response for 5+ years
- Clinical course of 10+ years

2.1.4 Epidemiology of Parkinson's disease

Methodological differences between studies make comparing the worldwide prevalence of PD difficult. Crude estimates in European populations suggest a prevalence range in the general population of 100 to 200 per 100,000 inhabitants (*Alves et al.,* 2008*, von Campenhausen et al*., 2005). The strongest risk factor for developing PD is increasing age, with prevalence estimated at 1% in the over 60s and 4% in the over 80s (*de Rijk et al.,* 1995*, Nussbaum and Ellis*, 2003). Hence, one might expect PD prevalence in the developing world, where life expectancy is lower, to be less. Estimates from work in Asia and Africa suggest this may be the case, with age-standardized figures of between 50-175 per 100,000 and 64 per 100,000 inhabitants, respectively (*Dotchin et al.,* 2008*, Muangpaisan et al*., 2009). However, with the developing world ageing faster than was historically true for now developed countries, the global prevalence of PD is likely to rise further.

Incidence figures, being independent of mortality, may be a more accurate reflection of the frequency of PD in the population. European and North American studies suggest an incidence range from 8.6 to 19.0 per 100,000 inhabitants (*Twelves et al.,* 2003), the lower limit of this range agreeing well with incidence estimates from Muangpaisan et al. (2009) in their systematic review of studies from Asia.

2.1.5 Genetic and environmental factors

The factors influencing the development of PD are still poorly understood and most cases are thought to be due to an interaction between genetic profile and environmental exposure. Several gene mutations lead to familial PD, both with autosomal dominant (α-synuclein, leucine-rich repeat kinase 2 (LRRK-2)) and autosomal recessive (parkin, DJ-1, PINK-1) patterns of inheritance (*Bonifati et al.,* 2003*, Kitada et al*., 1998*, Paisan-Ruiz et al*., 2004*, Polymeropoulos et al*., 1997*, Valente et al*., 2004*, Zimprich et al*., 2004). The clinical characteristics of these Mendelian PD cases are often rather different from the “typical” features of idiopathic PD; with the exception of LRRK-2, all result in juvenile- or young-onset PD. In addition, few cases to date have come to post-mortem, and it remains to be seen how closely the pathology matches that seen in idiopathic PD. Nonetheless, they provide insight into the mechanisms underlying the development and progression of neurodegeneration in PD by highlighting proteins and cellular pathways that may be central to the disease process. This has led to hypotheses suggesting that an interplay between oxidative stress and dysfunction of both ubiquitin-proteasomal and mitochondrial systems contributes to neurodegeneration in PD (*Eriksen et al.,* 2003*, Shen and Cookso*n, 2004).

Despite this important work, monogenic PD accounts for less than 5% of all cases and twin studies in patients developing PD after the age of 50 years have failed to identify significant genetic factors (*Tanner et al.,* 1999). Marder et al. demonstrated only a small increase in risk of developing PD in first-degree relatives of patients compared to controls

(relative risk 2.3) (*Marder et al.,* 1996). This has fueled interest in the role of environmental factors in the development of PD. It is beyond the scope of this discussion to cover such a topic comprehensively. However, there is consistent and convincing evidence to suggest that occupational exposure to pesticides is associated with an increased risk of developing PD (*Lai et al.,* 2002*, Priyadarshi et al*., 2000), whereas smoking and caffeine intake are associated with a lower incidence of the disease (*Hernan et al.,* 2002*, Ross et al*., 2000). Whilst the precise nature of caffeine and nicotine's effects remain unclear, actions on the adenosine A2 receptor for the former, and nicotinic receptors for the latter, have been postulated for this potential protective effect.

2.1.6 Pathology and pathogenesis

The motor features of PD are a manifestation of dysfunction and neurodegeneration in dopaminergic cells of the substantia nigra (SN) in the brainstem. The consequence of this damage is a reduction in dopaminergic projections to the striatum. Associated with this cellular dysfunction is the accumulation of a misfolded protein (α-synuclein) into spherical pale intracellular inclusions known as Lewy bodies. In addition to the "classic" Lewy body structures seen in PD, α-synuclein immunohistochemistry can identify less well-defined inclusions within neuronal cell bodies as well as spindle-like and branching Lewy neurites in the neuronal cell processes themselves (*Spillantini et al.,* 1997*, Braak et al*., 1999). Synuclein accumulation is also seen in related neurodegenerative conditions such as dementia with Lewy bodies (DLB) and Multiple System Atrophy, which share some of the clinical features of PD and PDD.

Accumulation of α-synuclein within cells is associated with dysfunction and cell death, although the precise nature of this process is the subject of much debate. Certain neuronal cell populations are particularly vulnerable in PD and these are projection neurons with long, thin, sparsely or unmyelinated axons (*Braak et al.,* 2004). As such, the process of cell

damage is neither random nor is it solely confined to dopaminergic cell populations. Indeed, cholinergic, serotonergic and noradrenergic neurons are all affected in PD. One compelling hypothesis, based on neuropathological studies of early- and late-stage PD, suggests that motor symptoms present at a point where α-synuclein pathology has ascended from the lower brainstem (medulla and pons) to affect the substantia nigra (*Braak et al.,* 2003). The so-called Braak hypothesis goes on to postulate that pre-motor symptoms of PD may be accounted for by the initial accumulation of abnormal protein in lower brainstem centres as well as in the olfactory bulb. As PD progresses over time, α-synuclein pathology involves the limbic system as well as the prefrontal and neocortex, leading to widespread and debilitating non-motor complications of PD such as dementia and visual hallucinations (*Aarsland et al.,* 2005*, Braak et al*., 2006). As such, it has been suggested that synuclein pathology in PD may behave much like prion pathology in patients with Creutzfeldt Jakob disease, advancing through the brain from cell-to-cell via synaptic contacts (*Olanow and Prusiner,* 2009).

The validity of the Braak staging hypothesis is supported, in part, by work from a recent longitudinal PD cohort study, complete with autopsy data. In “typical” cases with relatively early symptom onset and slow disease progression, the spread of synuclein pathology mirrored the Braak staging hypothesis closely (*Halliday et al.,* 2008). Unlike these younger-onset patients however, those patients in the same study presenting at an older age had a more aggressive disease course with quicker progression to dementia. In addition, they exhibited more mixed neuropathology, including greater amounts of β-amyloid – a protein more commonly associated with Alzheimer’s disease (AD). Indeed, AD-like changes of β-amyloid and tau protein accumulation often co-exist with α-synuclein changes in PDD and seem likely to be influencing disease progression in at least a subset of PD patients (*Jellinger,* 2003). Arguing against a simple association between synuclein pathology and disease progression is recent work from Parkkinen et al. (2008) highlighting the presence of such

pathology in patients seemingly unaffected by either parkinsonism or dementia. It would appear that some subjects are able to tolerate significant synuclein burden without ill effect, perhaps supporting the hypothesis that such cellular inclusions are potentially cytoprotective and not directly involved in cell death (*Tanaka et al.,* 2004).

The pathological findings in PD are therefore heterogeneous, progressive and involve a range of different neuronal cell types in a variety of brain regions. Whilst the precise nature of the neurodegeneration seen in PD remains a subject of considerable debate, what is beginning to emerge is the consensus that the clinical manifestations of PD are due to a dynamic interaction between advancing age, still the strongest predictor of poor outcome, the location and extent of α-synuclein, β-amyloid and tau pathology and the subsequent impact these have on cellular integrity through mitochondrial dysfunction and oxidative stress (*Levy,* 2007).

2.1.7 Cognition and PD

Prominent among the non-motor complications of PD are cognitive impairment and dementia, the latter now a well-recognised complication of PD. A systematic review of 12 studies of PD estimates the point-prevalence of PD dementia (PDD) in established cohorts to be 25-30% (*Aarsland et al.,* 2005). More recent studies, with prevalent case selection and longitudinal follow-up, suggest this figure may be an underestimate, with a four-year cumulative dementia prevalence of 35-50% and 8-year figures of 78% (*Aarsland et al.,* 2003*, Hobson and Mear*a, 2004). These figures are in broad agreement with a long-term, longitudinal study of incident PD cases, which has demonstrated the presence of dementia in over 80% of 20-year survivors (*Hely et al.,* 2008). To date, only one study has been published examining the cognitive profile at follow-up of an incident, early-stage PD cohort. Here, 10% of patients fulfilled criteria for PDD at a mean of 3.5 years from diagnosis, although 57% demonstrated cognitive impairments falling short of dementia criteria (*Williams-Gray et al.,* 2007). As such, incidence figures for cognitive impairment in PD range

from 30-107 per 1000 person years (*Hobson and Meara,* 2004*, Williams-Gray et al*., 2007) with an estimated 6-fold increase in risk of dementia for patients with PD (*Aarsland et al.,* 2003).

The definition of dementia in PD has varied widely between studies but usually involves;

a) scores on selected cognitive assessment below a pre-defined cut-off *and*

b) fulfilment of DSM-IV criteria for a diagnosis of dementia (*DSM-IV,* 1994)

Recently, a Movement Disorder Society task force developed consensus clinical diagnostic criteria for PDD **(Table 2)** requiring a diagnosis of PD according to UK Brain Bank criteria, a dementia syndrome of insidious onset and slow progression, with cognitive deficits severe enough to impair daily life, independent of impairment ascribable to motor or autonomic symptoms (*Emre et al.,* 2007).

Table 2. Consensus criteria for a diagnosis of Parkinson's disease dementia.

Features of dementia associated with Parkinson's disease

I. Core features

1. Diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria

2. A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson's disease and diagnosed by history, clinical, and mental examination, defined as:

- Impairment in more than one cognitive domain
- Representing a decline from premorbid level
- Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms

II. Associated clinical features

1. Cognitive features:

- Attention: Impaired. Impairment in spontaneous and focused attention, poor performance in attentional tasks; performance may fluctuate during the day and from day to day
- Executive functions: Impaired. Impairment in tasks requiring initiation, planning, concept formation, rule finding, set shifting or set maintenance; impaired mental speed (bradyphrenia)
- Visuo-spatial functions: Impaired. Impairment in tasks requiring visual-spatial orientation, perception, or construction
- Memory: Impaired. Impairment in free recall of recent events or in tasks requiring learning new material, memory usually improves with cueing, recognition is usually better than free recall
- Language: Core functions largely preserved. Word finding difficulties and impaired comprehension of complex sentences may be present

2. Behavioral features:

- Apathy: decreased spontaneity; loss of motivation, interest, and effortful behavior
- Changes in personality and mood including depressive features and anxiety
- Hallucinations: mostly visual, usually complex, formed visions of people, animals or objects
- Delusions: usually paranoid, such as infidelity, or phantom boarder (unwelcome guests living in the home) delusions
- Excessive daytime sleepiness

III. Features which do not exclude PD-D, but make the diagnosis uncertain

Co-existence of any other abnormality which may by itself cause cognitive impairment, but judged not to be the cause of dementia, e.g.
presence of relevant vascular disease in imaging
Time interval between the development of motor and cognitive symptoms not known

IV. Features suggesting other conditions or diseases as cause of mental impairment, which, when present make it impossible to reliably diagnose PD-D

Cognitive and behavioral symptoms appearing solely in the context of other conditions such as: Acute confusion due to

a. Systemic diseases or abnormalities
b. Drug intoxication Major Depression according to DSM IV

Features compatible with "Probable Vascular dementia" criteria according to NINDS-AIREN (dementia in the context of cerebrovascular disease as indicated by focal signs in neurological exam such as hemiparesis, sensory deficits, and evidence of relevant cerebrovascular disease by brain imaging AND a relationship between the two as indicated by the presence of one or more of the following: onset of dementia within 3 months after a recognized stroke, abrupt deterioration in cognitive functions, and fluctuating, stepwise progression of cognitive deficits)

Criteria for the diagnosis of probable and possible PDD

Probable PDD

A. Core features: Both must be present

B. Associated clinical features:

- Typical profile of cognitive deficits including impairment in at least two of the four core cognitive domains (impaired attention which may fluctuate, impaired executive functions, impairment in visuo-spatial functions, and impaired free recall memory which usually improves with cueing)
- The presence of at least one behavioral symptom (apathy, depressed or anxious mood, hallucinations, delusions, excessive daytime sleepiness) supports the diagnosis of Probable PD-D, lack of behavioral symptoms, however, does not exclude the diagnosis

C. None of the group III features present

D. None of the group IV features present

Possible PDD

A. Core features: Both must be present

B. Associated clinical features:

- Atypical profile of cognitive impairment in one or more domains, such as prominent or receptive-type (fluent) aphasia, or pure storage-failure type amnesia (memory does not improve with cueing or in recognition tasks) with preserved attention
- Behavioral symptoms may or may not be present

OR

C. One or more of the group III features present

D. None of the group IV features present

Distinct from dementia, cognitive impairment not deemed severe enough to impact on activities of daily life can be found even in early, incident (*Foltynie et al.,* 2004*, Muslimovic et al*., 2005) and drug-naïve cohorts of PD patients (*Aarsland et al.,* 2009). Again, definitions of cognitive impairment vary between studies, and incidence and prevalence figures depend heavily upon the cognitive assessment tools utilised (*Riedel et al.,* 2008*, Uc et al*., 2009). For example, using a generic cognitive screen such as the mini-mental state examination (MMSE) (*Folstein et al.,* 1975), cognitive impairment can be demonstrated in 17.5% of a prevalent cohort of PD patients, whereas a more disease-specific tool for assessing cognition in PD (Parkinson Neuropsychometric Dementia Assessment) detected cognitive impairment in 41.8% of the same group (*Riedel et al.,* 2008).

More detailed neuropsychological assessment of individual cognitive domains such as memory, attention, executive and visuospatial function in non-demented PD patients has also been used in an attempt to define mild cognitive impairment (MCI). As there is no accepted definition of MCI in PD, methodology varies considerably between studies. Most define MCI as deviation from the mean for a control group in one or more cognitive domains under examination – in line with established criteria for diagnosing MCI in populations at risk of developing AD (*Petersen,* 2004). The magnitude of such deficits range from 1 to 2 standard deviations from the normative sample mean and, depending on definition, demonstrate cognitive impairment in 18.9% (*Aarsland et al.,* 2009), 24% (*Muslimovic et al.,* 2005) and 36% (*Foltynie et al.,* 2004) of incident cases.

The profile of cognitive impairment in PD is qualitatively different from the type of MCI seen in the general ageing population. In the latter, an amnestic phenotype predominates (*Petersen et al.,* 1999), whereas the most frequent deficits in PD are in non-amnestic domains such as attention, executive and visuospatial function (*Aarsland et al.,* 2009*, Foltynie et al*., 2004*, Janvin et al*., 2006a*, McKinlay et al*., 2010). That MCI is an evolving rather than stable condition is demonstrated by a faster rate of progression to dementia in PD-MCI cohorts compared to PD non-MCI

groups (60% progression to PDD in MCI cf. 20% in non-MCI) (*Janvin et al.,* 2006b) and the association between verbal memory, executive, attentional and visuospatial deficits in prevalent PD cohorts and the development of dementia (*Levy et al.,* 2002*, Mahieux et al*., 1998). There is debate, however, about the predictive value of early cognitive deficits in PD and the subsequent evolution of dementia, with some workers arguing that pure executive deficits are not necessarily of sinister portent, compared with dysfunction in other domains such as semantic fluency and pentagon copying (*Williams-Gray et al.,* 2007). If confirmed, these observations would have implications, not only for the pathophysiological basis of "MCI", but also for potential prognostic and management decisions.

2.2 Clinical features of Parkinson's disease dementia (PDD)

A diagnosis of PDD, with its resultant increase in mortality, has far reaching consequences both for patients and their families (*Marder et al.,* 1991). Their is a significant impact on caregiver quality of life (*Aarsland et al.,* 1999) and the combination of motor and neuropsychiatric features are key contributors in admissions to institutional care (*Aarsland et al.,* 2000). Factors associated with an increased risk of developing PDD, include patient age (*Aarsland et al.,* 2007b), motor phenotype (*Alves et al.,* 2006*, Burn et al*., 2003), presence of cognitive impairment (*Janvin et al.,* 2006b) and visual hallucinations (*Aarsland et al.,* 2003*, Aarsland et al*., 2004).

2.2.1 Cognitive phenotype

Multiple cognitive domains are affected in PDD including memory (*Kuzis et al.,* 1999*, Whittington et al*., 2006), executive function (*Aarsland et al.,* 2003*, Litvan et al*., 1991), attention (*Ballard et al.,* 2002*, Beatty et al*., 2003) and visuospatial and visuoconstructive abilites (*Cormack et al.,* 2004*, Crucian and Oku*n, 2003*, Emre et al*., 2004*, Mosimann et al*., 2004b). The pattern of such deficits, with marked attentional, executive and visuospatial dysfunction and less dramatic memory disturbance, not only mirrors the cognitive changes in early PD but is also strikingly similar

to DLB, with which PDD shares many features in terms of clinical presentation. Whilst it remains possible to demonstrate neuropsychometric differences between PDD and AD in early and moderate dementia, as the disease progresses, there is increasing convergence of cognitive phenotypes (*Aarsland et al.,* 2003*, Bronnick et al*., 2007).

2.2.2 Visual cognition in Lewy body disorders

Visuoperceptual and visuospatial deficits are characteristic of the cognitive decline in PD and become more marked both as disease progresses or as cognition declines (*Levin et al.,* 1991). A wide range of deficits in visual attention, spatial and motion perception and visual and verbal working memory can be seen in non-demented PD patients and both cognitive and visual factors impact negatively on measures of functional independence (*Uc et al.,* 2005). PDD and DLB patients are well matched in visuocognitive impairments such as pentagon copying (*Cormack et al.,* 2004), visual discrimination, object-form perception and space-motion perception (*Mosimann et al.,* 2004b) and these deficits are more marked than in AD patients or controls. In addition, those suffering visual hallucinations (VH) perform less well on these visuoperceptual tasks than PDD or DLB patients without VH (*Mori et al.,* 2000*, Mosimann et al*., 2004b). Indeed, even in non-demented PD patients, differences in cognitive profiles can be demonstrated between hallucinators and non-hallucinators both in terms of executive function (*Barnes and Boubert,* 2008), visuoperceptual abilities and sustained attention (*Koerts et al.,* 2010*, Meppelink et al*., 2008).

This pattern of cognitive deficits in PD and PDD suggests dysfunction of widespread cortical and subcortical regions including fronto-parietal attentional and executive networks as well as occipito-temporal and occipito-parietal visuoperceptual and visuospatial processing streams. The cognitive phenotype is also highly relevant when considering the genesis of clinical features such as VH, where impairments in attention and visual perception in particular may play an integral role (*Collerton et al.,* 2005*, Diederich et al*., 2005).

2.2.3 Neuropsychiatric disturbance

Behavioural and neuropsychiatric symptoms such as low mood (58%), apathy (54%), anxiety (49%) and delusions (25%) all contribute to the complex behavioural phenotype of PDD (*Aarsland et al.,* 2007a) and form one of the cornerstones of the consensus diagnostic criteria (*Emre et al.,* 2007). When grouped into clusters, based on the relative patterns of cognitive symptomatology, low mood and apathy groups emerge as the predominant reported features (11% and 24% respectively), with agitation and psychosis clusters making up a smaller percentage. In a community-based sample, application of formal diagnostic criteria gives a lower rate of major depression in PDD of 13%, compared to 9% for non-demented patients, and 19% for patients with DLB (*Aarsland et al.,* 2001*, Aarsland et al*., 2007a). There is increasing evidence linking depression in general, and apathy specifically, with risk of cognitive decline in PD (*Santangelo et al.,* 2009).

2.2.4 Visual hallucinations

Hallucinations occur both in population- and hospital-based studies of PD with a prevalence of 20 – 40% (*Fenelon et al.,* 2000*, Goetz et al*., 2001) rising to 60 – 80% in studies of patients with PDD and DLB (*Aarsland et al.,* 2001*, Emr*e, 2003*, McKeith et al*., 2004). Other visual experiences, often defined as "visual hallucinations" in clinical studies of PD, include a sensation of movement in the visual periphery, a sense of presence in the room and illusory misperceptions of a visual stimulus (*Fenelon et al.,* 2000*, Mosimann et al*., 2006).

Once assumed to be a consequence of dopaminergic therapy, evidence now suggests that there is no clear association between levodopa dose and CVH, although dopamine agonists as a class are associated with an small increased risk of CVH (*Fenelon et al.,* 2000*, Goetz et al*., 1998*, Williams et al*., 2008). There are historical reports of hallucinations complicating late-stage PD in the pre-levodopa era (*Fenelon et al.,* 2006) and DLB patients frequently experience florid CVH despite no exposure to

dopaminergic therapy. Once present, CVH are persistent and progressive, causing increasing neuropsychiatric impact and remain strong predictors of nursing home placement and even mortality (*Aarsland et al.,* 2000*, de Maindreville et al*., 2005*, Goetz and Stebbin*s, 1993*, Goetz and Stebbin*s, 1995*, Goetz et al*., 2006). Illusory misperception, feelings of presence and passage often co-occur with CVH but also exist in isolation and may not have the same predictive value in terms of the development of PDD (*Llebaria et al.,* 2010).

Visual hallucinations are not unique to PD and DLB and are seen in a variety of other neurological, psychiatric and ophthalmological conditions. A broad range of hallucinatory experiences are reported by psychologically normal people in the setting of significant visual impairment – the so-called Charles Bonnet Syndrome (CBS). In this condition, patients experience a variety of visual phenomena from simple visual disturbances (flashes of light) through to well-formed CVH of people, animals and panoramic scenes (*Santhouse et al.,* 2000*, Teunisse*, 1997*, Teunisse et al*., 1999). Visual loss is typically due to age-related macular degeneration although a wide variety of other causes are also recognised (*Nesher et al.,* 2001*, Ashwin and Tsaloumas*, 2007*, Khan et al*., 2008). Insight is typically retained in CBS, while CVH seem to occur most commonly in situations of dim light or low arousal. Non-disclosure of CVH is common, with patients typically fearful of the response of doctors or worried about being branded “insane” (*Teunisse et al.,* 1996).

Functional MRI (fMRI) imaging in actively hallucinating CBS patients has implicated the inferior occipitotemporal 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 VH occur in CBS and PD. Visual acuity is classically significantly impaired in CBS, in contrast to PD, and simple visual disturbances outweigh CVH in terms of frequency (*ffytche and Howard,* 1999). Nevertheless, the concept of “de-afferentation” of the visual cortex by ocular disease (*Burke,* 2002*, Coga*n, 1973) priming the system for VH-generation has been offered as a potential explanation for

the development of hallucinations in CBS and may provide some insight into CVH in PD and PDD.

Vivid nocturnal hallucinatory experiences are also seen in some patients with brainstem disorders, where they are referred to as “peduncular” hallucinations (*Benke,* 2006) and transient hallucinations are also seen in the hypnopompic (waking up) and hypnagogic (falling asleep) state in narcolepsy, and indeed in the general population as well (*Ohayon,* 2000*, Ohayon et al*., 1996). Extracampine hallucinations are so-called due to their unique feature of occurrence outside the normal field of vision, often in the absence of an accompanying “visual” experience (*Manford and Andermann,* 1998). Peduncular and extracampine hallucinations share phenomenological features with “presence” hallucinations seen in PD and PDD, and raise the possibility of links between sleep disorders, brainstem dysfunction and the development of hallucinations in PD (*Manni et al.,* 2002*, Onofrj et al*., 2002*, Pacchetti et al*., 2005).

2.3 PD and sleep

Sleep disorders are common both in PD and PDD with insomnia, loss of muscle atonia during REM sleep, frank REM sleep behaviour disorder (RBD) and excessive daytime somnolence (EDS) all being more frequent than in control populations (*Comella,* 2006). Daytime somnolence, present in over 50% of patients, is now included in the diagnostic criteria for PDD as a core clinical feature (*Emre et al.,* 2007; *Boddy et al.,* 2007). Even in non-demented PD cohorts EDS is well-recognised, affecting 15% of patients at baseline in one study, with follow-up demonstrating an increase in prevalence at four years (29%) in the same study group (*Gjerstad et al.,* 2002*, Tandberg et al*., 1999). In these and other studies, EDS was associated with increased rates of cognitive decline, visual hallucinations and motor disability (*Fenelon et al.,* 2000). Similarities have been drawn between the somnolence of PD and that seen in narcolepsy, a condition where loss of the hypocretin-secreting neural population of the hypothalamus leads to EDS and disrupted sleep architecture (*Arnulf et al.,* 2000). Indeed, hypocretin cells are diminished in post-mortem studies of

PD (*Thannickal et al.,* 2007*, Fronczek et al*., 2007), although to a lesser degree, and without the detectable drop in cerebrospinal fluid levels of hypocretin-1 typically seen in narcolepsy (*Compta et al.,* 2009).

RBD, where the loss of normal muscle atonia results in dream enactment, with risk to patient and bed partner, is another common sleep disorder in PD (*Onofrj et al.,* 2002). Indeed, in longitudinal follow-up of subjects with so-called idiopathic RBD, around 40% have been shown to go on to develop neurodegenerative synucleinopathies such as PD, DLB and MSA (*Olson et al.,* 2000). Recently, RBD both in its idiopathic form and in the context of PD has been associated with cognitive impairment (*Gagnon et al.,* 2009). Vivid dreams and nightmares are a frequent accompaniment to RBD in PD and are associated with, but not predictive of, the presence and severity of CVHs (*Goetz et al.,* 2005).

Several studies have suggested that RBD is an independent risk factor, along with cognitive impairment, for developing visual hallucinations in PD and, intriguingly, a small study using ambulatory polysomnography demonstrated temporal relationships between both REM and non-REM sleep and hallucinations in 30% of a PD cohort (*Manni et al.,* 2002*, Onofrj et al*., 2002*, Pacchetti et al*., 2005). This has led some authors to suggest that CVH in PD might be the result of the intrusion of abnormal dream imagery into periods of wakefulness. However, these studies included presence, passage and illusions in the same category as CVH and hence may not have taken into account potential differences in aetiology between separate hallucinatory experiences. In addition, most studies to date have suffered from small group numbers or the lack of a control group and a clear correlation between RBD, CVHs and motor and non-motor outcome has not been confirmed in other studies (*Lavault et al.,* 2010*, Meral et al*., 2007).

2.4 The visual system in PD

There is dysfunction at several levels of the visual pathway in PD. This includes psychophysical, electrophysiological and morphological evidence

of disruption of retinal structure and function, in addition to disorders of "higher" (cortical) visual processing. In order to appreciate the impact Parkinson's disease has on the visual system, we must break it down into its composite parts - retina, subcortical visual pathways, primary (striate) and associated (extra-striate) visual cortex and those areas that provide "top-down" modulation of the incoming visual information.

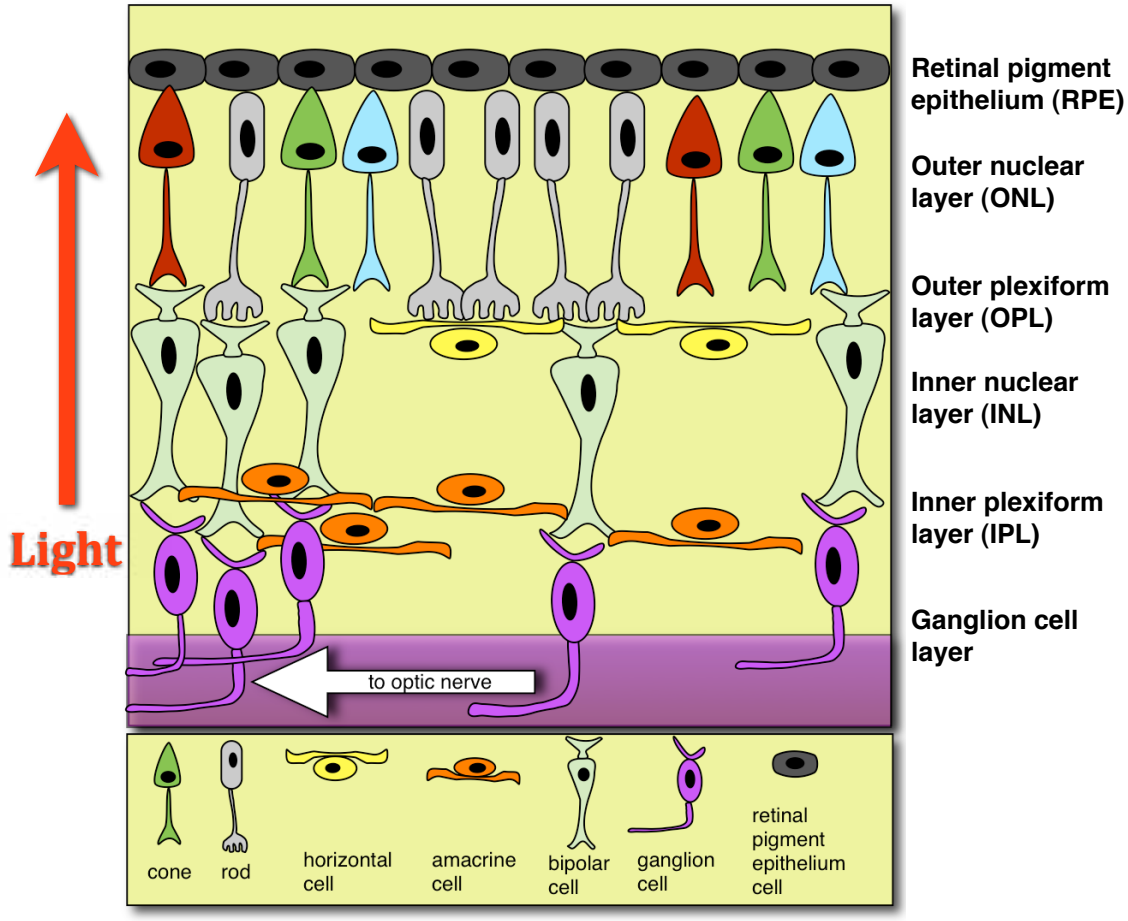
First we will re-visit some of the basic retinal anatomy described by Cajal in 1892 **(Figure 1)**. The organisation of the retina, with the photoreceptors arranged abutting the retinal pigment epithelium (RPE), means that, with the exception of the fovea, light has to penetrate the cell bodies and unmyelinated 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 specialised 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 (RGC) and it is the RGC that 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 (OPL) and bipolar cell to RGC neurotransmission occurs in the synaptic zones of the inner plexiform layer (IPL). 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 OPL and IPL, and these are vital in shaping the temporal and spatial qualities of scotopic and photopic vision. Horizontal cells synapse in the

OPL, affecting photoreceptor/bipolar cell interactions, while amacrine cells perform a similar role in the IPL for bipolar to ganglion cell transmission. 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-bipolar cell and bipolar-to-ganglion cell in the central fovea, facilitating high acuity colour vision. In contrast, there is considerable convergence in the rod-to-ganglion cell pathway, allowing this part of the retina to detect low intensity signals but at the cost of much lower spatial resolution.

Figure 1. Schematic of human retina.



RGC 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 (*Ferrera et al.,* 1992*, Ferrera et al*., 1994*, Malpeli et al*., 1996*, Maunsell et al*., 1990*, Nealey and Maunsell*, 1994*, Tobimatsu et al*., 1995). It is beyond the scope of this discussion 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 larger receptive fields and altered sensitivity to temporal-frequency modulation (*Martin et al.,* 2001*, Solomon et al*., 2005*, Solomon and Lenni*e, 2007).

Aside from the LGN, other subcortical targets for these retinal efferents are the superior colliculus, the pulvinar complex of the dorsal thalamus and the mid-brain tectum. It is the axons of LGN neurons that project to striate visual cortex in a retinotopic fashion, initially terminating in area V1. From here visual information passes into the extra-striate visual areas (V2-V5). Beyond 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 (*Goodale and Westwood,* 2004*, Goodale and Milne*r, 1992*, Ungerleider and Mishki*n, 1982*, Ungerleider and Haxb*y, 1994). In a similar fashion, visual information from the superior colliculus 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*, Kaas and Lyo*n, 2007*, Grieve et al*., 2000). In addition to its inputs to the pulvinar, the superior colliculus

is also responsible for integrating responses to visual, auditory and somatosensory stimuli.

Whilst this description is an over-simplification of the hugely complex structural organisation of the visual system, it serves to illustrate the hierarchical nature of the visual system from retina to cortex. A more detailed discussion of the cortical processing of visual information will be provided later, but for now, it should be borne in mind that the “anterior” visual system does not exist in isolation and many abnormalities of visual function can be attributed to cortical as well as retinal dysfunction.

2.4.1 Retinal physiology

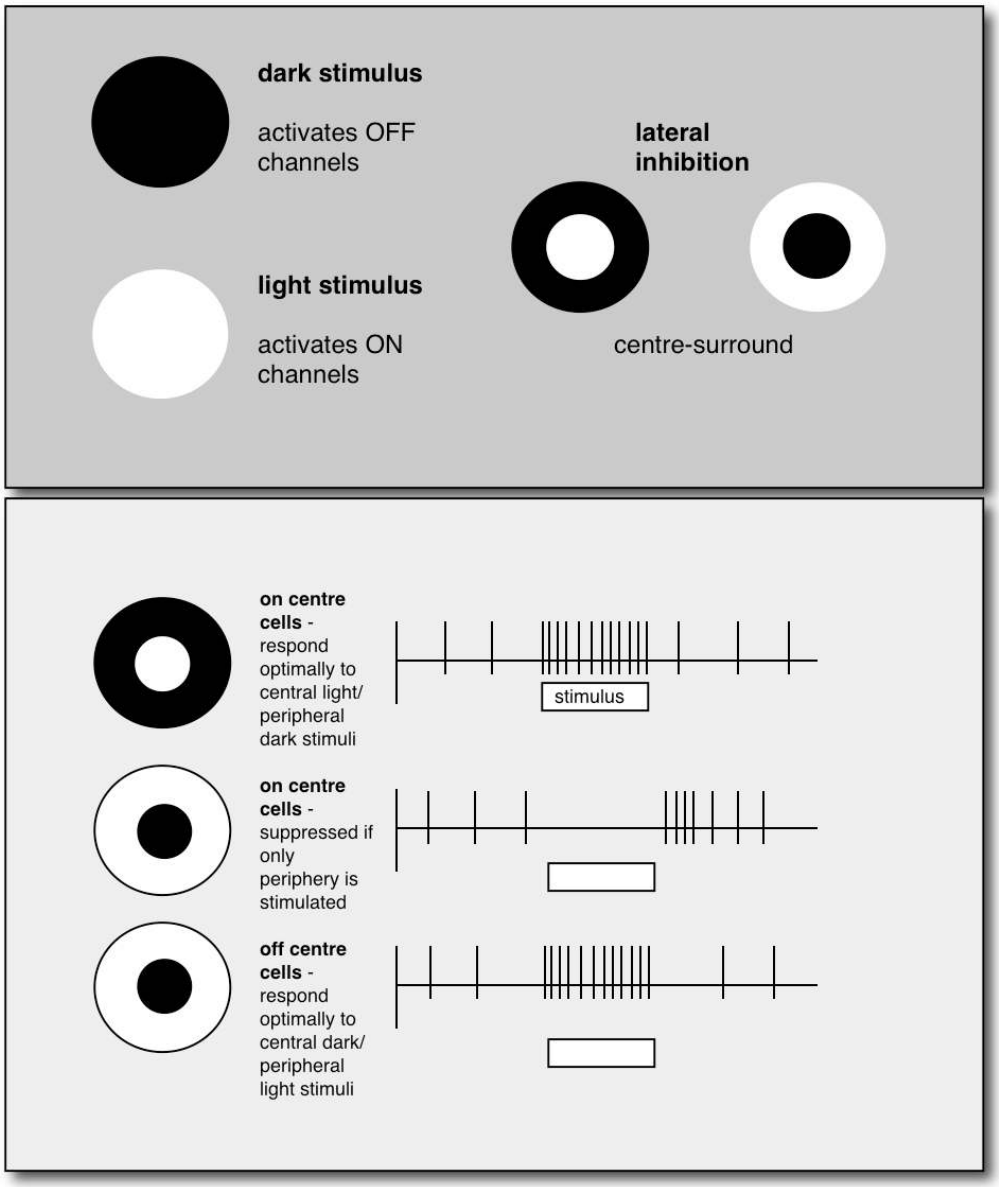
Photoreceptors exist in a depolarised state in the dark, constantly releasing glutamate, and hyperpolarise when stimulated by light. Unlike most other neurons, they do not produce action potentials but instead respond to changing light stimuli with graded alterations in membrane potential. When light excites a photoreceptor, glutamate release from the hyperpolarised 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.

Each RGC is influenced by light falling on a discrete area of the retina. This is known as the receptive field of the RGC and its size and photosensitive properties are dependent on the extent of synaptic contact made in the OPL and IPL, 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 **(Figure 2)**. Hence a further layer of complexity is added to the light response, with a “centre and surround”

component to RGC 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 (*Baylor et al.,* 1971*, Hartlin*e, 1940*, Shapley and Perr*y, 1986*, Werbli*n, 1991*, Werblin and Dowlin*g, 1969).

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



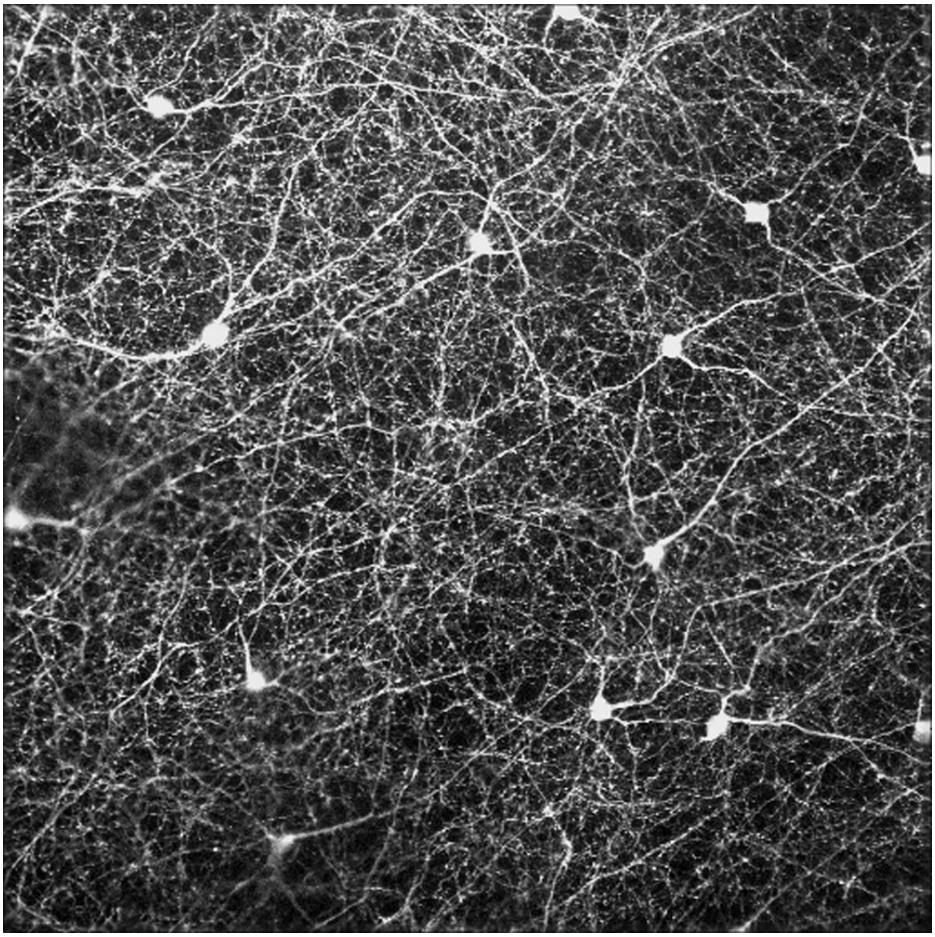
In reality, there are numerous subtypes of bipolar cells, RGCs, amacrine and horizontal cells, utilising different neurotransmitter systems and making synaptic contact in specific sub-layers of the IPL and OPL. Only those with potential relevance to PD will be discussed later. One of the key concepts 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 (*Gardner et al.,* 2005*, Kohn and Movsho*n, 2003*, Ohzawa et al*., 1985). Appreciation of the multiple sites of, for instance, contrast modulation is vital if we are to localise PD-specific alterations in such processing to the anterior or posterior visual system.

2.4.2 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 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 (*Kolb et al.,* 1990*, Mariani*, 1990*, Mariani*, 1991*, Witkovsky et al*., 2005). The density of A18 neurons is low but their widespread dendritic arborisation and long fine axons ensure overlap with neighbouring DA cells as well as other amacrine cells and bipolar cells **(Figure 3)** (*Dacey,* 1990*, Kolb et al*., 1990*, Pourcho*, 1982*, Voigt and Wassl*e, 1987). The inputs to DA amacrine cells are still not precisely

defined anatomically although it is known that A18 cells receive input predominantly from rod bipolar cells (*Kolb et al.,* 1990). 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).

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



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

AII cells express D1-subtype dopamine receptors and gamma-aminobutyric acid type-A ($GABA_A$) receptors; activation of the former leading to "excitation" (*Contini and Raviola,* 2003*, Veruk*i, 1997*, Veruki and Wassl*e, 1996). 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 (*Feigenspan et al.,* 1998*, Gustincich et al*., 1999*, Gustincich et al*., 1997). As well as direct synaptic effects on amacrine and bipolar cells, diffusion of dopamine in the retinal extracellular matrix exerts a paracrine effect, obviating the need for direct synaptic contact, and extending the range of action over many microns (*Witkovsky et al.,* 1993). Knowledge of these anatomical connections demonstrates that dopaminergic A18 cells, via their complex interactions with rod and cone bipolars, AII and A17 cells have a pivotal role in modulating the flow of rod-driven visual information through the retina.

Dopamine acts through G-protein coupled receptors, which regulate production of cyclic AMP. Dopamine receptor subtypes D1 and D5, often collectively referred to as the D1- receptor family, increase cAMP levels and, in this context, are excitatory, whereas subtypes D2, 3 & 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 utilise an autoreceptor of the D2 family to modulate their own DA release (*Muresan and Besharse,* 1993*, Nguyen-Legros et al*., 1997*, Veruk*i, 1997). Dopamine has direct effects on gap junction permeability both at the level of rod and cone interactions with horizontal cells (*He et al.,* 2000*, Nelso*n, 1977*, Xin and Bloomfiel*d, 1999) and at the level of AII:AII and AII:cone bipolar cell communication (*Xia and Mills,* 2004). The net effect is a reduction in gap junction permeability with rising dopamine concentrations and a resultant reduction in receptive field size (*Ribelayga et al.,* 2008)

In addition to this highly variable excitatory and inhibitory feedback system, there is a more “tonic” diurnal variation in retinal dopamine concentration, with low levels at night and higher levels during the day. This circadian rhythm is in counterphase with the retinal concentrations of melatonin, and indeed, DA and melatonin have mutually inhibitory effects on each other’s production – acting as a “biological clock” for the retina (*Doyle et al.,* 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-adapted to light-adapted state (*Cahill,* 1996*, Doyle et al*., 2002b*, Ribelayga et al*., 2008*, Tosini and Menake*r, 1996).

2.4.3 Summary – Dopamine and the retina

DA 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 (*Deans et al.,* 2002*, Hampson et al*., 1992*, Jense*n, 1989*, Jensen and Da*w, 1984*, Witkovsky et al*., 1988). In essence therefore, dopamine is a chemical messenger for light adaptation, promoting the flow of information through cone circuits while diminishing that through rod circuits.

2.5 Testing visual function

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

Visual acuity (VA) 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 **Figure 4a**, the letter 'E' falls on a specific area of the retina, measured in degrees and minutes of visual arc (one degree = 60 minutes). The area of retina exposed to the stimulus depends on the size of the letter and the distance from the eye. Hence, Snellen VA is defined by the distance at which the chart is read and the size of the letters discriminated. "Normal" Snellen VA (6/6 or 20/20) describes the ability to discern a letter 'E', subtending 5 minutes of visual arc on the retina (Snellen line 6), when presented at 6 metres (20 feet).

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

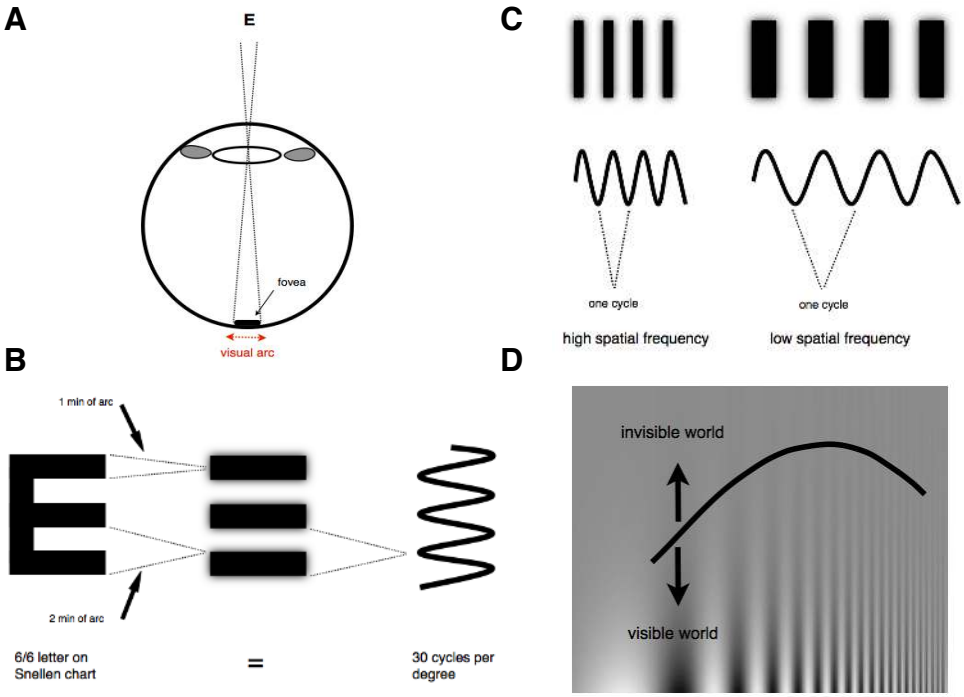
Snellen acuity would equate to a spatial frequency of 30 cycles per degree **Figure 4b & c**.

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 measurement of VA difficult, particularly at lower levels of acuity. These problems have led to the increasing use of the logMAR system for measuring VA. Here, each line contains 5 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 VA.

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 utilised. 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 **(Figure 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 (CS). Plotting CS 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 PD.

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 minutes, with each component of the stimulus taking up 1 minute. A full "cycle" from black-white-black therefore takes 2 minutes 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.



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, VA and CS 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 (*Altpeter et al.,* 2000*, Dacey and Petersen*, 1992*, Perry and Cowey*, 1985*, Silva et al*., 2008*, Thibos et al*., 1987).

2.6 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 PD, might affect the retina, is less clear. The hypothesis that the retina is a site of functional and structural change in PD raises a number of questions. Firstly, given that PD prevalence increases with age, if there is evidence of retinal dysfunction in PD, 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 PD 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 PD 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 discussion.

2.6.1 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 (*Johnson,* 2001*, Klein et al*., 1992*, Mangione et al*., 1994*, Owsley et al*., 2000*, Owsley et al*., 2001). Even in the absence of such overt pathology, however, visual function declines with age. Such changes include reduction in the accommodative 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 (*Curcio,* 2001*, Pitt*s, 1982*, Weal*e, 1987). 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.

Snellen charts provide a measure of VA 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 relevant stimulus components if the image is to be maintained on the optimal part of the retina.

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

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

Colour vision relies on the cone photoreceptor population and is therefore largely confined to the central retina. Because there is a segregation of colour-specific information at the retinal level into blue-yellow (BY) and red-green (RG) pathways, it is possible to use colour discrimination tasks to assess cone and RGC subpopulations. Colour vision is affected by the

ageing process particularly along the BY (tritan) axis, possibly due to cone dysfunction and opacified lens absorption of short wavelength light (*Knoblauch et al.,* 1987*, Nguyen-Tri et al*., 2003). However, scotopic vision is more vulnerable to the ageing affect and rod photoreceptors are particularly at risk (*Curcio et al.,* 1993*, Jackson and Owsle*y, 2000*, Jackson et al*., 2002). This has implications for dark adaptation in the elderly eye, a potential additional problem in the dopamine-deficient retina.

2.6.2 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 5 patients with PD (*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 fifteen hours 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 intra-retinal scotopic electrophysiological responses, an effect reversed by the addition of dopamine and consistent with dopaminergic modulation of amacrine function (*Naarendorp et al.,* 1993). These studies, despite their limitations, provided a tantalizing link between previously documented electrophysiological and psychophysical evidence of retinal dysfunction in PD and the hypothesis that it was dopaminergic deficiency itself that mediated these changes.

2.7 Evidence of visual dysfunction in Parkinson's disease

2.7.1 Visual acuity

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

2.7.2 Contrast sensitivity (CS)

The first clinical reports of abnormal contrast sensitivity in PD came from Regan and Neima (1984) when they investigated the vision of ten patients using letter charts similar to Snellen cards, but with varying contrast levels (*Regan and Neima,* 1984a). Half of the PD patients 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 CS loss at a variety of spatial frequencies (*Bulens et al.,* 1986*, Delalande et al*., 1996*, Harris et al*., 1992*, Langheinrich et al*., 2000). Bodis-Wollner and Yahr reported that the spatial frequency loss in PD was most marked at 4.8 cpd, the normal peak CS region in controls (*Bodis-Wollner et al.,* 1987). Such modification of the CS curve in PD was exaggerated when temporal variation was introduced at the 4-8 Hz range (*Bodis-Wollner et al.,* 1987*, Regan and Maxne*r, 1987). In addition, spatiotemporal CS to moving gratings was diminished in PD in

a different pattern to the reductions seen in age-matched controls, suggesting a disease-specific “motion blur” in contrast perception (*Masson et al.,* 1993*, Mestre et al*., 1990).

That these alterations are driven by dopaminergic deficiency is supported by the findings that CS improves after the administration of levodopa (*Bulens et al.,* 1987*, Hutton et al*., 1993) and that similar alterations occur in drug-induced parkinsonism (*Bulens et al.,* 1989). In addition, PD patients with marked motor fluctuations between their “on” and “off” state, show a mid-spatial frequency decrease in CS similar to that observed in stable parkinsonian patients. When tested in an “on” condition, the CS curves more closely resembled age-matched controls (*Bodis-Wollner and Onofrj,* 1987). These psychophysical tests of presumed retinal function are, however, relatively complex tasks drawing on attentional and cognitive abilities and contrast is processed in retinal, subcortical and cortical regions (*Crucian and Okun,* 2003*, Geldmache*r, 2003). Given that few studies have controlled for these potential confounders, it is difficult to know how much of the CS change can be truly attributed to retinal dysfunction. CS losses have been identified as orientation-specific in some cases (*Bulens et al.,* 1988*, Regan and Maxne*r, 1987) arguing for a degree of cortical influence, as orientation specificity is not determined at a retinal level (*Hubel and Wiesel,* 1977*, Hubel et al*., 1977*, Hubel et al*., 1978*, Regan and Maxne*r, 1987).

Static measures of CS are attractive due to their ease of application in a clinical setting but they cover a relatively narrow range of spatial frequencies and have been criticised for their lack of test-retest reliability (*Reeves et al.,* 1991). Contrast charts 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 CS (*Buttner et al.,* 1996*, Pieri et al*., 2000*, Price et al*., 1992*, Uc et al*., 2005) with evident progression in one longitudinal follow-up study over 20 months (*Diederich et al.,* 1998*, Diederich et al*., 2002).

Contrast sensitivity is vital for a range of day-to-day activities and diminished CS has been implicated in falls, difficulties in reading and driving performance, as well as with activities of daily living in elderly patients (*de Boer et al.,* 2004*, Ivers et al*., 1998*, Kooijman and Cornelisse*n, 2005*, Lor*d, 2006*, Owsley and Sloane*, 1987*, West et al*., 2002*, Worringham et al*., 2006). The functional significance of CS changes in PD specifically is less clear. A similar change in CS 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 PD patients with visual hallucinations had significantly worse CS than those without hallucinations, suggesting a putative role for retinal dysfunction in the development of visual complications in PD (*Diederich et al.,* 1998).

2.7.3 Colour vision

Deficits in colour vision in PD 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 PD 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), PD patients demonstrate significantly higher error rates on

the FM test than age-matched controls (*Pieri et al.,* 2000*, Price et al*., 1992). 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.,* 1995*, Haug et al*., 1994*, Regan et al*., 1998).

Silva et al. (2005) probed chromatic and achromatic contrast sensitivity changes in PD using complex psychophysical measures designed to isolate parvocellular, koniocellular and magnocellular pathways (*Silva et al.,* 2005). Significant impairment in all three pathways was found, more marked along the protan/deutan (RG) axis than the tritan (BY). This pattern contrasts with that typically seen in ageing - a 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 (*Castelo-Branco et al.,* 2004). Such comparisons suggest a disease-specific pattern of retinal impairment in PD 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 pattern electroretinogram (PERG) responses in PD when compared to controls and subjects with Multiple System Atrophy (MSA) (*Sartucci et al.,* 2006b).

2.7.4 Motion perception

In addition to changes in VA and CS, perception of motion is also affected in PD and PD dementia (*Mosimann et al.,* 2004b*, Trick et al*., 1994). Uc et al. (2005) studied visual attention and motion perception in PD patients and age-matched controls using the useful field of vision (UFOV) test and random dot cinematograms (*Uc et al.,* 2005). 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 present a motion signal amid spatially random background noise. PD patients demonstrated impairments of visual attention, spatial and motion detection compared to controls. These group differences became non-significant when CS and VA 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 PD.

One recent approach that sheds further light on this area involves 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 to study their inter-dependence (*Castelo-Branco et al.,* 2008). PD patients, screened for ophthalmological disorders and matched for cognition by MMSE, demonstrate 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 PD group. This recent work, demonstrating a dissociation between low- and high-level visual processing in PD, suggests that motion perception in the higher visual centres of the cortex is affected in PD and that not all such perceptual impairments can be explained by abnormalities in the early magnocellular pathway from retina to subcortical, 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.

2.7.5 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 subcortical 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 PD and other Lewy body disorders. One 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 (DLB). 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 generalise from this small study in DLB to the PD population, however, and further studies are required.

Optical Coherence Tomography (OCT) is a technique for obtaining cross-sectional images of the retina in a non-invasive fashion with a resolution of 10 microns. “Time-domain” methods function effectively as ‘optical ultrasound’, projecting a near-infrared light beam onto the retina and comparing the echo time delays of light reflected from the retina with that returned from a reference mirror. More recently, “frequency-domain” OCT has become available, permitting faster signal acquisition, a better signal-to-noise ratio and 3-dimensional image reconstruction with an axial spatial resolution of 3-5 microns. OCT is capable of assessing the thickness of retinal nerve fibre layers (RNFL) around the optic nerve head, thus providing a measure of the integrity of the retinal ganglion cell axons as they exit the retina, as well as providing information of macular morphology in the central retina.

OCT is accurate and reproducible in the assessment of glaucoma and ageing (*Blumenthal et al.,* 2000*, Budenz et al*., 2005*, Paunescu et al*., 2004) provided signal strength, an automated measure of signal-to-noise ratio and signal uniformity, is adequate (*Cheung et al.,* 2008). Factors such as age, ethnicity, axial length and optic disc size all influence RNFL thickness as measured by OCT and should be taken into account when interpreting results (*Budenz et al.,* 2007). OCT demonstrates morphological changes in retinal structure in multiple sclerosis, Alzheimer’s disease and glaucoma (*Iseri et al.,* 2006*, Kanamori et al*., 2003*, Parisi et al*., 1999). RNFL thinning has been found in PD, albeit in relatively small numbers of patients (*Altintas et al.,* 2007*, Inzelberg et al*.,

2004*, Moschos et al*., 2010) and macular thickness has also been reported to be reduced (*Altintas et al.,* 2007*, Cubo et al*., 2010*, Hajee et al*., 2009). One possible hypothesis to explain morphological changes in the PD retina is that dopaminergic deficiency deprives the retina of key trophic factors vital to maintaining structural integrity. To date, the functional implications of these reported morphological changes are unclear.

2.7.6 VEP & ERG

Retinal responses to visual stimuli generate clinically measurable 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 PD. Early work from Bodis-Wollner and Yahr demonstrated a delay in the VEP latency to sinusoidal gratings at a mid-spatial frequency (*Bodis-Wollner and Yahr,* 1978) and these findings have been replicated in a number of subsequent studies using a variety of spatial and temporal stimulus parameters (*Ikeda et al.,* 1994*, Marx et al*., 1986*, Nightingale et al*., 1986*, Regan and Neim*a, 1984b*, Tartaglione et al*., 1987). Such VEP latency changes can be reversed with the administration of levodopa 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 PD 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).

The 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 PD (*Gottlob et al.,* 1987*, Langheinrich et al*., 2000*, Nightingale et al*., 1986*, Peppe et al*., 1998*, Peppe et al*., 1992*, Sartucci et al.*, 2006, Stanzione et al., 1990). In contrast to the "global" reduction in amplitude of PERG response in age-matched controls compared to young controls, PD patients show a specific medium-frequency deficit to a variety of sinusoidal grating spatial frequencies (*Tagliati et al.,* 1996). These changes respond to administration of levodopa (*Peppe et al.,* 1998*, Peppe et al*., 1995) 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 PD (*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 compared to pre-administration results. Treatment with levodopa produced transient recovery both in parkinsonian signs and pattern VEP 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 levodopa administration (*Bodis-Wollner and Tzelepi,* 1998*, Ghilardi et al*.,

1989). 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).

2.7.7 Summary – PD and the "subcortical" visual system

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 is 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 RGC function implicates dopamine heavily in organising the receptive field of these output cells of the retina. Thus the spatiotemporal contrast sensitivity abnormalities in PD, particularly at the point where the normal peak of CS occurs, are a measure of dopaminergic influences on the "centre-surround" receptive fields of RGCs. The striking similarity between the CS function curves of dark-adapted normal retina and light-adapted PD retina implicate DA in the transition from scotopic to photopic vision (*Harris et al.,* 1992*, Wink and Harri*s, 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 RGC receptive fields and lower spatial and temporal resolving potential with an ultimate impact on visual acuity, contrast sensitivity and colour and motion 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 PD, 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 subcortical and cortical components to visual symptomatology in PD and PD dementia. Visuocognitive and visuoperceptual impairments are most striking in PDD, where visual hallucinations are particularly prominent (*Mosimann et al.,* 2004b). Cognitive impairment is common in PD, even in incident cohorts with mild or early disease and simple screening tools for cognitive dysfunction such as the MMSE will miss many PD 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 PDD, in conjunction with a better appreciation of mild cognitive impairment as a precursor to more marked decline (*Janvin et al.,* 2006b*, Williams-Gray et al*., 2007), should allow separation of these patients from cognitively intact PD patients – a vital step if we are to integrate both “bottom up” and “top down” approaches to vision research in PD and PDD (*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 CBS and a similar pathogenic mechanism may occur in PD and PDD. Impaired visual acuity and contrast sensitivity are risk factors for hallucinations in PD but it seems unlikely that the subtle changes seen in PD 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 PD (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 PD. 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 (*Castelo-Branco et al.,* 2008*, Uc et al*., 2005).

Structural degeneration of the retina has been reported in PD, 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 not only to confirm these findings in larger cross-sectional cohorts but also to embark on longitudinal studies to address the role of OCT as a potential biomarker of neurodegeneration in PD. 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 PD.

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 PD 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 PD, 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 PD is overdue, particularly as effective treatments exist for many of the concomitant ocular disorders that may contribute to visual symptoms in PD. Successful intervention therefore offers the prospect of improvements in the quality of life of PD 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 PD. In addition, understanding neurodegeneration within the retina, both at a microscopic and macroscopic level, may provide a clearer window through which to view the disease process itself and its influence, not just on the eye, but also on visuoperceptual, visuocognitive and visuomotor performance as well.

2.8 Visual cortex: structure and function

So far, we have focused on the hierarchical organisation of the visual system up to the point that visual information converges on the primary (striate) visual cortex. We now begin to see considerable divergence through the so-called extra-striate or visual association areas. In addition to this forward flow of visual information, there is also a process of feedback, modulating responses at various cortical and subcortical levels. Our understanding of the visual system in humans has traditionally been based on experimental data from non-human primates and patients with discrete lesions in the visual pathways. More recently, work utilising tools such as fMRI and transcranial magnetic stimulation (TMS) has

transformed the field, demonstrating for the first time how cortical visual processing occurs both in normal subjects and those with neurodegenerative disorders.

Primary visual cortex, also known as area V1, is the region of visually-responsive cortex that receives the bulk of the retino-geniculate input. Located in the calcarine sulcus of the occipital lobe it contains a retinotopic representation of the contralateral visual field. From here, visual information is passed to area V2, the first extra-striate visual region, where further analysis and sorting of “raw” data is achieved. Neurons in V1 and V2 have relatively simple response properties to stimulation in appropriate parts of their receptive field. Cells in this region selectively respond to stimuli of, for example, a specific spatial frequency, orientation, colour or direction of motion (*Hubel and Wiesel,* 1959*, Zek*i, 1978*, Tootell et al*., 1988*, Burkhalter and Bernard*o, 1989).

Area V3 is located adjacent to V2 and can be subdivided into a dorsal and ventral component. In addition to this, further subdivisions such as areas V3A and V3B have been proposed in humans. Dorsal V3, V3A and V3B seem to receive input from both V1 and V2 and are, in part, responsible for processing information on motion. The properties of ventral area V3 are less completely understood, at least in humans, but cells in this area seem to project to visual association areas in the temporal lobe (*Tootell et al.,* 1997).

Area V4, located on the ventral surface of the brain, is involved both in object recognition (*Gallant et al.,* 2000), motion- (*Tootell and Hadjikhani,* 2001) and colour-perception (*Zeki et al.,* 1991*, Howard et al*., 1998). Responses in V4 are optimal to geometric shapes and contours rather than complex figures such as animals, objects or faces (*Desimone et al.,* 1985*, Kastner et al*., 2000). The flow of visual information from V1 and V2, through ventral V3, to V4 marks the anatomical beginning of what is often referred to as the “ventral stream” of visual processing.

Visual information is also directed in a more dorsal direction, passing from V1 and V2, through the dorsal divisions of V3 and also into area V5/MT, located at the junction between the lateral occipital and medial temporal cortex (*Ungerleider and Desimone,* 1986*, Tootell and Taylo*r, 1995). This extensively studied area also receives input from subcortical visual structures such as the pulvinar nucleus of the thalamus and the LGN (*Kaas and Lyon,* 2007). Output from V5/MT flows both to the ventral stream via area V4, and also in a more dorsal direction, to regions such as the posterior parietal cortex (PPC), intraparietal sulcus (IPS) and the parietal and frontal eye fields. V5/MT is primarily involved in integrating simple information on visual motion into a more complete representation of the coherent movement of complex objects (*Tootell et al.,* 1995*, Smith et al*., 1998*, Welchman et al*., 2005).

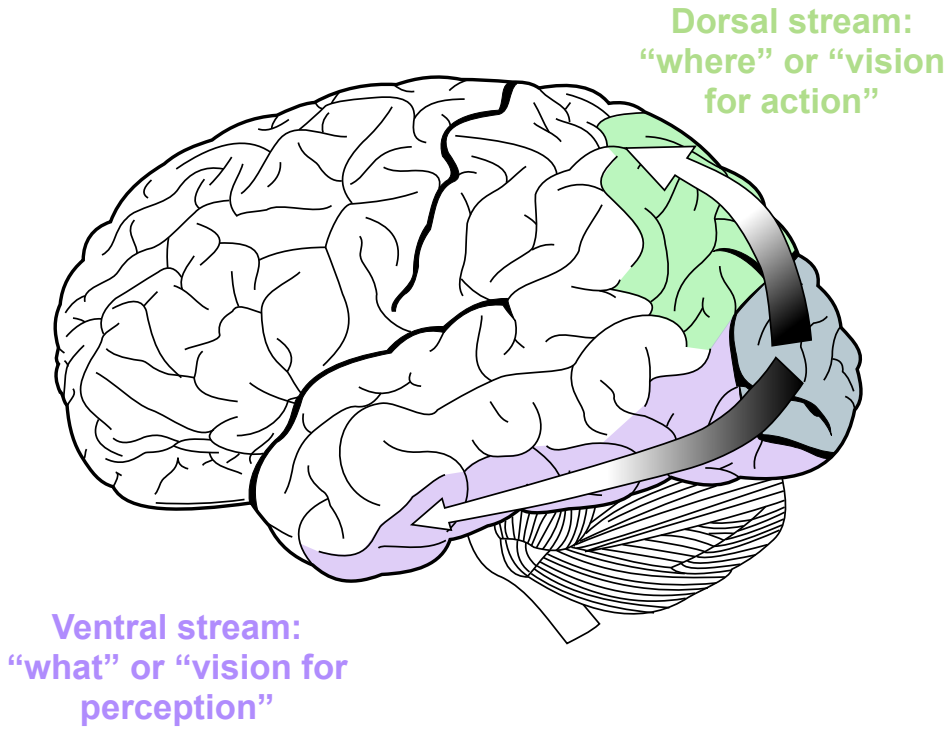
This division of the visual pathways into a dorsal and ventral stream was first hypothesised by Ungleleider and Mishkin in 1982 based on work in primates (*Ungerleider and Mishkin,* 1982). In their seminal article, it was suggested that the ventral stream was specialized for object-form identification – the “what” pathway - with the dorsal stream subserving spatial assessment – the “where” pathway **(Figure 5)**. Although now thought to be an oversimplification, the concept of two parallel and complementary streams of visual information processing remains valid. More recently, the hypothesis has been revised by Goodale and Milner to highlight the role of the dorsal (visuomotor) stream in *integrating* visual information for use in motor tasks, whereas the ventral (visuoperceptual) stream *interprets* visual information, assembling a conscious percept that can be allied with other cognitive constructs to aid recognition and identification (*Goodale and Milner,* 1992*, Goodale and Westwoo*d, 2004).

2.8.1 Ventral stream

The ventral stream terminates in ventral and medial temporal lobe cortex in defined regions such as the lateral occipital complex (LOC), fusiform face area and parahippocampal place area. Such regions demonstrate attribute-based, category-specific activation to objects for the LOC (*Eger*

et al., 2008*, Vinberg and Grill-Specto*r, 2008), novel and famous faces for the fusiform face area (*Clark et al.,* 1998*, Grill-Spector et al*., 2004*, Kanwisher et al*., 1997*, Chao et al*., 1999), and scene recognition for the parahippocampal place area (*Epstein et al.,* 1999*, Park and Chu*n, 2009). In addition to ventral stream activity during face perception and picture encoding tasks, there is also activation evident in hippocampal and parahippocampal regions, suggesting that these repositories of semantic and episodic memory are accessed concurrently with object perception to allow integration of visual perception with prior experience (*Ricci et al.,* 1999*, Stern et al*., 1996).

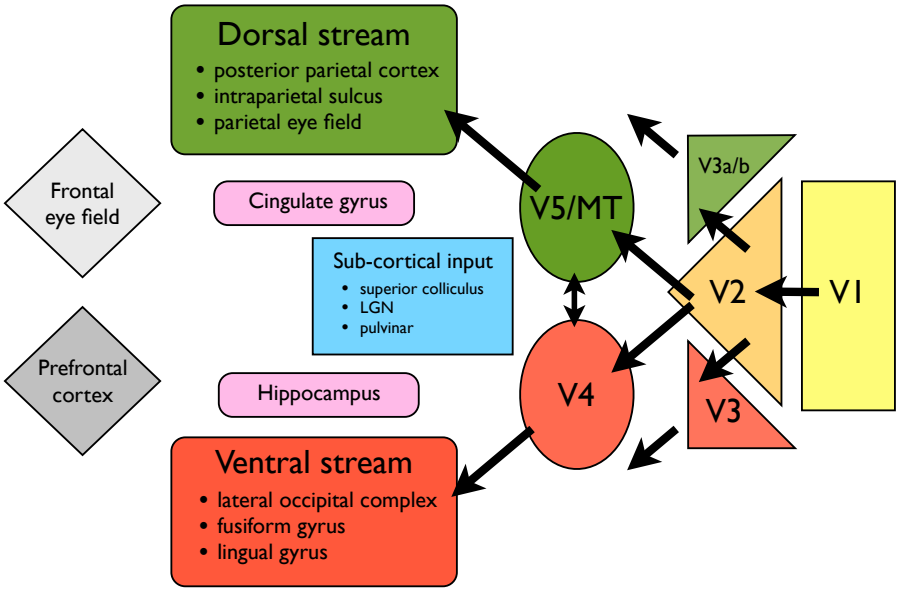
Figure 5. Schematic representation of dorsal and ventral stream pathways as they flow from occipital to parietal and temporal lobes respectively.



Complementing this "bottom up" driven process of building a complex visual percept, there appears to be "top down" modulation mediated by activation in frontal and parietal regions. For example, visual *imagery* activates identical areas of the temporal lobe to those used for visual *perception*, albeit to a less marked extent. This is associated with attribute-

dependent activation of the prefrontal cortex, and content-unrelated activity in the posterior parietal cortex, suggesting that these areas have a role in retrieval and maintenance of visual memories from storage **(Figure 6)** (*Ishai et al.,* 2002*, Ishai et al*., 2000*, Mechelli et al*., 2004).

Figure 6. Schematic of the principal cortical regions involved in dorsal and ventral stream processing. Note the communication between V5/MT and V4, thereby ensuring that motion perception is also served by the ventral stream. Note also the close association between dorsal stream, cingulate gyrus and parietal and frontal eye fields and between ventral stream, hippocampus and prefrontal cortex.



2.8.2 Dorsal stream

The dorsal stream terminates in the posterior regions of the parietal lobe (PPC), where integration occurs between visuospatial input and motor planning. In particular, regions such as the PPC seem to be vital in the planning, initiation and adjustment of visually-guided limb and eye movements (*Milner and Goodale,* 1995). In Perenin and Vighetto's study of 10 patients with unilateral lesions of the posterior parietal lobe, deficits in coordination and accuracy of visually-elicited hand movements (so-called "optic ataxia") were noted despite an absence of limb weakness or

visual space misrepresentation (*Perenin and Vighetto,* 1988). In addition, lesions in the human PPC also impact on the ability to make “online” corrections to movements once they have begun, suggesting a role for the PPC in integrating visual feedback in the adjustment on ongoing motoric output (*Pisella et al.,* 2000). In support of this lesion data is evidence from functional imaging studies, demonstrating increased activity in the PPC during visually-guided reaching (*Clower et al.,* 1996*, Desmurget et al*., 2001) and disruption to the accuracy of these reaching movements when TMS is applied to the contralateral PPC (*Desmurget et al.,* 1999).

Distinct from this “vision for action” role of the PPC, fronto-parietal networks are also involved in the deployment of visuospatial attention (*Corbetta et al.,* 1993). Posner et al. (1984) demonstrated that parietal stroke patients, as compared to stroke controls with other patterns of cortical injury, struggle to disengage attention from one stimulus and re-engage with a second (*Posner et al.,* 1984). Furthermore, there are decrements in vigilance in PPC-lesioned patients when sustained attention is required for spatial compared to verbal tasks (*Malhotra et al.,* 2009). Tests of working memory, “visual detection versus identification” and visuospatial ability invoke changes in fMRI PPC activity, suggesting roles for this region in directing spatial attention, non-spatial tasks and overall attentional vigilance (*Coull and Frith,* 1998*, Newman et al*., 2003*, Vandenberghe et al*., 1996). In addition, PPC provides “top down” modulation of visual cortex excitability for attended stimuli (*Silvanto et al.,* 2009*, Slotnick et al*., 2003) and contributes to attentional selection of pertinent visual stimuli among distractors (*Kastner et al.,* 1999*, Battelli et al*., 2009).

2.8.3 Prefrontal cortex

The frontal lobe, and specifically the prefrontal cortex (PFC), plays an important part both in attention and memory and hence influences the processing of visual information in both dorsal and ventral streams. For example, visual perception and imagery both activate the PFC in a category-selective fashion (*Mechelli et al.,* 2004*, Haxby et al*., 2000) and

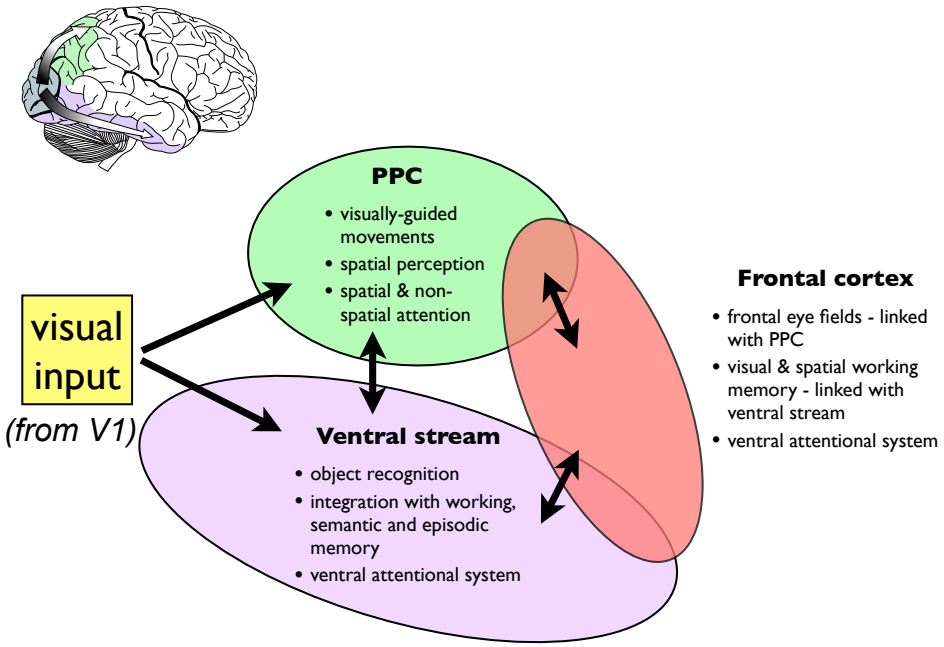
TMS of different PFC regions leads to specific deficits in both spatial and non-spatial tasks (*Mottaghy et al.,* 2002). In addition, visual and spatial working memory is a key component of PFC function and, due to its connectivity to medial temporal, hippocampal and parahippocampal regions, the PFC is also vital to the integration of working memory with semantic and episodic memory (*Courtney et al.,* 1998*, Ranganat*h, 2006).

Several models have been proposed in an attempt to integrate this fronto-parietal contribution to visuospatial and visuoperceptual processing with Ungerleider and Mishkin's (1982) and Goodale and Milner's (1995) original hypotheses. One such model divides the parietal lobe anatomically and functionally into a superior parietal lobe (SPL) devoted to visuomotor integration and online correction of ongoing movements and an inferior parietal lobe (IPL) more involved with action understanding and spatial perception (*Rizzolatti and Matelli,* 2003). Regions of the IPL are also active in non-spatial tasks, arguing for a crucial role in sustaining intensity of attention and attentional selectivity **(Figure 7)** (*Husain and Nachev,* 2007).

Corbetta and Shulman's influential model focuses more on the role of fronto-parietal networks in visuospatial attention (*Corbetta and Shulman,* 2002). As such, the SPL and inferior parietal sulcus are implicated in deploying attention and selecting suitable responses from a range of potential competing stimuli in a goal-directed fashion. In contrast, inferior regions of the PPC, ventral PFC and the temporoparietal junction (TPJ), act as a "ventral attentional network", allowing attention to be switched from one part of the visual field to another in response to a novel or highly salient event. This "circuit-breaker" pathway is strongly lateralized to the right hemisphere and implies a "bottom up" contribution to selective attention, rather than the more conventional "top down" control suggested by earlier models (*Rees and Lavie,* 2001). This rightward bias for the attention system may help explain why hemispatial neglect and visual inattention is most marked after lesions to the right hemisphere.

The neuropsychological deficits in attention, frontal executive, visuospatial and visuoperceptual abilities characteristic of PD and PDD argue strongly for dysfunction in a variety of cortical regions such as PFC, PPC and the dorsal (occipito-parietal) and ventral (occipito-temporal) streams as an explanation for some of the visual and cognitive symptoms encountered in the disorder. If so, imaging and post-mortem studies should provide evidence to support this notion.

Figure 7. Depiction of the key networks involved in the control of visual attention. Although distinctions are made between parietal, temporal and frontal regions, in essence they function as an interconnected and interdependent functional network.



2.9 Cortical impact of PD and PDD

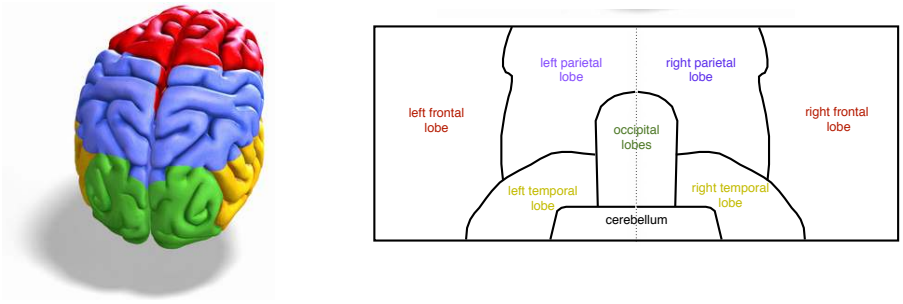
A variety of neuroimaging approaches have been used to highlight the structural and functional consequences of the neurodegeneration evident in PD and PDD. Bruck at al (2004) demonstrated hippocampal and PFC atrophy in non-demented PD patients compared to HC, the former being associated with memory deficits and the latter with attentional impairments on cognitive testing (*Bruck et al.,* 2004). More diffuse, but subtle, atrophy has also been detected in superior parietal, occipital, fusiform and parahippocampal regions of non-demented PD patients, correlating with visuospatial and visuoperceptual impairments (*Pereira et al.,* 2009). Greater reductions in grey matter density in limbic, paralimbic and neocortical regions are evident in PD hallucinators compared to non-hallucinators suggesting a link not just with cognitive profile but also visual symptomatology (*Ramirez-Ruiz et al.,* 2007*, Ibarretxe-Bilbao et al*., 2009).

As one might expect, atrophy is much more dramatic in studies focusing on PDD or the closely related DLB. Hippocampal, parahippocampal, frontal, parietal and occipital regions are all affected (*Burton et al.,* 2005) although those cortical areas involved in dorsal and ventral stream processing seem particularly vulnerable (*Beyer et al.,* 2007*, Ramirez-Ruiz et al*., 2005). Diffusion tensor imaging, which provides a surrogate measure of the integrity of neural connectivity, suggests that communication between precuneus, posterior cingulate and posterior parietal regions is damaged in PDD and DLB (*Firbank et al.,* 2007*, Matsui et al*., 2007). A pictorial representation of the referenced studies on PD, PDD and DLB, and the brain regions affected, is provided in **Figures 8 & 9**.

Single photon emission computed tomography (SPECT) studies, measuring regional cerebral blood flow, provide a functional rather than structural measure of cortical integrity. SPECT studies in DLB and PDD have demonstrated reductions in blood flow in occipital and posterior parietal areas (*Abe et al.,* 2003*, Mito et al*., 2006) and these changes are associated with both cognitive and behavioural features such as

attentional deficits and hallucinations (*O'Brien et al.,* 2005). In addition to this occipito-parietal change, hypoperfusion is also evident in inferior temporal and fusiform regions in hallucinators compared to non-hallucinators (*Matsui et al.,* 2006*, Oishi et al*., 2005). Subtle perfusion changes are even demonstrable in parieto-occipital regions in PD patients with MCI compared to a cognitively normal PD cohort (*Nobili et al.,* 2009). MR spectroscopy and positron emission tomography also highlight reductions in metabolic activity in occipital (*Summerfield et al.,* 2002), temporal and frontal areas (*Perneczky et al.,* 2008).

Figure 8. Imaging studies in PD. In this depiction, the lobes of the brain have been flattened out to allow a better appreciation of the principal regions affected in PD. Note the bias toward involvement of medial temporal, occipito-parietal and prefrontal regions even early in the disease course.



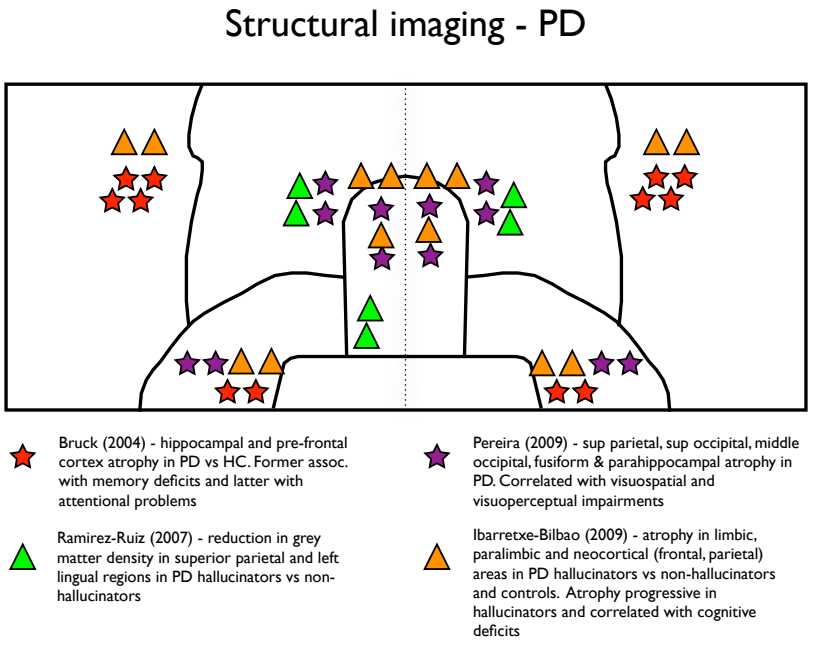
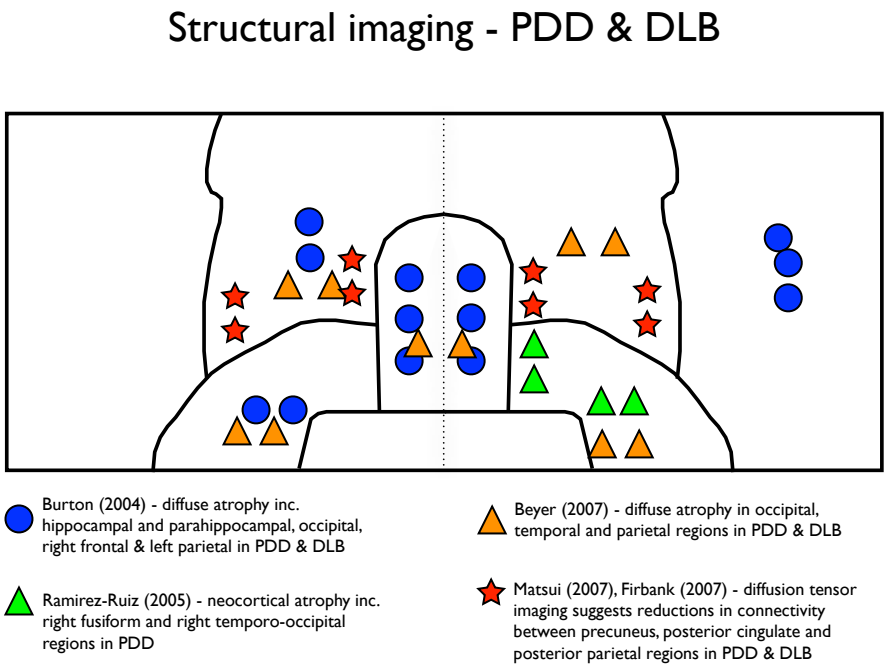


Figure 9a. Imaging studies in PDD and DLB. Here we see a similar, but more marked, pattern of involvement to that in non-demented PD patients. In particular, the occipito-parietal and temporal regions are targets for the degenerative process.



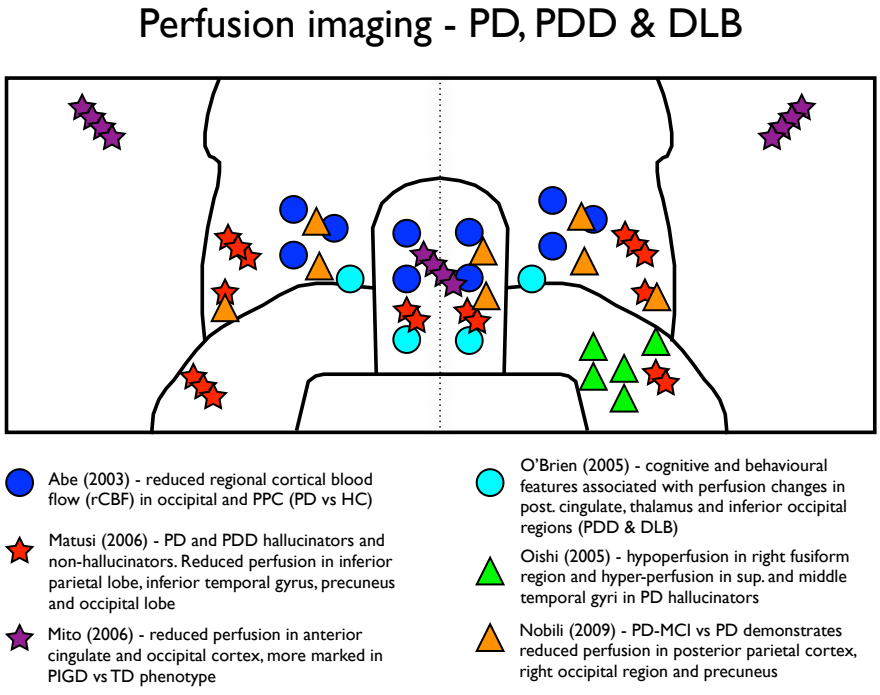
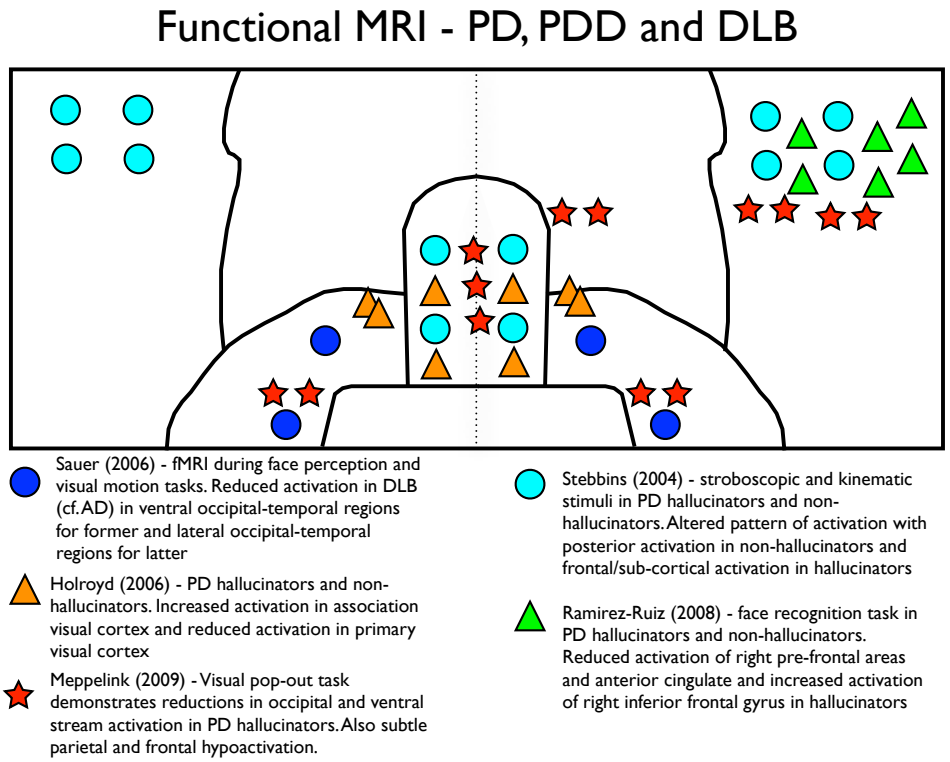


Figure 9b. In addition to the occipital and temporal changes we see reduced activation in temporal and primary visual cortex and aberrant frontal and subcortical activation in hallucinators compared to non-hallucinators.



Another powerful imaging tool employed to study the neuroanatomical substrate of cognitive impairment and associated symptomatology in PD is fMRI. During stroboscopic and kinematic stimulation of the visual pathway, PD hallucinators show an altered pattern of activation in the visual pathways, with reduced activity in occipital and parietal, and increased activation in frontal, subcortical and visual association areas compared to non-hallucinators (*Stebbins et al.,* 2004*, Holroyd and Wooten*, 2006). DLB patients demonstrate reduced activation in ventral occipito-temporal regions for face perception tasks and reduced activation of lateral occipito-temporal for visual motion tasks (*Sauer et al.,* 2006). Results from face recognition and visual pop-out tasks in PD hallucinators and non-hallucinators highlight the role of pre-frontal, cingulate and temporal regions in this task, with hallucinators showing reductions in activation in these key areas (*Ramirez-Ruiz et al.,* 2008, *Meppelink et al.,* 2009).

We have already touched upon the extensive neuropathological changes seen in PD and PDD as α-synuclein and tau burden increase with disease progression. Two studies have examined the neuropathology of Lewy body dementias (PDD and DLB) specifically with CVH in mind. Consistent to both is a putative link between α-synuclein burden in the medial temporal lobe (particularly the amygdala) and visual hallucinations in life (*Harding et al.,* 2002*, Kalaitzakis et al*., 2009).

2.9.1 Summary - Cortical visual processing in PD

In essence, visual perception appears to be dependent on two main factors - the characteristics of the visual input to both dorsal and ventral streams in terms of object colour, motion and form, which can activate visual centres directly or “capture” attentional networks to facilitate perceptual awareness in a “bottom up” fashion. The second key component is the ongoing monitoring of visual information by the fronto-parietal attentional networks to allow selection and suppression of visual stimuli dependent upon the prevailing requirements of the moment in a goal-directed, “top down” fashion (*Kimchi,* 2009). Evidence from neuropsychological, neuropathological and imaging studies would support the notion that PD interferes with these ventral (“vision for perception”) and dorsal (“vision for action”) streams as well as damaging the brain’s abilities to modulate visual attention and effectively respond in a goal-directed fashion and that it is these changes that contribute to the development of CVH in PD and PDD.

2.10 Control of eye movements

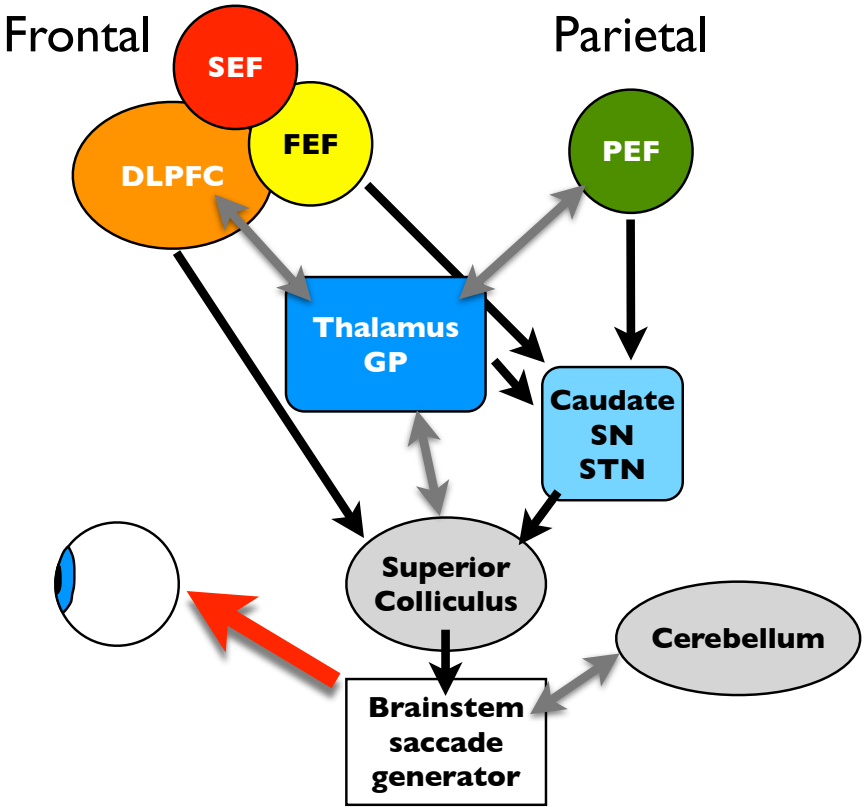
In order to make sense of the visual environment humans must direct the fovea, the area of highest visual acuity, to appropriate parts of a given scene. The eye movements required for this task must be rapid, accurate and proceed in an order that will allow us to build an internal representation of what we are viewing as quickly as possible. Such movements are known as saccades and are a controlled by a complex network of cortical and subcortical structures.

The brainstem saccade generator, a network of functionally interconnected excitatory and inhibitory premotor burst neurons (PBNs), is required to generate a saccade. PBNs show an intense discharge before each saccade and project monosynaptically to ocular motoneurons (*Scudder et al.,* 2002). These form the final common pathway innervating the extraocular muscles to effect rapid saccadic eye movements. PBNs are only active during a saccade and are inhibited tonically by omnipause neurons in the pons to allow fixation on a particular target until another saccade is required (*Horn et al.,* 1994). It is not enough, however, merely to generate a saccade - the movement must be made at the right time, in the right direction and be brought to an end without overshooting the target. Control of saccadic accuracy is achieved by the superior colliculus (SC) and the dorsal vermis and caudal part of the fastigial nucleus of the cerebellum (*Robinson and Fuchs,* 2001). Direct electrical stimulation of the SC is capable of producing saccades in primates (*Robinson and Fuchs,* 2001) and further work suggests that not only does the SC play an important role in the initiation of saccades but that it is also involved in specifying direction and amplitude (*Scudder et al.,* 2002).

Higher centres also influence the SC, which is tasked with integrating spatial cues from cortical and subcortical areas, driving the brainstem to generate spatially accurate and temporally appropriate saccades. Important cortical areas that contribute to saccade generation include: the frontal eye field (FEF) which lies in the precentral gyrus and sulcus; the supplementary eye field (SEF), just anterior to the supplementary motor area of the paracentral sulcus; and the parietal eye field (PEF), lying in the IPS. In addition, the dorsolateral prefrontal cortex (DLPFC) and PPC are also vital in the cortical programming of appropriate spatial saccades (*Pierrot-Deseilligny et al.,* 1995*, Pierrot-Deseilligny et al*., 2005). These areas project to the SC as well as to areas of the thalamus and subthalamic nuclei, caudate, globus pallidus and substantia nigra. In turn, these thalamic and basal ganglia regions project to the SC, providing cortical regions and the basal ganglia with direct and indirect access to the SC and lower brainstem structures concerned with saccadic eye

movements **(Figure 10)**. It seems likely that the basal ganglia in general, and the SN in particular, exert a tonic inhibitory effect on the brainstem saccade generator whereas the direct cortical input to SC and brainstem is principally excitatory (*Hikosaka et al.,* 2000).

Figure 10. Network of cortical, subcortical and brainstem regions responsible for saccadic control. Note the complex interaction between frontal, parietal and subcortical structures that directly and indirectly influence the superior colliculus and brainstem saccadic generator.



When viewing a natural visual environment, numerous saccades, interspersed with periods of foveal fixation, are deployed in a structured fashion to make sense of the surroundings. In this way, complex scenes can be explored efficiently, selecting areas of particular relevance whilst ignoring others (*Noton and Stark,* 1971*, Rayner and Pollatse*k, 1992*, Henderson and Hollingwort*h, 1999). Foveal fixation is integral to visual perception, as visual information processing is suppressed during a saccade, and one can therefore view saccadic output as the “means to an

end” for building up a representation of the external world. This process of selection is coordinated by “top down” control, and visual exploration proceeds in a goal-directed fashion, using endogenously-cued saccades, guided by cognitive processes such as spatial attention, working and explicit memory (*Henderson,* 2003).

“Bottom up” factors such as the visual properties of the scene being viewed (novel versus familiar shapes, colour, contrast, motion) are also important in determining visual exploration (*Krieger et al.,* 2000*, Parkhurst and Niebu*r, 2003*, Frey et al*., 2007). This latter property is referred to as “visual saliency” and computational models, based on “saliency maps” within the visual system are, to some extent, capable of predicting subsequent human fixations (*Itti and Koch,* 2001). Saccades cued primarily by the characteristics of the visual environment have a greater *reflexive* bias.

Such distinctions between “reflexive” and “voluntary” saccades are artificial in the sense that cognitive control is exerted, to a greater or lesser extent, on most of the saccades we make. Endogenously-triggered saccades have longer latencies compared to exogenously-cued saccades, reflecting the degree of cognitive control exerted over them (*Walker et al.,* 2000). However, even “reflexive” saccades, with typical latencies in the region of 150-200 ms, take longer to execute than one might expect from a circuit involving solely brainstem and cerebellar regions (*Carpenter,* 1981*, Hutto*n, 2008). In addition, they also show considerable variability in latency. This is necessitated by our limited resources for processing the wealth of potential visual input confronting us, meaning even reflexive saccades must be cognitively biased in favour of stimuli worthy of further attention (*Carpenter,* 2001).

In a laboratory setting, saccades are typically subdivided into four main types:

- *prosaccades* – made in response to, and in the direction of, a sudden-onset visual stimulus (reflex-biased, exogenously triggered)

- *antisaccades* - volitional saccades made in the opposite direction to a brief visual stimulus (cognitively-biased, exogenously triggered)
- *memory-guided saccades* - generated to a remembered location after removal of a visual stimulus (cognitively-biased, endogenously triggered) and
- *predictive saccades* - made prior to a regularly recurring visual stimulus at a predictable location (cognitively-biased, endogenously triggered)

As previously discussed, several cortical regions are involved in the control of saccadic eye movements and both lesional, TMS and fMRI work has unveiled the anatomical substrates of eye movement control. Prosaccades are largely under the control of the PEF located within the PPC. Lesions in the PEF in humans lead to increased latency and reduced accuracy of these saccades (*Pierrot-Deseilligny et al.,* 1991b). In addition, TMS applied to the PPC region early during the preparation for a memory-guided saccade, i.e. prior to the movement beginning, causes errors in amplitude of the subsequent saccade (*Muri et al.,* 1996). The PEF therefore would appear to be involved both in early saccade programming and integration between incoming visual information and subsequent eye movements. Understanding of the role of the SEF is much less complete, however, a key role in facilitating switching between competing voluntary saccadic responses has been hypothesised based on lesional and fMRI studies (*Parton et al.,* 2007*, Nachev et al*., 2005).

The FEF has an important role in generating voluntary saccades to visual stimuli. Lesions lead to increased latency of antisaccades, suggesting that the FEF facilitates disengagement of fixation from one visual stimulus to allow a saccade to begin to another (*Rivaud et al.,* 1994*, Pierrot-Deseilligny et al*., 1995). In contrast, lesions in the DLPFC lead to an increase in unwanted reflexive saccades during an antisaccade task, presumably by removing inhibitory influences on other cortical and subcortical areas. In addition, the DLPFC is key to the generation of accurate memory-guided and predictive saccades (*Pierrot-Deseilligny et al.,* 1991a*, Pierrot-Deseilligny et al*., 1995). TMS applied to the DLPFC

prior to memory-guided saccades causes an increase in amplitude errors during subsequent movements. This effect is seen late in the preparation phase for the saccade, suggesting an additional role for the DLPFC related to processing spatial memory for eye movements (*Muri et al.,* 1996).

Given the anatomical overlap between the regions involved in programming saccades and those controlling attention, working memory, spatial and visual perception, one can begin to see how measurements of eye movements might provide a window onto the integrity of these cognitive domains themselves. That an important relationship exists, for example, between spatial attention and saccadic output is not in doubt. Numerous experiments utilising both prosaccade and antisaccade tasks have demonstrated the intimate links between attention, saccadic characteristics and object recognition (*Deubel and Schneider,* 1996*, Kristjansso*n, 2007*, Rizzolatti et al*., 1987). Despite a variety of models having been proposed to characterize the relationship, however, the precise nature of the interaction remains a matter for debate (*Clark,* 1999*, Klei*n, 1980*, Rizzolatti et al*., 1994*, Henderso*n, 2003).

Likewise, performance on saccade tasks can provide an insight into working memory. For example, error rates on antisaccade tasks increase with rising demands on tests of working memory load (*Mitchell et al.,* 2002). In addition, when participants in an antisaccade study were dichotomised into groups with high- and low-span working memories, those falling into the lower-span group made more errors on an antisaccade task and had longer saccadic latencies when the correct response was selected (*Unsworth et al.,* 2004).

2.11 Eye movements, neurodegeneration and dementia

Eye movement abnormalities are well recognised in patients with PD, both in terms of deficient smooth pursuit, restricted vergence, reduced range of eye movements and alterations in saccadic output (*Corin et al.,* 1972*, White et al*., 1983*, Rascol et al*., 1989*, Repka et al*., 1996*, Bares et al*.,

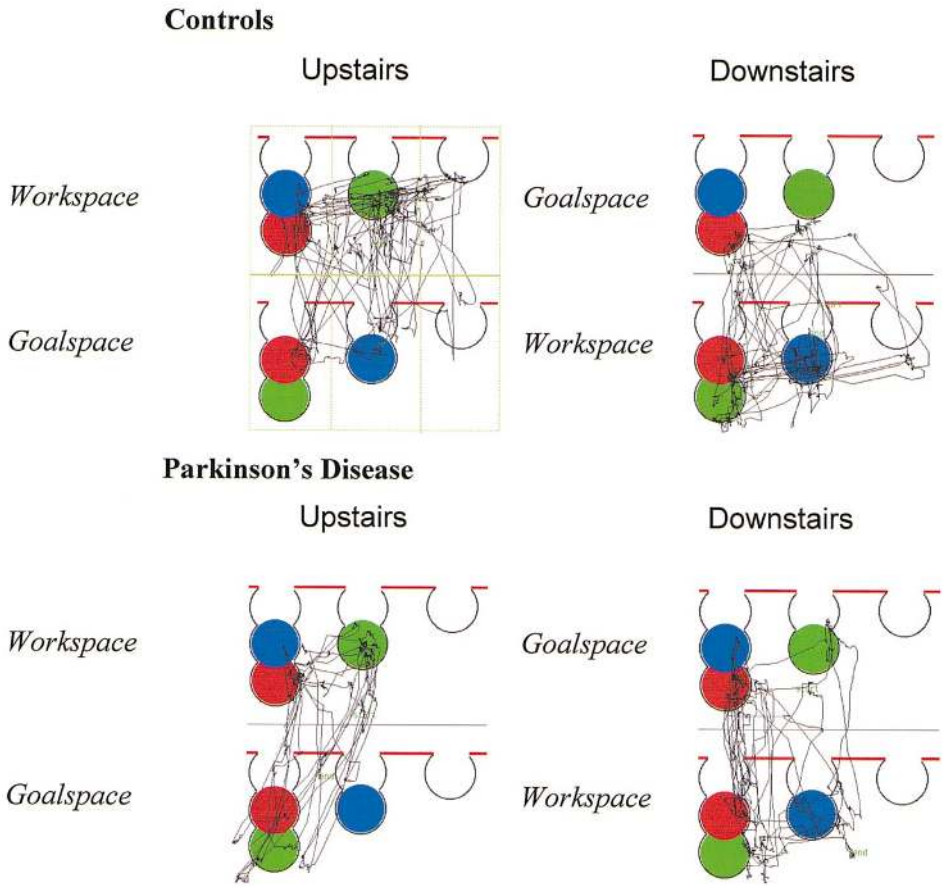
2003). Evidence for disease-specific disruption of exogenously-cued, reflexive saccades in PD is contradictory. Whereas some studies have demonstrated increases in saccadic latency and reductions in amplitude (*Rascol et al.,* 1989*, MacAskill et al*., 2002), others have not replicated these findings (*Vidailhet et al.,* 1994*, Briand et al*., 1999*, Briand et al*., 2001*, Mosimann et al*., 2005). Both the properties of the stimulus used and medication effects are important determinants of saccadic metrics and may help explain some of the inconsistencies in the reported literature (*Chambers and Prescott,* 2010*, Michell et al*., 2006*, Hood et al*., 2007).

There is some evidence to support the notion that endogenously-cued saccades are sensitive to the effects of PD both in terms of saccadic latency, amplitude and error rates (*Kennard and Lueck,* 1989*, Briand et al*., 1999*, Hood et al*., 2007*, MacAskill et al*., 2002*, van Stockum et* al., 2008) although, again, results are inconsistent (Lueck et al., 1990*, Vidailhet et a*l., 1999, Mosimann et al., 2005). Cognitive impairment is an important determinant both of error rates, saccade latency and gain in PD and PDD (*Hodgson et al.,* 1999*, Mosimann et al*., 2005) and the cognitive heterogeneity of PD subjects in previous studies remains an important potential confounder when interpreting these results.

In support of this assertion is the finding that patients with Huntington's disease (HD), a condition characterised by cortical and subcortical dementia and parkinsonism, show prolonged saccadic latencies and increased error rates on voluntary saccades compared to pre-symptomatic gene carriers for HD or controls (*Blekher et al.,* 2006*, Golding et al*., 2006). In addition, patients with AD, PDD and DLB show longer fixation durations, increased saccadic latencies and increased saccadic errors (*Lueck et al.,* 2000*, Ogrocki et al*., 2000*, Abel et al*., 2002*, Mosimann et al*., 2005) with oculomotor reaction times increasing in line with dementia severity (*Pirozzolo and Hansch,* 1981). It seems likely, therefore, that both reflex-biased, exogenously-cued and cognitively-biased, endogenously-cued saccades are affected by the neurodegeneration of cortical and subcortical structures seen in PD, but that saccades requiring greater cognitive modulation and preparation prior to triggering are most susceptible.

Eye movement recording during more “everyday” tasks such as facial emotion recognition, text- and clock-reading can provide valuable insight into not just the visual exploration strategies used in reaching a decision, but also the cognitive processes required to do so. For example, PD patients demonstrate less structured visual strategies for solving the Tower of London task than HC and these strategies correlate closely with deficits in visual working memory and/or attention **(Figure 11)** (*Hodgson et al., 2002)*. Consistent with the view that visual exploration strategies can provide a window onto cognitive decline, subjects with AD employ a less structured approach to clock reading than HC, with fewer fixations within specified regions of interest and greater delay in time to first fixation within these regions of interest (Mosimann et al., 2004). Similar strategy deficits are also evident during reading and face emotion recognition tasks (*Lueck et al.,* 2000*, Ogrocki et al*., 2000) and visual search strategies in HD become less systematic and structured as the disease progresses (*Blekher et al.,* 2009).

Figure 11. Example of visual exploration strategies during Tower of London task in PD and HC. Note the distribution of fixations and saccades in favour of the workspace in the HC group. In contrast, PD patients have a more even distribution suggesting deficits in visual working memory and/or visual attention (Hodgson et al., 2002).



2.12 Summary – Eye movements in PD and insights into cognition

Saccadic characteristics and hence visual exploration strategies are influenced by a variety of factors - FEF and PEF activity, input from ventral and dorsal streams and fronto-parietal attentional and executive networks. Indeed, many of these visual, cognitive and oculomotor functions co-localize to neuroanatomically linked cortical regions and convergent evidence supports the notion that the cognitive deficits seen in conditions such as AD, DLB and PDD interfere with “top-down” control of endogenous saccades. It follows that measurements of visual exploration behaviour might therefore provide novel insights into the contribution various cognitive domains make to the neuropsychological deficits evident in PD and PDD, and may even act as a surrogate biomarker for those at risk of cognitive impairment. In addition, given that visuomotor control of saccades is closely linked with areas vital for visuospatial and motoric output integration, and contributes to effective visual perception by foveation of salient areas of the visual environment, disruption of efficient visual exploration strategies in PD may promote the development of visuoperceptual impairment and CVH as well as contributing to motor complications such as visually-induced gait freezing.

3. Methods

3.1 Case ascertainment and diagnostic procedures

The study was approved by the NHS Local Research Ethics Committee and all participants gave written informed consent prior to study inclusion. The study design was cross-sectional with Parkinson's disease (PD) participants over the age of 49 years consecutively recruited from the Newcastle upon Tyne NHS Trust Movement Disorder service over a two year period (June 2008 - June 2010). In addition, patients with Parkinson's disease dementia (PDD) were approached from PD nurse-specialist clinics making the recruitment of this cohort non-consecutive. We chose an age restriction in order to allow potentially closer age-matching of the PD and PDD groups.

A total of 154 PD patients were approached, with 63 declining to participate. Non-participants were older than those agreeing to take part in the study (74.2 vs. 70.2 years, $p = <0.001$) but there was no difference in gender distribution. One PD participant was considered to have atypical clinical features and subsequent investigation revealed a normal DATSCAN, with evidence suggesting a diagnosis of dystonic tremor. The healthy, age-matched control (HC) cohort comprised spouses/partners of study participants and was supplemented from an existing research database held at the Institute for Ageing and Health, Newcastle University, UK. These HC participants had expressed an interest in taking part in clinical research projects if they fulfilled inclusion criteria and were approached consecutively.

Inclusion criteria for the study were:

- diagnosis of PD or PDD
- ability to give informed consent
- suitable caregiver to provide additional information

Exclusion criteria:

- severe dementia (MMSE <10)
- poor sitting stability − making clinical evaluations difficult for the patient
- absence of a regular caregiver to provide support
- active medical psychiatric illness which could interfere with assessment
- alcohol abuse, head injury, stroke, epilepsy or other major physical illness
- severe visual loss

No restriction was made on medications and stable doses of cholinesterase inhibitors and antipsychotic medications were permitted. All participants fulfilled UK Brain Bank Criteria for a diagnosis of PD (*Hughes et al.,* 1992) and PDD participants met MDS consensus criteria for dementia in Parkinson's disease (*Emre et al.,* 2007). These require a diagnosis of PD according to UK Brain Bank criteria, a dementia syndrome of insidious onset and slow progression, with cognitive deficits severe enough to impair daily life, independent of impairment ascribable to motor or autonomic symptoms **(Tables 1 & 2)**. These criteria have been operationalised and are the current "gold standard" for the clinical diagnosis of PDD (*Dubois et al.,* 2007).

Demographic data was collected via separate participant and spouse/ partner interviews in the home setting by the principal investigator (NA). Activities of daily living (ADL) were recorded using the Unified PD Rating Scale (UPDRS) part II and Bristol ADL (*Bucks et al.,* 1996*, Fahn and Elto*n, 1987). Both measures are well validated in PD and dementia, with higher scores reflecting greater deficits. Extrapyramidal motor features were assessed with the UPDRS part III and gait disturbance using the Freezing of Gait Questionnaire (FOG), the latter six-part questionnaire providing general information on gait control and functional independence (parts 1 & 2) and gait freezing (parts 3-6) (*Giladi et al.,* 2000). Quality of

life data was collected using the Parkinson's Disease Quality of Life Questionnaire (PDQ-8) (*Peto et al.,* 1998), depressive symptoms with the Beck Depression Inventory (BDI) (*Levin et al.,* 1988) and behavioural symptoms with the caregiver questionnaire form of the Neuropsychiatric Inventory (NPI-Q) (*Kaufer et al.,* 2000). Sleep symptoms were screened using an abbreviated form of the Mayo Sleep Questionnaire (MSQ) (*Boeve et al.,* 2002) and excessive daytime somnolence (EDS) with the Epworth Sleepiness Score (ESS) (*Razmy et al.,* 2004). ESS scores were dichotomised around a cutoff of 9 to define a group with EDS in the study cohort (*Brodsky et al.,* 2003). A positive response to two questions from the MSQ: "Have you ever seen the patient appear to act out his/her dreams while sleeping?" and "Has the patient told you about dreams of being chased, attacked, or that involve defending himself or herself?" has a sensitivity and specificity for REM sleep behaviour disorder (RBD) of 85% and 100% respectively (*Boeve et al.,* 2002).

Medications were documented individually and converted to levodopa equivalent doses (LED) using recently published criteria to allow comparison between PD groups of total exposure to dopaminergic treatments (*Tomlinson et al.,* 2010).

Details of visual symptoms and hallucinations were qualitatively and quantitatively assessed using the North East Visual Hallucination Inventory (NEVHI), which provides information on visual symptoms ranging from floaters, feelings of presence and passage, perceptual disturbances and complex visual hallucinations. The NEVHI also examines the impact that these symptoms have on patients and the thoughts and emotions accompanying them (*Mosimann et al.,* 2008). Screening questions include:

1. *Do you feel like your eyes ever play tricks on you? Have you ever seen something (or things) that other people could not see?*
2. *Have you ever looked at an object or pattern and something else suddenly appeared or disappeared?*
3. *Have you ever had the feeling of the presence of somebody or something in the corner of your eye?*
4. *Have you ever seen somebody or something, like a shadow, in the corner of your eye?*
5. *Have you ever had any other visual experiences?*
6. *Have you experienced seeing dots, flashes, patterns of light or similar that were not there?*

Additional visual symptoms were elicited using a semi-structured interview with questions derived from the 25-item National Eye Institute Visual Function Questionnaire (*Mangione et al.,* 2001) in combination with questions on spatial and motor symptoms used in an earlier study of visual symptoms in PD (*Davidsdottir et al.,* 2005).

3.2 Neuropsychological assessment

Global cognition was assessed using the Folstein Mini-Mental State Examination (MMSE) (*Folstein et al.,* 1975) and the Mattis Dementia Rating Scale (DRS-2) (*Brown et al.,* 1999). The DRS-2 is a widely used assessment tool taking around 20-25 minutes to complete and consists of five subscales, providing information on cognitive domains such as attention (ATT), initiation/perseveration (IP), construction (CONST), conceptualization (CONCEPT) and memory (MEM). The scores of the five sub-scales contribute to a total DRS-2 score and normative data is available such that scores can be adjusted for age and, in the case of total DRS-2 score, education (Age and education adjusted MOANS sub-scale score (AEMSS)). The CONST sub-scale score of the DRS 2 has a relatively low ceiling effect and has been shown to be insensitive to subtle changes of visuo-constructional impairment in PD. Additional tests have been recommended when using the DRS 2 to screen this cognitive

domain for problems in PD and, for this reason, clock drawing was included as part of the cognitive assessment (*Brown et al.,* 1999). Clock drawing was scored “out of 5” using the Shulman method (5=perfect; 4=minor visuospatial errors; 3= inaccurate representation of time when visuospatial organisation is only slightly impaired; 2= moderate visuospatial disorganisation such that time depiction is impossible; 1= severe level of disorganisation; 0= no reasonable representation of a clock) (*Brodaty and Moore,* 1997*, Shulma*n, 2000*, Cahn-Weiner et al*., 2003).

In order to address the potential impact of cognitive heterogeneity on the eye-tracking measures of the non-demented PD cohort, we defined two sub-groups: cognitively normal (PD-CNL) and possible mild cognitive impairment (PD-pMCI). In the absence of published criteria for MCI in PD, we used both a global cognitive score (AEMSS) and domain sub-scale scores (ATT, I/P, CONST, CONCEPT, MEM, CDT) to identify possible MCI. An AEMSS score 1.5 SD below the HC group mean or 2 or more domain sub-scale scores 1.5 SD below HC group mean values was taken as evidence of PD-pMCI. This approach split the PD group into 37 PD-CNL patients (58%) and 27 with possible PD-MCI (42%).

3.3 Ophthalmological assessment

Ophthalmological assessment included measurement of logMAR visual acuity (VA) and contrast sensitivity (CS – Mars letter CS chart, Mars Perceptrix™). The former presents rows containing 5 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 robust measure of VA than that afforded by a Snellen chart. Lower logMAR scores reflect better VA, with a logMAR score of 0.0 equivalent to 6/6. Testing distance was 4 metres and both uncorrected (UCVA) and “best at presentation” (BAPVA) visual acuity was documented.

The Mars CS chart consists of rows of letters with sequentially reducing contrast presented under standarised lighting conditions. Viewing distance was 40 centimetres with the head stabilised and normal near refractive correction utilised. CS threshold is reached when letters can no longer be resolved from the background. Higher scores on CS testing reflect better performance.

Intraocular pressure (IOP) was recorded with an Icare^{TM} automated tonometer. Cataract severity was graded by two independent assessors (NA - neurologist, MC - ophthalmologist) on a pragmatic scale for cortical, nuclear and posterior capsular lens opacity (0 = absent; 1^+ = mild; 2^+ = moderate; 3^+ = marked; 4^+ = severe) with consensus sought between both assessors in the event of discrepancy. Slit lamp examination was used to document structural corneal, retinal or optic nerve pathology. Visual fields were examined by confrontation. Saccadic, pursuit and vergence eye movements were assessed clinically and cover testing performed to detect ocular misalignments.

3.4 OCT

A consecutively selected proportion of study participants were approached to participate in a sub-study examining retinal morphology in PD using Optical Coherence Tomography (OCT) - a technique for obtaining cross-sectional images of the retina in a non-invasive fashion. “Time-domain” methods function effectively as ‘optical ultrasound’, projecting a near-infrared light beam onto the retina and comparing the echo time delays of light reflected from the retina with that returned from a reference mirror. This reflectivity profile, called an axial depth scan (A-scan), contains information about the spatial dimensions and location of structures within the item of interest. A cross-sectional tomograph (B-scan) is then created by combining a series of these A-scans, providing a composite image with an axial resolution of 10 microns. More recently, “frequency-domain” OCT has become available, permitting faster signal acquisition, a better signal-to-noise ratio and 3-dimensional image reconstruction with an axial spatial resolution of 3-5 microns. OCT is capable of assessing the thickness of

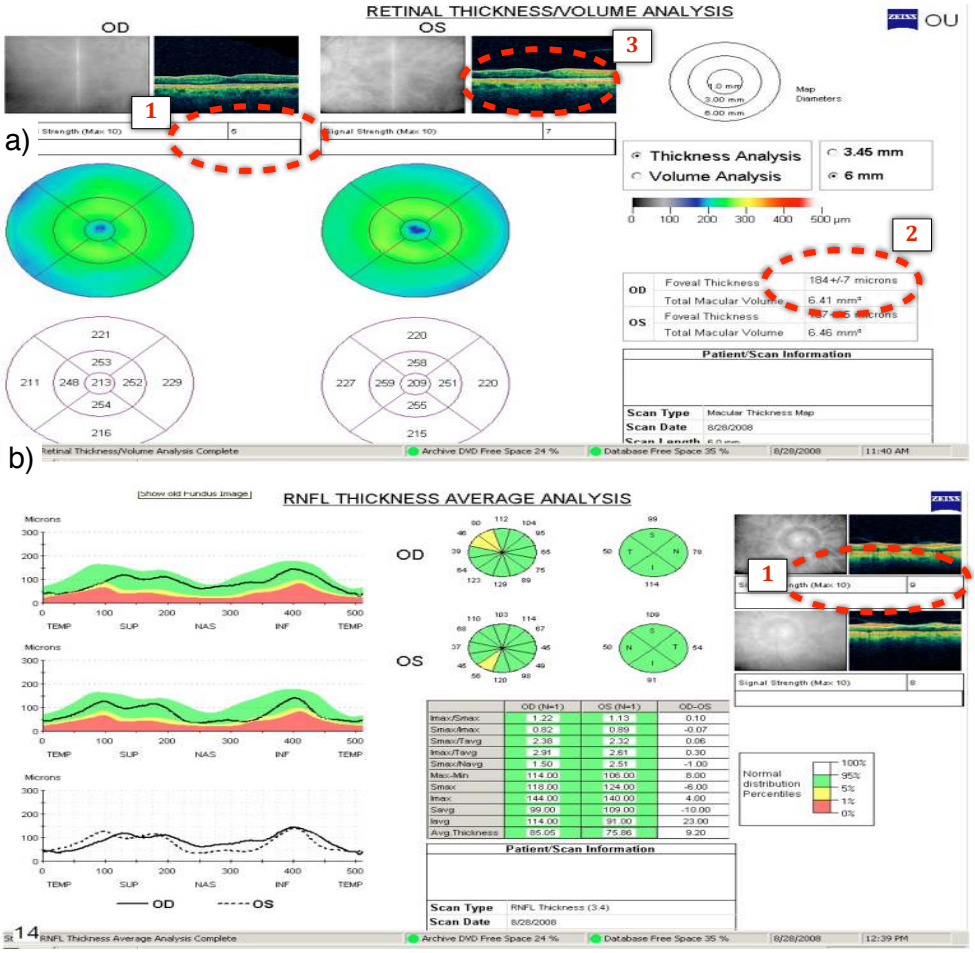
retinal nerve fibre layers (RNFL) around the optic nerve head, thus providing a measure of the integrity of the retinal ganglion cell axons as they exit the retina, as well as providing information of macular morphology in the central retina.

Measures of peri-papillary RNFL, macular thickness and volume were made using a commercially available Ocular Coherence Tomography (OCT) device (Zeiss Stratus 3000^{TM}) following pupillary dilation. Throughout scanning, participants kept the eye constantly fixed on an internal target provided by the OCT machine. Scan quality was assessed by examining the signal strength and confidence limits generated by the automated software analysis. OCT scans with a signal strength < 5/10 or with a macular protocol confidence limit >20 microns were reviewed for “best fit” automated contour lines. Scans with poor fit contour lines or missing data were excluded from analysis **(Figure 12).**

The fast RNFL scan protocol consisted of a single 360° circular scan with a diameter of 3.4 mm centered on the optic disc, containing 256 A-scans taken in a single session of 1.92 seconds. Peri-papillary RNFL thickness parameters were automatically calculated by OCT 3000 unit software and included: average thickness (360° measurement), temporal quadrant thickness (226–315°), superior quadrant thickness (316–45°), nasal quadrant thickness (46–135°), and inferior quadrant thickness (136–225°)**.**

The fast macula scan protocol consisted of 6 mm radial line scans centered on the macula, each containing 128 A-scans taken in a single session of 1.92 seconds. Six sets of intersecting and equally spaced scans were obtained each crossing the central fovea. The automated analysis program presents both mean foveal thickness and total macular volume in a 6.00 mm macular map.

Figure 12. Example of macular and RNFL OCT scans. Scan quality was judged by three parameters: 1) signal strength 2) automated foveal thickness confidence limit and 3) "best fit" contour lines.



3.5 Neurophysiological assessment

A consecutively selected proportion of study participants were approached to participate in a sub-study examining the retinal and early visual cortical responses to visual stimuli in PD. The stimulus used was an alternating checkerboard pattern, which reverses its local luminance while keeping average luminance constant. Luminance signals cancel out, leaving non-linearities that have been shown to originate mainly in the retinal ganglion cell (RGC) layers of the retina. This massed RGC response forms the electrical basis of the pattern electroretinogram (PERG).

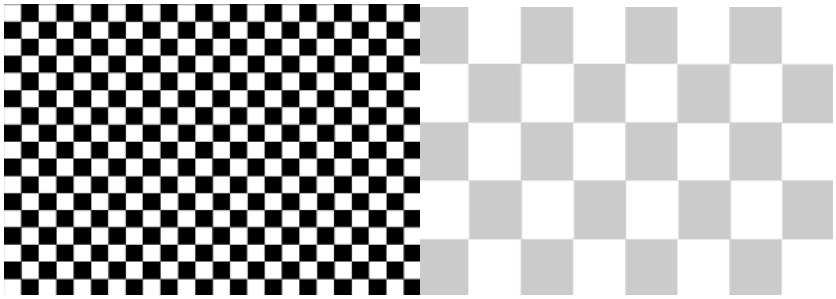
PERG and visual-evoked potential (VEP) recordings were made to stimuli designed to bias responses from two separate retino-geniculo-striate

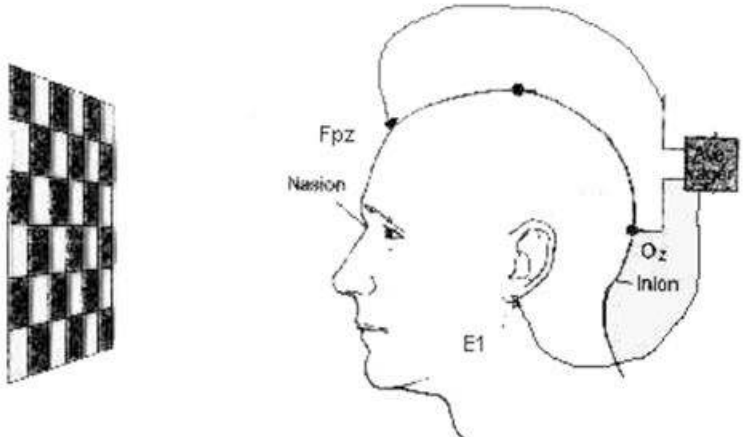
pathways – the magnocellular (M) and parvocellular (P) systems. Larger RGCs, more prominent in the peripheral retina, and known as magnocellular RGCs respond optimally to stimuli with high temporal and low spatial frequencies, particularly when contrast levels are low. Parvocellular RGCs, most prominent in the central retina, respond most strongly to stimuli with low temporal and high spatial frequencies, particularly when contrast is high (*Ferrera et al.,* 1992*, Ferrera et al*., 1994*, Malpeli et al*., 1996*, Maunsell et al*., 1990*, Merigan and Maunsel*l, 1990*, Skottu*n, 2000). As such, M-pathways are specialised for motion perception at low contrast and P-pathways for fine feature and colour perception in the central retina. This segregation of information is maintained in early visual cortex but, beyond V1, M- and P-pathways intermingle such that, for example, motion information is also delivered into the ventral stream (*Ferrera et al.,* 1994*, Nealey and Maunsel*l, 1994*, Merigan et al*., 1991).

3.5.1 Stimuli

The stimulus set-up for electrophysiological testing is presented schematically in **Figure 13**. A variety of achromatic and chromatic stimuli have previously been employed in an attempt to probe M- and P-pathways in healthy controls (*Tobimatsu et al.,* 1995) and disease populations such as schizophrenia (*Butler et al.,* 2005) and PD (*Silva et al.,* 2005). It has been argued that by varying the spatial frequency and contrast of achromatic stimuli (checks or gratings) it is possible to bias responses from the M- and P-pathways. Using such methods, a predominant magnocellular pathway deficit has been postulated in schizophrenia, although the functional implications of this in terms of visual and cognitive impairment remain unclear (*Butler et al.,* 2007*, Slaghuis and Bisho*p, 2001). Problems have arisen in interpreting findings from many of the studies in schizophrenia however, as stimuli may have cross-activated both pathways due to shared spatio-temporal and contrast properties (*Blakemore and Vital-Durand,* 1986*, Levitt et al*., 2001*, Skottun and Skoyle*s, 2007a*, Skottun and Skoyle*s, 2007b).

Figure 13. PERG/VEP stimuli and experimental set-up. Small check size, high contrast stimulus to bias parvocellular response from the central retina and large check size, low contrast stimulus to bias magnocellular response from peripheral retina. Below is the typical set-up for gathering the experimental data.





3.5.2 PERG

The PERG is a retinal bio-potential evoked by an alternating pattern - in our case a checkerboard - and reflects the massed response of the RGCs to an isoluminant stimulus. Transient PERG responses are complete before the next pattern reversal occurs, at least for low temporal frequencies, and allow separation of the PERG components into troughs (N35, N95) and a single, positive peak (P50) **(Figure 14)**. For the purpose of this study, we have measured the amplitude (μV) of the P50 and N95 components as well as their respective implicit times (msecs). Higher temporal frequencies lead to an overlapping of successive waveforms and the generation of a “steady-state” PERG. The steady-state PERG (ssPERG) waveform is roughly sinusoidal and interpretation requires

Fourier analysis of the second harmonic, giving an amplitude and phase shift measurement relative to the stimulus **(Figure 14)**.

Typically, PERG responses are small in comparison to flash-evoked potentials and are critically dependent on stimulus characteristics. PERGs are difficult to record with low stimulus luminance and cannot be elicited from very low contrast stimuli. The PERG P50 amplitude increases with luminance contrast between the black and white checks and a maximal contrast as close as possible to 100% is desired. For the transient PERG, recordings require a temporal frequency of 6 rev/sec (3Hz) or less whereas for the ssPERG, a reversal rate of 15 rev/sec (7.5Hz) demonstrates the best correlation to check size. In addition, higher stimulus temporal frequencies are not recommended when recording the PERG due to a decreasing signal:noise ratio when reversal rates become higher than 18 rev/s (8Hz) (*Holder et al.,* 2007).

3.5.3 VEP

Visual-evoked potentials (VEP) are visually evoked electrophysiological signals extracted from the electroencephalographic activity in the visual cortex. As such, they reflect a composite response of subcortical structures (retina, optic nerve, LGN, optic radiation) and the visual cortex itself. VEPs can be elicited by flashes of light as well as alternating patterns and it is the pattern-reversal VEP (PVEP) that we have utilised in this study.

As previously mentioned for PERG recordings, the waveform of a VEP depends on the temporal frequency of the stimulus. At low frequencies, a transient PVEP is recorded and as temporal frequency rises, the waveform becomes sinusoidal and is termed “steady state”. The transient pVEP waveform consists of two negative troughs (N75 and N135) and a single positive peak (P100). For the purpose of our study, we measured both the right, left and midline occipital P100 amplitude (μV) and latency (msec) **(Figure 14)**.

Whilst the responses of both PERG and PVEP increase with increasing stimulus field size, the amplitude of the PVEP is more macular-dependent. Whereas pattern contrast is crucial in driving a measurable PERG response, contrast has little effect on the PVEP response for contrasts above 50%.

Figure 14. Stylised PERG and VEP waveforms. a) Typical transient PERG waveform allowing measurement of P50 and N95 amplitude and implicit time; b) typical transient pVEP response – the amplitude of the waveform is considerably greater than that generated by the PERG; c) steady-state PERG – Fourier analysis of the waveform allows dissection of the significant second harmonic from background noise.

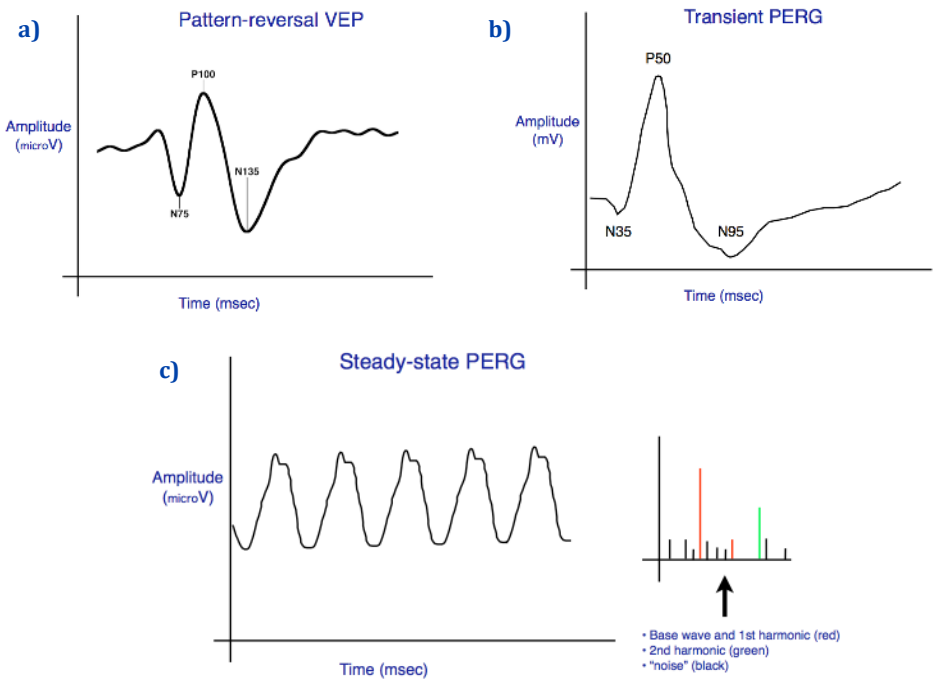
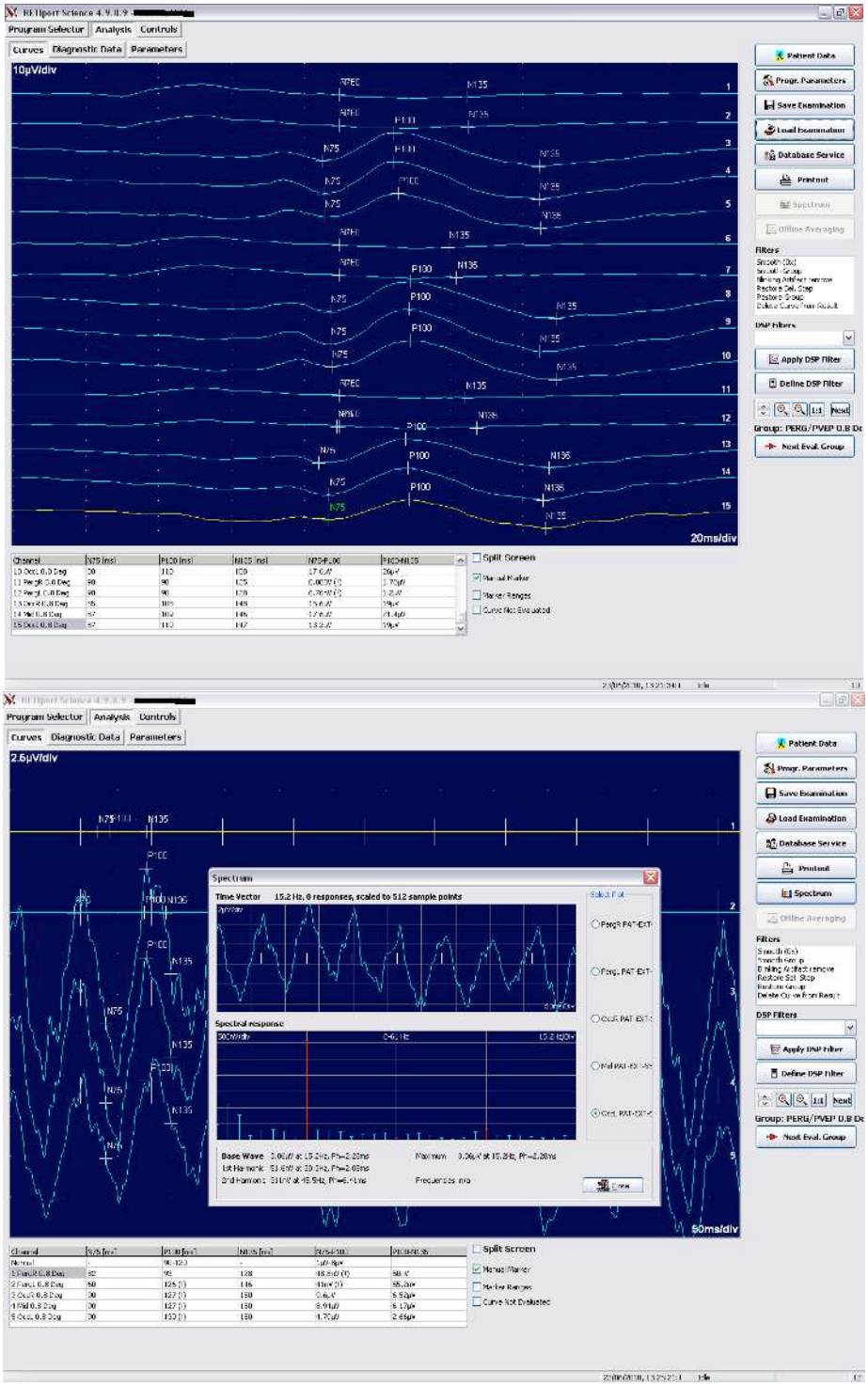


Figure 15. PERG and VEP recordings. Examples of the transient and steady-state data collection. Note the automated Fourier analysis of the steady-state recording (below).



3.5.4 Stimulus characteristics

The visual stimuli were created on a Cambridge Research System, Visage graphics module and presented on a high-resolution widescreen plasma display. Check size, contrast and frequency of temporal modulation were varied to bias responses from M- and P-pathways.

Examining ERG and VEP responses in PD poses some practical problems, which necessarily had a bearing on the choice of the stimuli chosen. Both PD and HC participants were elderly with a range of co-morbid ocular and retinal disease (e.g. cataract, macular degeneration). In addition, to minimize the impact of tremor artifact, mobility problems and fatigue during assessment, the study protocol was designed to last no more than 30 minutes and require only one hospital visit. This necessitated the simultaneous recording of ERG and VEP responses, impacting on the spatio-temporal frequency, contrast and luminance of checkerboard stimuli in the study. We chose wide-screen stimulus presentation to minimize the effect of loss of central fixation on data acquisition and monitored attention to the task using a video camera. In addition, the larger stimulus field provided more reliable peripheral retinal stimulation and increased the overall amplitude of data recordings. Medications were not withheld on the day of assessment.

The properties of both stimuli used in the protocol are summarized below:

- M-pathway – check size: 30^{o}; temporal frequency: 7.5 Hz (15 reversals/sec); luminance: 40 cd-s/m^2/sec; contrast: 40%
- P-pathway – check size: 0.8^{o}; temporal frequency: 2Hz (4 revs/ sec); luminance: 80 cd-s/m^2/sec; contrast: 98%

Although M-biased pathways should ideally be driven with very high temporal frequencies at very low contrasts, the requirement for simultaneous recording of the PERG and PVEP led to higher contrast and lower frequencies being employed in the M-pathway condition.

What evidence, therefore, do we have that our M- and P-biased protocols achieved some separation of the two key pathways under investigation?

In the study, HC were tested with additional protocols to examine macular and peripheral retinal contributions to the PERG. We reasoned that if the M-pathway is largely dependent on a peripheral retinal contribution, then, under M-biased conditions, patching the central 15^{o} of the stimulus screen would make little difference to the measured responses, whereas patching all but the central 15^{o} of the screen would effectively abolish the PERG response. Similarly, in the P-biased condition, patching the central 15^{o} of the field should substantially reduce the PERG response whereas patching of all but the central 15^{o} of the screen should have little impact on PERG response.

Under M-biased conditions, in almost all cases, there was no reduction in P50 amplitude when the central 15^{o} patch was used. When the stimulus field size was reduced to 15^{o}, the PERG was virtually non-detectable above the background noise. We can therefore infer that no contributions from the central 15^{o} of retina contributed to the pattern ERG obtained from the M-biased protocol i.e. the response was derived from peripheral retina beyond the central 15^{o} either side of fixation. In contrast, repeating these protocols for the P-biased stimuli, P50 amplitudes in both full-field and central 15^{o} only conditions were similar, demonstrating that the bulk of the P-biased response derived from the central 15^{o} of the retina.

3.5.5 Electrophysiological recordings

The PERG was recorded in each eye by placing thin gold-plated foil electrodes into the conjunctival sac near the lower limbus. Reference electrodes were attached to the temples and the earlobes were grounded. VEPs were recorded from the scalp at right, midline and left occipital regions. Electrode impedance was measured and was not allowed to exceed 5kΩ and balanced. Signals were recorded using a Roland electrodiagnostic acquisition system with external triggers.

Participants fixated a central LED and binocularly viewed the patterns, with natural pupils, while ERGs and VEPs were simultaneously recorded. The viewing distance was constant at 50 cm. Normal refractive correction was worn where required, but participants were not formally refracted prior to ERG and VEP recording. Stimuli were presented for bursts of 15 seconds with 15 second pauses until a minimum of 150 repetitions had been achieved per condition. This was to minimise blink artifact and ensure attention was effectively directed to the central fixation point of the plasma display.

3.6 Eye tracking assessment

Participants viewed a range of visual stimuli (angle matching, clock matching, inverted clock matching, shape position and overlapping figure tasks) as part of an eye tracking battery **(Figure 16)**. Overlapping figures, first described by Ghent and Poppelreuter (*Ghent,* 1956*, Poppelreute*r, 1917) and formalized by De Renzi et al. (1969) have been used in previous studies of PDD and DLB (*Mori et al.,* 2000*, Mosimann et al*., 2004b) to provide information on impairment of object-form perception. Given that the overlapping figures and comparator images are identifiable and complex objects, we hypothesised that impairment on this task would reflect “ventral” stream dysfunction. In our experimental paradigm, participants were required to study a central composite image of animals, clothing, utensils or fruit and choose which one of four individual comparators underneath was present centrally. In order to compare visual exploration across different tasks within the battery we standarised the screen layout for all conditions to present a central stimulus and four comparator images.

Impairment in the judgment of line orientation has been demonstrated in patients with right parietal lobe damage (*Benton et al.,* 1978) and is also impaired in PD and PDD (*Montse et al.,* 2001*, Mosimann et al*., 2004b). Due to screen layout constraints we modified Benton’s original task, requiring participants to match a centrally presented angle to one of four comparator angles underneath. We hypothesised that this task would

have a greater spatial than perceptual bias, with performance linked to the integrity of the “dorsal” stream.

We also introduced a clock-matching task to the eye tracking battery. Clock reading is an over-learned perceptual task that is impaired both in AD, DLB and patients with parietal lobe lesions (*Schmidtke and Olbrich,* 2007). fMRI studies in AD suggest that the lingual and superior temporal lobe, cuneus and precuneus are involved in clock reading (*Leyhe et al.,* 2009*, Saur et al*., 2010). Visual exploration of clock faces is impaired in AD with patients making fewer fixations at the ends of the clock hands and taking longer to explore the clock face (*Mosimann et al.,* 2004a). Although clock drawing is frequently impaired in PDD (*Cahn-Weiner et al.,* 2003), clock reading has not been studied in PD and PDD. For this reason, we included a clock task requiring participants to perform both clock reading and clock matching. An inverted clock task was also included in the test battery, introducing a greater spatial component to the clock task by requiring participants to mentally rotate the comparators by 180^{o} prior to giving their response (*Amick et al.,* 2006).

Finally, we included a shape position in the battery. This task incorporated elements of the position discrimination task of Warrington and James (*Warrington and James,* 1988) and the spatial location task of MacQuarrie (*MacQuarrie,* 1953) previously found to be impaired in PDD and DLB (*Mori et al.,* 2000*, Mosimann et al*., 2004b). In addition to having a visuospatial bias, this task also depends upon the recognition of individual elements of the pattern (triangles, squares) as well as the relationship of the component parts to each other.

Stimuli were presented on a 20” TFT computer monitor enabled with an EyeLink 1000 remote eye tracker with a temporal resolution of 1000 Hz, spatial resolution of 0.05^{o} and average accuracy of 0.5^{o} (SR Research Ltd., Mississauga, Ontario, Canada). Participants were positioned 80 cm from the stimulus monitor and wore normal refractive correction. In the event of spectacle lenses precluding acquisition of data, participants were auto-refracted and wore an appropriate pair of eye tracker-compatible

goggles incorporating a near correction instead. All participants were able to resolve the stimuli presented during the training phase of the experiment. Viewing was binocular, unless diplopia was encountered during testing (when one eye was patched). All recordings were monocular. A chin rest and forehead bar maintained the participant's head position and distance from the computer monitor. Measurements of eye movements were conducted in a dimly lit room and online viewing of data collection was undertaken behind a blackout curtain.

The eye tracker was calibrated for each participant before the experiment began. Calibration consisted of having the participant fixate on nine calibration points (3 points each across the top, middle and bottom of the screen), one at a time. Re-calibration after each image in the eye tracking battery was achieved by virtue of required fixation on a central target before the next stimulus could be presented. Stimuli were presented in blocks - angle-clock-inverted clock; shape position; overlapping figure – in a pseudorandom fashion. Each block began with a previously viewed practice image followed by 16 trial images presented in one of six randomised orders. A total of 80 images were viewed for each participant and the battery took 10-15 minutes to complete. Participants were encouraged to take a break if required. Screen layout was identical for each stimulus with a central stimulus and four comparators arrayed beneath. All comparators appeared equally for each category to ensure no bias emerged for any particular choice option. Participants gave a verbal response ("1","2","3" or "4") at which point the investigator (NA) activated a game pad keypress and the stimulus moved on to a central fixation point prior to the next stimulus presentation.

The EyeLink 1000 system incorporates a unique on-line parsing system which analyzes eye position data into meaningful events and states (saccades, fixations, and blinks). For each data sample, the parser computes instantaneous velocity and acceleration and compares these to the velocity and acceleration thresholds. These thresholds are 30^{o} per second for velocity and 8000^{o} per sec^{2} for acceleration. If either is above threshold, a saccade signal is generated. The parser will check that the

saccade signal is on or off for a critical time before deciding that a saccade has begun or ended. This check does not affect the recorded time of the saccade start or end, but adds some delay to the real-time events sent through the link. Fixations are defined as anything that is not a saccade or a blink.

In addition to general characteristics of response, such as response time and average duration of fixations, the screen was sub-divided into interest areas (IA) such as the central stimulus, four comparator stimuli and correct/incorrect IAs. Analysis of the distribution of fixations in correct and incorrect IAs, the first IA explored and the number of times a given IA is re-visited during exploration reveal the strategy employed by participants to solve the visual task presented to them. We chose three measures to define visual exploration strategy:

1) Time to first fixation in the correct IA

2) Run count (RC) into the central stimulus

3) RC ratio

The RC ratio is generated from the mean RC into the 3 incorrect IAs vs. the RC into the correct IA. As such, low RC ratios are likely to reflect a strategy where the correct IA is explored in preference to incorrect regions and a RC ratio of 0.5 reflects a strategy where exploration of the correct IA is twice as frequent as that of the incorrect IAs. High RC ratios suggest either a less structured strategy, where incorrect IAs are re-visited repeatedly, or a cautious approach aimed at minimising errors.

Figure 16. Battery of tests employed in the eye tracking experiment. Angle, clock and inverted clock tasks were always presented as a hierarchical block, mixed randomly with shape position and overlapping figure blocks. Participants were randomised to one of 6 protocols with a different external "block" order (i.e. shape position – [angle-clock-inverted clock] – overlapping figure). Each block began with a practice image to ensure participants understood the task, followed by 16 trial images presented in a pseudo-random order.

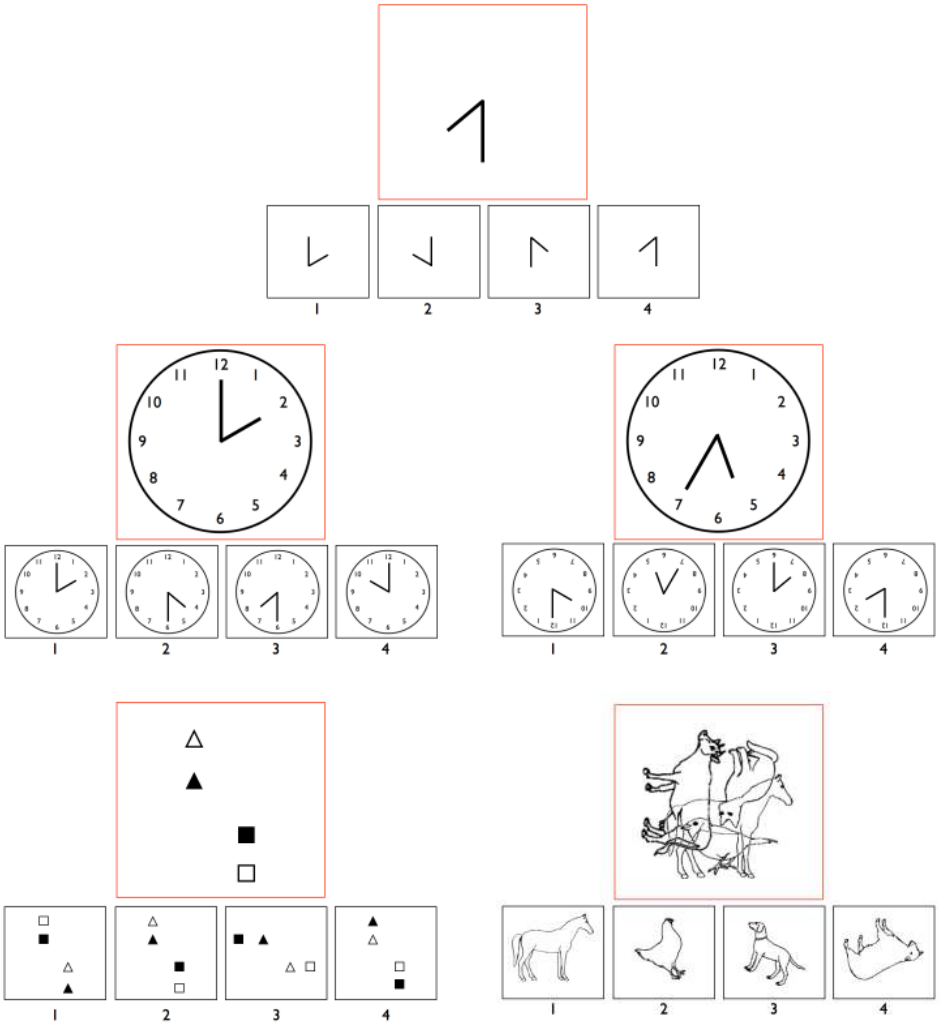
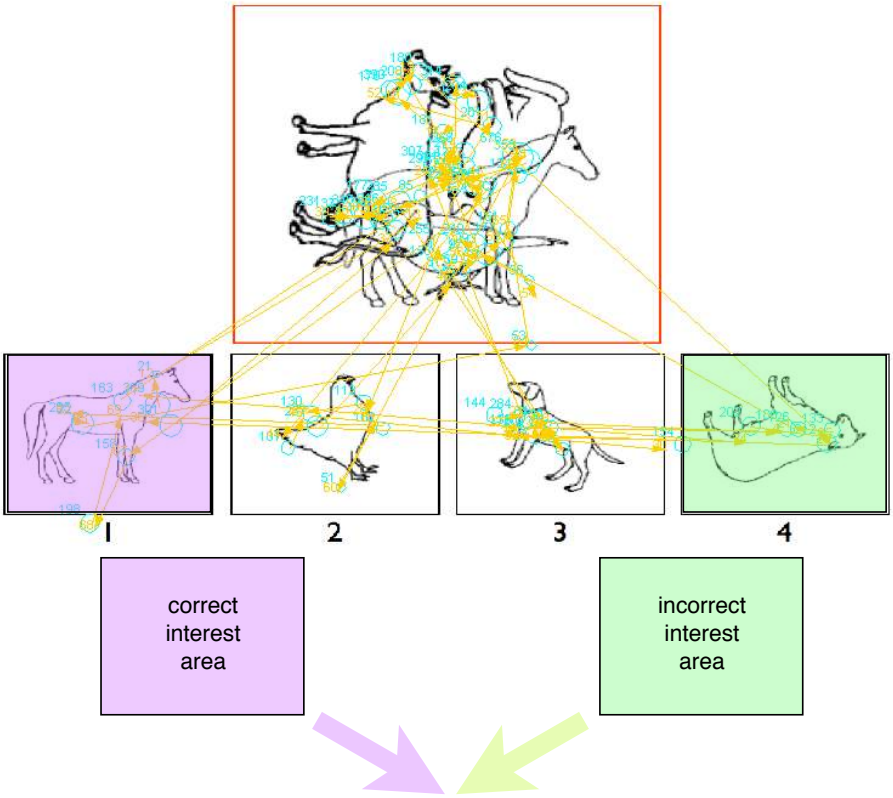


Figure 17. Example of fixation/saccade map for a single study participant. Interest area analysis provides insight into the visual exploration strategy employed for each image viewed.



Eye tracking outcome variables

1. Overall response time (msec)
2. Average fixation duration (msec)
3. Time to first correct fixation - time (msec) from stimulus onset to first fixation in the correct interest area (IA)
4. Central run count (RC) - Number of times the central stimulus is entered during a single image trial
5. RC ratio - ratio of RC into incorrect IA : RC into correct IA; reflects the requirement to check correct and incorrect comparators against each other

3.7 Statistics

Data were analysed using the JMP 8 statistical package (SAS Institute Inc). The distribution of data was examined for normality (Shapiro-Wilk test). Means and standard deviations (SD) were calculated. Normally distributed data were analysed with parametric tests (Independent sample t-tests, ANOVA) and non-normally distributed data with non-parametric tests (Wilcoxon Rank Sum, Kruskal-Wallis). For comparison between more than two groups, post-hoc tests were employed only if the omnibus statistical test result was significant. Pearson chi-square test was employed for comparison of frequencies and Fisher's exact-Test utilised when expected frequency in either group was < 5. All reported p values are two-tailed for parametric tests. Wilcoxon Rank Sum test results are presented using normal approximation and a p value of <0.05 was considered significant. Significance values are reported to 3 decimal places and values less than 0.001 abbreviated to p = <0.001. Non-significant results are highlighted with the suffix 'ns'. Statistical techniques specific to various chapters will be included in the appropriate sections. Error bars on graphs reflect 95% confidence intervals.

4. Visual symptoms in Parkinson's disease and PD dementia

4.1 Background

Visual symptoms are common in Parkinson's disease (PD) and include difficulty reading and diplopia (*Biousse et al.,* 2004*, Chaudhuri et al*., 2006), illusory misperception, feelings of presence and passage and CVH (*Fenelon et al.,* 2000). Although presence, passage and illusions are often classified as hallucinations, similar experiences are reported in the general population (*Ohayon,* 2000), in patients with brainstem disorders (*Benke,* 2006), and in narcolepsy (*Manford and Andermann,* 1998). Such similarities may help explain the putative link between sleep disorders, brainstem dysfunction and hallucinations in PD (*Pacchetti et al.,* 2005) and why minor hallucinatory experiences do not have the same predictive value in terms of the development of PDD (*Llebaria et al.,* 2010). The cause of diplopia in PD is unclear and no studies have addressed this symptom explicitly.

Visual acuity (VA) (*Matsui et al.,* 2006), contrast sensitivity (CS) (*Bodis-Wollner et al.,* 1987*, Uc et al*., 2005), colour perception (*Price et al.,* 1992) and motion perception (*Castelo-Branco et al.,* 2008) are all impaired in PD, with VA and CS identified as risk factors for CVH (*Diederich et al.,* 1998*, Matsui et al*., 2006). A potential criticism of some studies of visual function in PD is a failure to take into account the cognitive requirements for completing tests of VA and CS accurately. Whilst CVH have been closely studied in the context of cognitive decline in PD, the association between cognition and other visual phenomena such as illusions, presence and passage has not been specifically addressed.

With this in mind, we set out to characterise the range of visual symptoms seen in PD and PDD and assess their correlations with ocular pathology and cognition exploring the following hypotheses: First, that visual symptoms are more common in PD than healthy controls and will be more common still in PDD. Second, that cognitive impairment may contribute to

reduced VA and CS in PD. Finally, we hypothesized that CVH, presence, passage and illusions may not share a common aetiology and, as such, should be analysed individually in studies of visual symptoms in PD.

4.2 Specific Methods

To compare informant-to-patient rater reliability on the NEVHI, we used the Kappa measure of agreement and the McNemar test for significance (here the null hypothesis proposes that both patient and informant ratings are equivalent and we sought a p value > 0.05).

Cortical and nuclear lens opacities were graded on a scale from 0-4, with grades 2-3 denoting moderate/marked cataract. None of the cohort had severe cataract (grade 4). Results were dichotomised into a group with "none or mild" and a group with "moderate or marked" cataract.

To explore factors predictive of VA and CS in the whole PD cohort (n = 90), stepwise linear regression was conducted using a standard least squares approach with backward elimination. The following variables were submitted into the model: Age, PD duration, UPDRS III, AEMSS, MMSE, retinal abnormality, cortical and nuclear cataract severity. Stepwise logistic regression with backward elimination was utilised to identify predictors for diplopia. We entered basic demographic factors (age, disease duration, UPDRS III, LED), presence of cognitive decline (diagnosis of dementia, AEMSS, MMSE), severity of somnolence (ESS) and oculomotor abnormalities (abnormal ocular alignment, hypometric saccades and reduced convergence amplitude) into our model.

We also conducted stepwise logistic regression after having dichotomised the PD group into those with CVH and those without (CVH^+/CVH^-). Variables entered into the model included basic demographic factors (age, disease duration, UPDRS III, LED, agonist use), neuropsychiatric features (BDI score, NPI symptom score), presence of sleep disorders, somnolence (RBD, EDS) or visual impairment (BAPVA, CS) and presence of cognitive decline (diagnosis of dementia, AEMSS, MMSE). In addition, we also separated the PD group into those with and without illusory

misperceptions (illusion^{+}/illusion^{-}), feelings of presence (presence^{+}/ presence^{-}) and sensations of passage (passage^{+}/passage^{-}), performing regression analyses in a similar manner to that outlined above.

4.3 Results

4.3.1 Demographic characteristics

Total recruitment figures were: PD n = 64; PDD n = 26; HC n = 32 and basic group demographics are shown in **Table 3**. All three groups were well matched for age (ANOVA (df 2, n = 122) = 0.66, p = 0.517; ns) and education (Kruskal-Wallis (df 2, n = 122) = 2.06, p = 0.357; ns). Males were over represented in the PDD group compared to HC (Fisher's exact (df 1, n = 58) = 8.85, p = 0.003) and although there was a similar trend in gender difference between PD and PDD groups this did not reach significance (Fisher's exact (df 1, n = 90) = 3.2, p = 0.080, ns). As expected, PD duration was longer for PDD than PD patients (t-Test (df 88, n = 90) = 2.33, p = 0.022) and estimated dementia duration was 1.8 years (range 0-3 years, where 0 = newly diagnosed at study entry). The disease groups differed in their total dopaminergic medication dosage (expressed as LED), with the PD group taking the lowest daily dose (t-Test (df 88, n = 90) = 2.23, p = 0.028). PD patients were more likely to be using alternative dopaminergic agents such as monoamine oxidase inhibitors (Fisher's exact (df 1, n = 90) = 9.06, p = 0.003), and dopamine agonists (Fisher's exact (df 1, n = 90) = 13.2, p = <0.001) whereas PDD patients were predominantly treated with levodopa monotherapy. As expected PDD participants were taking more anti-psychotic and cholinesterase inhibitor medications than other groups.

Table 3. Basic group demographics of the visual symptoms study.

	HC n=32	PD n=64	PDD n=26	p value
Age (years)	72.2 (7.7)	70.2 (8.1)	71.2 (6.5)	‡0.517(ns)
Education (years)	11.6 (2.6)	12.2 (3.2)	11.3 (3.0)	*0.357 (ns)
Gender (%Male)	47	66	84	** 0.122[a] (ns), 0.003[b], 0.080[c] (ns)
PD duration (years)	n/a	8.4 (5.7)	11.5 (5.8)	§0.022
Estimated dementia duration (years)	n/a	n/a	1.8 (0.9)	
Total LED	n/a	668 (432)	893 (436)	†0.028
Agonist use (%)	n/a	48	8	**<0.001
MAOI use (%)	n/a	34	4	**0.003
COMT-I use (%)	n/a	31	36	**0.623 (ns)
ChE inhibitor use (%)	n/a	2	42	**<0.001
Antipsychotic use (%)	n/a	2	23	**<0.001
UPDRS II	n/a	13.2 (6.1)	22.0 (5.9)	§<0.001
UPDRS III	n/a	23.1 (10.0)	35.4 (14.7)	§<0.001
FOG	n/a	6.0 (5.0)	11.0 (6.9)	§0.003
BADLS	n/a	4.1 (5.5)	18.4 (9.6)	§<0.001
PDQ-8	n/a	25.6 (18.6)	42.3 (17.9)	§<0.001
NPI Q (symptom scale)	n/a	2.9 (3.8)	9.4 (4.6)	§<0.001
NPI Q (carers distress)	n/a	2.3 (3.1)	10.8 (7.4)	§<0.001
BDI	4.4 (4.6)	10.7 (8.3)	15.6 (6.5)	§<0.001[a,b], <0.001[c]
ESS	3.9 (2.7)	9.0 (5.6)	11.8 (4.5)	§<0.001[a,b], 0.038[c]
EDS (%)	3	46	77	**<0.001[a,b], 0.010[c]
RBD (%)	4	36	58	**<0.001[a,b], 0.094[c] (ns)

Values expressed as means (+/- SD) (unless otherwise stated)

Statistical tests: ‡ANOVA; † t Test; *Kruskal-Wallis; §Wilcoxon rank sum; **Pearson χ^2 +/- Fisher's exact test where groups frequency < 5

(ns = non-significant)

a = HC vs PD; b = HC vs PDD; c = PD vs PDD

LED - Levodopa equivalent dose; MAOI - Monoamine oxidase inhibitor; COMT-I - Catechol-O-methyl transferase inhibitor; ChE - Cholinesterase UPDRS - Unified Parkinson's Disease Rating Scale; FOG - Freezing of Gait; BADLS - Bristol Activities of Daily Living Scale; PDQ-8 = Parkinson's Disease Quality of Life 8; NPI-Q; Neuropsychiatric Inventory- Questionnaire form; BDI - Beck Depression Inventory; ESS - Epworth Sleepiness Scale; EDS - Excessive Daytime Somnolence; Mayo RBD-Q - abbreviated version of Mayo REM sleep Behaviour Disorder Questionnaire.

There were differences between HC and both disease groups in measures of depression (BDI : Wilcoxon rank sum HC = 32, PD = 63, Z = 4.00, p = <0.001; HC = 32, PDD = 26, Z = 5.62, p = <0.001), excessive daytime somnolence (EDS: HC vs. PD Fisher's exact (df 1, n = 93) = 17.9, p = <0.001; HC vs. PDD (df 1, n = 58) = 33.8, p = <0.001) and REM sleep behaviour disorder (RBD: HC vs. PD Fisher's exact (df 1, n = 84) = 11.0, p = <0.001; HC vs. PDD (df 1, n = 55) = 19.6, p = <0.001). Comparison between PD and PDD groups revealed significant differences in motor function (UPDRS III: Wilcoxon rank sum PD = 64, PDD = 25, Z = 3.59, p = <0.001; FOG: PD = 64, PDD = 26, Z = 3.01, p = 0.003), activities of daily living (UPDRS II: Wilcoxon rank sum PD = 64, PDD = 26, Z = 5.08, p = <0.001; BADLS: PD = 59, PDD = 25, Z = 6.08, p = <0.001), quality of life (PDQ-8: Wilcoxon rank sum PD = 63, PDD = 26, Z = 3.76, p = <0.001) and neuropsychiatric burden (NPI Q symptom: Wilcoxon rank sum PD = 60, PDD = 25, Z = 5.59, p = <0.001; Carer distress scale: PD = 64, PDD = 25, Z = 5.81, p = <0.001; BDI : PD = 63, PDD = 26, Z = 3.49, p = <0.001). PDD patients scored higher than PD patients on the ESS (Wilcoxon rank sum PD = 61, PDD = 26, Z = 2.07, p = 0.038) and when this variable was dichotomised such that an ESS score > 9 reflected excessive daytime somnolence (EDS), 46% of PD and 77% of PDD patients fulfilled criteria for EDS (Fisher's exact (df 1, n = 87) = 7.1, p = 0.010). There was no significant difference between disease groups for frequency of RBD (Fisher's exact (df 1, n = 81) = 3.3, p = 0.094, ns).

4.3.2 Cognitive features

As expected, PDD patients scored significantly lower than PD or HC patients on both tests of global cognitive function (MMSE, AEMSS) and all cognitive domain sub-scale scores **(Table 4)**. Mean MMSE scores were 29.5 and 28.9 for the HC and PD groups, respectively, demonstrating a small but significant difference (Wilcoxon rank sum HC 32, PD = 64, Z = 2.34, p = 0.019). The AEMSS revealed more striking differences between HC and PD groups (Wilcoxon rank sum HC 32, PD = 64, Z = 3.05, p = 0.002). PD and HC group comparisons on DRS 2 sub-scale scores

revealed differences in measures of IP (Wilcoxon rank sum HC 32, PD = 64, Z = 2.84, p = 0.005) and CONCEPT (Wilcoxon rank sum HC 32, PD = 64, Z = 2.42, p = 0.016) but not in measures of ATT, CONST or MEM (ATT: Wilcoxon rank sum HC 32, PD = 64, Z = 1.87, p = 0.061, ns; CONST: HC 32, PD = 64, Z = 0.99, p = 0.322, ns; MEM: HC 32, PD = 64, Z = 0.40, p = 0.693, ns). Both PD and PDD group scores were lower than HC scores for the Shulman CDT (Wilcoxon rank sum HC 32, PD = 63, Z = 3.42, p = 0.001; HC = 32, PDD = 25, Z = 6.15, p = < 0.001).

Table 4. Cognitive features of visual symptoms study group.

	HC n=32	PD n=64	PDD n=26	p value
Global cognition				
MMSE	29.5 (0.8) (range 27-30)	28.9 (1.2) (range 25-30)	23.6 (3.8) (range 13-28)	§0.019[a], <0.001[b], <0.001[c]
AEMSS	12.5 (3.0) (range 8-18)	10.2 (3.3) (range 3-17)	3.8 (1.8) (range 1-7)	§0.002[a], <0.001[b,c]
Cognitive sub-scale scores				
ATT	12.3 (1.3)	11.6 (1.6)	9.8 (2.4)	§0.061[a] (ns), <0.001[b,c]
I/P	11.1 (1.3)	9.2 (2.9)	4.0 (2.0)	§0.004[a], <0.001[b,c]
CONST	10.0 (0.0)	9.9 (0.5)	8.1 (2.8)	§0.322[a] (ns), <0.001[b,c]
CONCEPT	11.3 (1.6)	10.1 (2.3)	7.7 (3.4)	§0.016[a], <0.001[b], 0.001[c]
MEM	9.7 (3.3)	9.5 (2.8)	4.6 (2.4)	§0.693[a] (ns), <0.001[b,c]
CDT	4.9 (0.3)	4.5 (0.8)	2.7 (1.5)	§0.001[a], <0.001[b,c]

Values expressed as means (+/- SD)

Statistical tests: §Wilcoxon rank sum

(ns = non-significant)

a = HC vs PD; b = HC vs PDD; c = PD vs PDD

MMSE - Mini-mental state examination; CDT - Clock drawing test (Shulman scoring method); AEMSS - Age and education-adjusted MOANS scaled score (from DRS); ATT - Attention; I/P - Initiation/perseveration; CONST - Construction; CONCEPT - Conceptualization; MEM - Memory.

4.3.3 Visual symptoms

Visual symptoms are shown in **Table 5**. Those reported significantly more commonly in the PD and PDD groups included diplopia (HC vs. PD Fisher's exact (df 1, n = 96) = 6.9, p = 0.009; HC vs. PDD (df 1, n = 58) = 18.3, p = <0.001; PD vs. PDD (df 1, n = 90) = 6.2, p = 0.017), difficulty reading despite appropriate refractive correction (Fisher's exact (df 1, n = 96) = 4.3, p = 0.047; HC vs. PDD (df 1, n = 58) = 10.7, p = 0.001; PD vs. PDD (df 1, n = 90) = 3.2, p = 0.122, ns), misjudging objects when walking (HC vs. PD Fisher's exact (df 1, n = 96) = 8.9, p = 0.001; HC vs. PDD (df 1, n = 58) = 14.9, p = 0.001; PD vs. PDD (df 1, n = 90) = 2.1, p = 0.195, ns) and freezing in narrow spaces (Fisher's exact (df 1, n = 96) = 8.9, p = 0.002; HC vs. PDD (df 1, n = 58) = 18.6, p = <0.001; PD vs. PDD (df 1, n = 90) = 4.5, p = 0.044).

PD subjects were more likely to report CVH and passage than their HC counterparts (Fisher's exact (df 1, n = 96) = 6.2, p = 0.014), but there was no difference in the frequency of either illusions or presence (illusions: Fisher's exact (df 1, n = 96) = 0.0, p = 1.000, ns; presence: (df 1, n = 96) = 1.7, p = 0.230, ns). In contrast, PDD subjects were more likely to report all four visual symptoms (CVH: Fisher's exact (df 1, n = 58) = 47.0, p = <0.001; illusions: (df 1, n = 58) = 9.5, p = 0.003; presence: (df 1, n = 58) = 11.2, p = 0.001; passage: (df 1, n = 58) = 22.3, p = <0.001). CVH, illusions and presence were more common in the dementia group than non-demented PD subjects (CVH: Fisher's exact (df 1, n = 90) = 40.0, p = <0.001; illusions: (df 1, n = 90) = 13.0, p = 0.006; presence: (df 1, n = 90) = 7.1, p = 0.010), but the comparison between these groups for passage did not reach significance (Fisher's exact (df 1, n = 90) = 3.2, p = 0.102, ns). There were no differences between the three groups in the frequency of floaters, simple visual hallucinations (phosphenes, brief flashes of lights) or migrainous aura.

Table 5. Visual symptoms of the study group.

%	HC n=32	PD n=64	PDD n=26	p
Diplopia	6	30	58	**0.009[a], <0.001[b], 0.017[c]
Difficulty reading	6	23	42	**0.047[a], 0.001[b], 0.122[c] (ns)
Misjudge objects	0	23	39	**0.001[a], 0.001[b], 0.195[c] (ns)
Freeze in narrow spaces	0	23	46	**0.002[a], <0.001[b],0.044[c]
CVH	0	17	89	**0.014[a], <0.001[b], <0.001[c]
preceding month	0	6	54	**0.298[a] (ns), <0.001[b], <0.001[c]
Illusion	25	25	65	**1.000[a] (ns), 0.003[b], 0.006[c]
preceding month	0	19	58	**0.007[a], <0.001[b], 0.007[c]
Presence	19	31	62	**0.230[a] (ns), 0.001[b], 0.010[c]
preceding month	0	22	50	**0.004[a], <0.001[b], 0.008[c]
Passage	9	48	69	**0.009[a], <0.001[b], 0.102[c] (ns)
preceding month	3	38	62	**<0.001[a], <0.001[b], 0.060[c] (ns)
Floater	13	11	8	*0.836 (ns)
SImple visual hallucinations	0	3	0	*0.398 (ns)
MIgrainous aura	16	3	4	*0.054 (ns)

Values expressed as %

Statistical tests: **Fisher's exact test, *Pearson Chi square (omnibus test) (ns = non-significant)

a = HC vs PD; b = HC vs PDD; c = PD vs PDD

If responses were restricted to the preceding month only, the pattern of visual symptoms changed significantly. Within this time frame, CVH rates between HC and PD subjects were equivalent (CVH: Fisher's exact (df 1, n = 96) = 2.09, p = 0.298) while illusions, presence and passage experiences were significantly more common in the PD group (illusions: Fisher's exact (df 1, n = 96) = 6.86, p = 0.007; presence: (df 1, n = 96) = 8.20, p = 0.004; passage: (df 1, n = 96) = 13.09, p = 0.001). Again, although there was a trend to a higher frequency of passage in PDD (vs. PD), the difference was not significant (Fisher's exact (df 1, n = 90) = 4.33, p = 0.060, ns).

For CVH, informant reports closely matched those of patients in both the PD and PDD cohorts (PD 17% vs. PD informant 14%, κ 0.76, p = 0.317;

PDD 89% vs. PDD informant 85%, κ 0.84, p = 0.317). There was poor agreement between HC, PD and PDD patients and informants for experiences of illusions (HC κ 0.33, p = 0.014; PD κ 0.33, p = <0.001; PDD κ 0.27, p = <0.001), presence (HC κ 0.45, p = 0.045; PD κ 0.53, p = <0.001; PDD κ 0.42, p = 0.034) and passage (HC n/a; PD κ 0.36, p = <0.001; PDD κ 0.24, p = <0.001). This suggests that CVH are not under-reported by PD subjects but that other visual symptoms (illusions, presence, passage) are not discussed openly with relatives or caregivers.

4.3.4 Ocular features

The three study groups were well matched for frequencies of diabetes mellitus, hypertension, glaucoma and previous cataract removal. No participants were known to have age-related macular degeneration (AMD), although branch retinal vein occlusions and posterior vitreous detachment had occurred in one each of the HC and PD cohort. In addition, one PD participant had known background diabetic retinopathy **(see Table 6)**.

Frequency of lens opacity in all three groups was equivalent (right lens: HC 66%, PD 73%, PDD 68%; Pearson $\chi 2$ (df 2, n = 120) = 0.61, p = 0.736; ns; left lens: HC 59%, PD 75%, PDD 60%; Pearson $\chi 2$ (df 2, n = 120) = 0.61, p = 0.217; ns). For cortical lens opacities there was no significant difference between groups in frequencies of moderate/marked cataract in either the right (Pearson $\chi 2$ (df 2, n = 114) = 2.2, p = 0.332; ns) or left eye (Pearson $\chi 2$ (df 2, n = 113) = 1.89, p = 0.388; ns). PDD patients differed from PD and HC patients in the frequency of moderate/marked nuclear cataract both in the right (HC vs. PDD Fisher's exact (df 1, n = 54) = 6.1, p = 0.013; PD vs. PDD (df 1, n = 82) = 4.6, p = 0.047) and left eye (HC vs. PDD Fisher's exact (df 1, n = 53) = 6.6, p = 0.010; PD vs. PDD (df 1, n = 81) = 9.4, p = 0.005).

Table 6. Ocular features of the visual symptoms study group.

	HC n=32	PD n=64	PDD n=26	p
DM (%)	9	8	4	**0.735 (ns)
HT (%)	34	27	12	**0.153 (ns)
Glaucoma (%)	6	2	4	**0.469 (ns)
Cataract removal (%)	9	13	12	**0.901 (ns)
AMD (%)	9	9	4	**0.685 (ns)
Cortical lens opacity - moderate/marked (%)				
Right	19	13	27	**0.332 (ns)
Left	19	15	29	**0.388 (ns)
Nuclear lens opacity - moderate/marked (%)				
RIght	6	12	32	**0.488[a] (ns), 0.013[b], 0.047[c]
Left	6	7	33	**1.000[a] (ns), 0.010[b], 0.005[c]
RIOP	14.5 (3.3)	13.0 (2.5)	14.3 (4.9)	‡0.086 (ns)
LIOP	14.7 (2.9)	13.3 (2.7)	14.5 (5.8)	‡0.133 (ns)
Retinal health				
Right normal (%)	69	79	79	**0.484 (ns)
Left normal (%)	69	78	79	**0.565 (ns)
Disc cupping	6	6	4	**0.490 (ns)
Peri-papillary atrophy	9	2	4	**0.481 (ns)
RIght AMD	9	8	4	**0.758 (ns)
Left AMD	9	8	4	**0.836 (ns)
Right macular sparing change	9	5	8	**0.598 (ns)
Left macular sparing change	13	5	8	**0.372 (ns)
Visual function				
Binocular UCVA	0.25 (0.28)	0.33 (0.28)	0.46 (0.28)	†0.259[a] (ns), 0.010[b], 0.085[c] (ns)
Binocular BAPVA	0.00 (0.11)	0.06 (0.14)	0.12 (0.15)	†0.035[a], 0.001[b], 0.068[c] (ns)
Binocular CS	1.68 (0.10)	1.63 (0.10)	1.49 (0.20)	†0.038[a], <0.001[b], <0.001[c]

Values expressed as means (+/- SD) (unless otherwise stated)

Statistical tests: ‡ANOVA; † t Test; **Pearson χ^2 +/- Fisher's exact test where groups frequency < 5

(ns = non-significant)

a = HC vs PD; b = HC vs PDD; c = PD vs PDD

DM - Diabetes mellitus; HT - Hypertension; AMD - Age-related macular degeneration; RIOP - Right intraocular pressure; LIOP - left intraocular pressure; UCVA - Uncorrected visual acuity; BAPVA - "Best at presentation" visual acuity; CS - Contrast sensitivity

Right and left intraocular pressures (IOP) were within normal ranges for all participants, even in those participants with treated glaucoma. There was no significant difference between group means (Right IOP: ANOVA (df 2, n = 117) = 2.51, p = 0.086; ns; Left IOP: ANOVA (df 2, n = 117) = 2.05, p =

0.133; ns). Retinal examination was normal in the majority of cases, with no significant group differences (Right retina normal: Pearson $\chi 2$ (df 2, n = 119) = 1.5, p = 0.484; ns; Left retina normal: Pearson $\chi 2$ (df 2, n = 119) = 1.1, p = 0.565; ns). We also specifically rated the appearance of the optic disc and documented the presence of macular sparing retinal change and AMD in all study participants. The commonest disc findings were - normal, disc cupping or peri-papillary atrophic change. There was no difference between groups in any of these findings (Right: Pearson $\chi 2$ (df 4, n = 120) = 3.4, p = 0.490; ns; Left: Pearson $\chi 2$ (df 4, n = 120) = 3.4, p = 0.481; ns). Disc cupping was seen in 6% of HC and PD and 4% of PDD patients. Peri-papillary atrophy was noted in 9% of HC, 2% of PD and 4% of PDD patients. Similar frequencies of right AMD (Pearson $\chi 2$ (df 2, n = 118) = 0.6, p = 0.758; ns), left AMD (Pearson $\chi 2$ (df 2, n = 117) = 0.6, p = 0.836; ns), right (Pearson $\chi 2$ (df 2, n = 118) = 1.0, p = 0.598; ns) and left macular-sparing drusen (Pearson $\chi 2$ (df 2, n = 98) = 2.0, p 0.372; ns) were seen in all groups.

Binocular uncorrected (UCVA) and “best at presentation” VA (BAPVA) was significantly better for the HC group than the PDD group. UCVA (mean ± SD) for the three study groups was as follows: HC 0.25 ± 0.28, PD 0.33 ± 0.28, PDD 0.46 ± 0.28, with only the HC vs PDD comparison reaching statistical significance (t-Test (df 49, n = 51) = 2.70, p = 0.010). In contrast, when normal refractive correction was worn, both PD and PDD groups demonstrated worse binocular BAPVA than controls (HC vs. PD t-Test (df 87, n = 89) = 2.14, p = 0.035; HC vs. PDD (df 51, n = 53) = 3.53, p = 0.001). For both binocular UCVA and BAPVA, there was a trend to better acuity in PD compared to PDD but neither comparison reached significance (UCVA t-Test (df 77, n = 79) = 1.75, p = 0.085; ns; BAPVA (df 80, n = 82) = 1.85, p = 0.068; ns). Binocular CS in the HC group was greater than in PD or PDD groups. These differences reached significance for all comparisons (HC vs. PD t-Test (df 87, n = 89) = 2.11, p = 0.038; HC vs. PDD (df 52, n = 54) = 5.73, p = <0.001; PD vs. PDD (df 81, n = 83) = 4.48, p = <0.001).

Three independent factors predictive of impaired acuity were identified – age, disease severity (UPDRS III) and presence of moderate or marked nuclear cataract. The model containing all three predictors was significant (df 3, n = 74) = 19.4, p = < 0.001, explaining 45% of the variance in BAPVA scores, with UPDRS III emerging as the strongest individual contributor to the model **(Table 7)**. Two independent factors predictive of impaired CS were identified – age and UPDRS III. The model containing both predictors was statistically significant (df 2, n = 78) = 27.0, p = < 0.001, explaining 42% of the variance in CS scores, with disease severity again emerging as the strongest individual predictor. Global cognition (AEMSS) did not influence either VA or CS, despite the trend to poorer acuity in the PDD group.

Table 7. Predictors of key visual symptoms in PD.

Regression models	Beta	Std error	Chi sq	df	p
BAPVA (high scores = worse acuity)					
Standard - full model (df 3, n = 74) = 19.4, p = < 0.001, R^2 0.45					
UPDRS III	.45	0.00			0.001
Age	.31	0.00			<0.001
Moderate/marked nuclear cataract	.24	0.03			0.011
CS (high scores = better CS)					
Standard - full model (df 2, n = 78) = 27.0, p = < 0.001, R^2 0.42					
UPDRS III	-.56	0.00			<0.001
Age	-.36	0.00			<0.001
Diplopia					
Logistic - full model (df 4, n = 86) = 26.5, p = < 0.001, R^2 0.23					
PD duration	.12	0.05	7.46	1	0.003
ESS	.10	0.05	3.63	1	0.049
Abnormal ocular alignment	1.11	0.52	4.53	1	0.020
Hypometric saccades	.61	0.28	4.61	1	0.026
CVH					
Logistic - full model (df 3, n = 81) = 57.9, p = < 0.001, R^2 0.54					
Dementia	1.84	0.44	17.39	1	<0.001
BDI	.14	0.05	7.18	1	0.001
BAPVA	9.17	3.42	9.50	1	0.001
Illusions					
Logistic - full model (df 2, n = 86) = 18.0, p = < 0.001, R^2 0.16					
ESS	.15	0.05	8.40	1	0.004
UPDRS III	.05	0.02	5.57	1	0.018
Presence					
Logistic - full model (df 2, n = 81) = 33.5, p = < 0.001, R^2 0.31					
RBD	1.19	0.30	15.85	1	<0.001
ESS	.20	0.06	10.07	1	0.002

BAPVA = Best at presentation visual acuity; CS = Contrast sensitivity; CVH = Complex visual hallucinations; UPDRS III - Unified Parkinson's Disease Rating Scale (part III); ESS - Epworth Sleepiness Scale; BDI - Beck depression inventory ; RBD - Rapid Eye Movement Sleep Behaviour Disorder

4.3.5 Risk factors for visual symptoms

Diplopia was a feature of 34 of the total PD and PDD cohort (38%) and stepwise logistic regression identified PD duration, ESS scores, abnormal ocular alignment and hypometric saccades as independent factors predictive of diplopia, with the full model (df 4, n = 86) = 26.5, p = < 0.001) accounting for 23% of the variance in reports of diplopia **(Table 7)**. The CVH^+ group consisted of 34 patients (38% of the total PD group). Three independent factors predictive of CVH^+ were identified – diagnosis of dementia, BDI , and BAPVA. The model containing all 3 predictors was statistically significant (df 3, n = 81) = 57.9, p = < 0.001, and predicted 54% of the variance in the documentation of CVH, with a diagnosis of dementia proving the strongest individual predictor. For other visual symptoms, the PD group breakdown was as follows: $illusion^+$ 33 patients (37% of combined PD/PDD group), $presence^+$ 36 patients (40%) and $passage^+$ 49 patients (54%). Independent factors for illusion+ categorization were ESS and UPDRS III scores, although the combined model predicted only 16% of the variance between groups (df 2, n = 86) = 18.0, p = < 0.001). With respect to sensation of presence, only RBD and ESS scores were independent predictors of presence+ status, the combined model explaining 31% of the variance in presence+/presence- status (df 2, n = 81) = 33.5, p = < 0.001). None of the variables outlined above contributed to a model predictive of sensations of passage.

4.4 Discussion

To the best of our knowledge this is the first time the full range of visual symptoms in PD have been combined in a single study utilising ophthalmological, neurological and cognitive assessment. Our study builds upon previous work that has either focused on the ophthalmic features of PD in isolation (Biousse et al., 2004, Repka et al., 1996), provided detailed phenomenological classification of a subset of visual symptomatology in PD (Fenelon et al., 2000), or examined the relationship between visual, cognitive and motor dysfunction in PD in the absence of

comprehensive ophthalmological assessment (Davidsdottir et al., 2005, Uc et al., 2005). In addition, this is the first study to describe the range of visual problems across cognitive sub-groups in PD.

Difficulty reading and diplopia were frequently reported visual symptoms. With respect to diplopia, we found a higher rate than previously reported in the PD literature, perhaps reflecting our larger sample size and case mix of cognitively normal and cognitively impaired subjects. Disease duration was an important factor in predicting diplopia, as was ocular misalignment and ocular motility, although only 20% of patients exhibited the latter findings. In addition, daytime somnolence was associated with diplopia suggesting that drowsiness may interfere with compensatory fusion of ocular misalignment in PD. There is scope for further work examining the prevalence of diplopia in PD and which disease-specific and oculomotor features contribute to the development of this troublesome symptom.

One of the *a priori* hypotheses of our study was that cognitive impairment impacts on tests of basic visual function, providing a possible explanation for the reductions in VA and CS previously reported in PD. We observed significant reductions in VA and CS in both PD and PDD, but neither AEMSS nor MMSE scores emerged as predictors in the regression analysis. Ocular health was similar between HC and PD groups, although there was a higher frequency of moderate/marked nuclear cataract in the PDD group. Despite this contributing to the model of VA predictors, it cannot account for reduced VA in the non-demented PD group, who were well matched with HC subjects for lens opacities. UPDRS III emerged as the most consistent independent predictor for VA and CS within the PD group, arguing in favour of a disease-specific impact on retinal, subcortical or central visual function in PD.

Fenelon et al. (2000) reported minor hallucinations (presence, passage, illusions) in 25% of PD patients and our results confirm this finding with respect to illusions and presence. Interestingly, our HC group also experienced a high rate of illusions and presence. Hallucinatory experiences are not uncommon in the general population (Ohayon, 2000)

and, in the clinical context, our results suggest that recently experienced symptoms are more informative than lifetime occurrence. The higher rates of recent illusions and presence symptoms in PDD are likely to reflect the impact of cognitive decline. In contrast, passage was uncommon in the HC group and common in both PD and PDD groups, suggesting a disease-specific contribution from PD, independent of the cognitive status of patients.

The overall rate of 38% for CVH in our combined PD and PDD cohort is higher than previous studies, which have yielded figures of 20-25% (Fenelon et al., 2000, Graham et al., 1997, de Maindreville et al., 2005). The most likely explanation was the “enrichment” of our cohort with PDD patients, whose CVH rate was almost 90%. CVH rate in the non-demented PD group alone was 17%, and thus more in line with previous reports. Interestingly, the inter-rater reliability between patients and informants for CVH was good, contrary to previous reports suggesting that hallucinations are rarely discussed openly by sufferers (Teunisse et al., 1996; McKinlay et al., 2008). As noted previously, other visual experiences are not routinely volunteered and need to be explicitly sought (Mosimann et al., 2008).

Several studies have suggested that RBD is an independent risk factor for developing visual hallucinations in PD, leading to the intrusion of abnormal dream imagery into wakefulness (Onofrj et al., 2002, Pacchetti et al., 2005). In general, these studies have considered presence, passage and illusions collectively as “visual hallucinations”, an approach that implicitly assumes a common aetiology for each symptom. Results from our regression analyses highlight the well-recognised association between cognitive impairment and CVH and also confirm previous reports that depressive symptoms and impaired VA are potential contributors. As such, both “bottom up” and “top down” disruption may be important in the development of CVH in PD and PDD. In contrast, measures of daytime somnolence and the presence of RBD contributed to models predictive of illusions and presence, suggesting that these visual experiences may be influenced by brainstem regions involved in sleep regulation and arousal

and, as such, bear similarities to extracampine and peduncular hallucinations.

There are some limitations to our study. Although we employed consecutive recruitment for the PD group, we were not able to use a similar approach for the PDD subjects. This was, in part, due to poor documentation of a diagnosis of “dementia” in the notes of PD patients under review in the Movement Disorder Service. Steps have now been taken to ensure that this issue is addressed. In addition, in order to ensure close age-matching of the groups, patients under the age of 50 years were excluded. As the average age of the PD population in clinic and community-based studies is 70-72 years (Lo et al., 2009, Newman et al., 2009), we feel our results are likely to have considerable external validity and that the sample is broadly representative.

There was significant cognitive heterogeneity in our PD group, and a more detailed assessment may have highlighted the contribution of mild cognitive impairment to visual symptoms in PD. We did not employ specific tests of visual cognition and the study was not designed to assess the functional impact of ocular features and visual symptoms. Although we used a validated measure of RBD, we did not perform formal polysomnographic studies to confirm or refute the presence of RBD. Finally, although we have constructed models to examine factors predictive of visual symptoms such as CVH, presence, passage and illusions, a cross-sectional study such as our own cannot make direct causative links between the two.

Nevertheless, our results raise important issues regarding the phenomenological classification of visual symptoms in PD that should be borne in mind for future longitudinal studies. Specifically, they caution against “lumping” illusions, presence and passage into the same category as CVH, particularly when examining the potential link between sleep disturbance and “hallucinations”. Furthermore, the high frequency of passage hallucinations in both cognitively intact and cognitively impaired

PD subjects cautions against necessarily regarding this phenomenon as a sinister prognostic indicator of incident dementia.

5. Retinal morphology in Parkinson's disease

5.1 Background

Whilst some of the visual symptoms common in PD are likely to stem from cortical visual processing deficits, others may be related to lower level disturbances of visual function. Visual acuity (VA) (*Matsui et al.,* 2006), contrast sensitivity (CS) (*Bodis-Wollner et al.,* 1987*, Uc et al*., 2005), colour perception (*Pieri et al.,* 2000*, Price et al*., 1992), motion perception (*Castelo-Branco et al.,* 2008) and the pattern electroretinogram (PERG) response (*Langheinrich et al.,* 2000*, Sartucci et al*., 2006a) are all impaired in PD, with retinal dysfunction advanced as one possible explanation for these findings. However, with the exception of PERG data, subcortical or central disturbances in visual processing could explain at least some of the visual deficits in PD, and tools to probe the retina in isolation are therefore important to address the retinal contribution to visual dysfunction in PD.

Optical Coherence Tomography (OCT) is a technique for obtaining cross-sectional images of the retina in a non-invasive fashion, with an axial resolution of 10 microns. OCT is capable of assessing the thickness of retinal nerve fibre layers (RNFL) around the optic nerve head, thus providing a measure of the integrity of the retinal ganglion cell axons as they exit the retina, as well as providing information on macular morphology. Previous OCT studies have demonstrated morphological changes in retinal structure in multiple sclerosis, Alzheimer's disease and glaucoma (*Iseri et al.,* 2006*, Kanamori et al*., 2003*, Parisi et al*., 1999). RNFL thinning has been found in PD, albeit in relatively small numbers of patients (*Altintas et al.,* 2007*, Inzelberg et al*., 2004*, Moschos et al*., 2010) and macular thickness has also been reported to be reduced (*Altintas et al.,* 2007*, Cubo et al*., 2010*, Hajee et al*., 2009). One possible explanation for these findings is that dopaminergic deficiency deprives the retina of key trophic factors vital to maintaining structural integrity (*Archibald et al.,*

2009). To date, the functional implications of these reported morphological changes are unclear.

The Biomarkers Definitions Working Group define a biomarker as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention (*Jones,* 2010). OCT might prove a useful potential biomarker for assessing disease progression in PD and fulfills the “objectivity” criterion of this definition. However, to be considered as a viable potential biomarker, altered retinal morphology in PD would need to be a robust and repeatable finding in larger cohorts, preferably with longitudinal follow-up, and be applicable to a typical cohort of elderly PD patients with a variety of co-morbidities (*i.e.* good external validity).

We therefore compared retinal structure in a PD and healthy age-matched control cohort for evidence of RNFL or macular thinning and assessed the utility of OCT as a potential biomarker for disease progression in PD. We hypothesised that PD patients would demonstrate thinning of the peri-papillary RNFL and the macula compared to HC, but that the use of OCT as a biomarker may be limited by the co-occurrence of retinal disease (macular degeneration, glaucoma) and tolerability in a representative PD sample.

5.2 Specific Methods

Measures of peri-papillary RNFL, macular thickness and volume were made using a commercially available Ocular Coherence Tomography (OCT) device (Zeiss Stratus 3000TM) following pupillary dilation. Scan quality was assessed by examining the signal strength and confidence limits generated by the automated software analysis. “Best fit” automated contour lines were reviewed for OCT scans with a signal strength < 5/10 or with a macular protocol confidence limit >20 microns. Scans with poor fit contour lines or missing data were excluded from analysis **(Figure 12)**. A more detailed discussion of the data acquisition and automated analysis is available in the main methods section.

5.3 Results

Basic group demographics are shown in **Table 8**. Both groups (HC = 25, PD = 51) were well matched for age (t-Test (df 74, n = 76) = 0.17, p = 0.864, ns) and gender (Fisher's exact (df 1, n = 76) = 0.54, p = 0.616, ns). Mean PD (± SD) duration was 9.1 ± 6.0 years. All PD patients were on pharmacological therapy, with a mean L-DOPA dose of 461 mg/day. Thirty-seven percent of the PD patients were also taking a dopamine agonist. UPDRS II and III mean scores were 14.9 ± 7.1 and 25.7 ± 12.5, respectively. Groups were also well matched for a history of hypertension, diabetes mellitus, glaucoma and prior cataract removal. There was no difference between the cohorts in terms of the frequency of lens opacity, age-related macular degeneration and optic atrophy. No participants had significant diabetic retinopathy or hypertensive retinal disease. Intraocular pressures in both right and left eye were within normal range for all participants, including the 2 PD participants with treated glaucoma, although both these participants demonstrated optic atrophy on slit lamp examination.

There was no difference in UCVA between the HC and PD groups (Right UCVA: Wilcoxon Rank Sum HC = 22, PD = 48, Z = 0.83, p = 0.407; Left UCVA: HC = 22, PD = 48, Z = 1.96, p = 0.051; Binocular UCVA: HC = 22, PD = 47, Z = 1.08, p = 0.279). Right and binocular BAPVA was significantly lower in the PD group, with measures of left BAPVA approaching significance (Right BAPVA: Wilcoxon Rank Sum HC = 23, PD = 47, Z = 1.98, p = 0.048; Left BAPVA: HC = 23, PD = 47, Z = 1.93, p = 0.054; Binocular BAPVA: HC = 23, PD = 46, Z = 2.41, p = 0.016). Similarly, all measures of CS were lower in the PD group with right and binocular CS reaching significance (Right CS: Wilcoxon Rank Sum HC = 23, PD = 45, Z = 2.34, p = 0.019; Left CS: HC = 23, PD = 44, Z = 1.87, p = 0.062; Binocular CS: HC = 23, PD = 47, Z = 2.63, p = 0.009).

Table 8. Basic demographics of OCT cohort.

	HC n=25	PD n=51	p
Age (years)	71.6 (7.8)	71.3 (7.7)	†0.864 (ns)
Gender (% male)	56	65	**0.616 (ns)
PD duration (years)		9.1 (6.0)	
L-dopa dose (mg/day)		461 (389)	
Agonist use (%)		37	
UPDRS II		14.9 (7.1)	
UPDRS III		25.7 (12.5)	
% Glaucoma (n)	0 (0)	4 (2)	**1.000 (ns)
% Previous cataract surgery (n)	12 (3)	8 (4)	**0.678 (ns)
% Diabetes mellitus (n)	8 (2)	6 (3)	**1.000 (ns)
% Hypertension (n)	32 (8)	20 (10)	**0.260 (ns)
% Right cataract (n)	64 (16)	73 (37)	**0.596 (ns)
% Left cataract (n)	60 (15)	73 (37)	**0.302 (ns)
% AMD (n)	8 (2)	10 (5)	**1.000 (ns)
% Optic atrophy (n)	12 (3)	10 (5)	**1.000 (ns)
RIOP (mmHg)	14.5 (3.4)	13.8 (2.7)	§0.466 (ns)
LIOP (mmHg)	14.6 (2.7)	14.1 (2.8)	§0.465 (ns)
Right UCVA	0.42 (0.37)	0.47 (0.29)	§0.407 (ns)
Left UCVA	0.32 (0.26)	0.47 (0.29)	§0.051 (ns)
Binocular UCVA	0.24 (0.27)	0.32 (0.26)	§0.279 (ns)
Right BAPVA	0.10 (0.24)	0.20 (0.24)	§0.048
Left BAPVA	0.10 (0.19)	0.20 (0.23)	§0.054 (ns)
Binocular BAPVA	-0.01 (0.12)	0.08 (0.15)	§0.016
Right CS	1.56 (0.19)	1.48 (0.17)	§0.019
Left CS	1.58 (0.14)	1.50 (0.17)	§0.062 (ns)
Binocular CS	1.68 (0.09)	1.60 (0.13)	§0.009

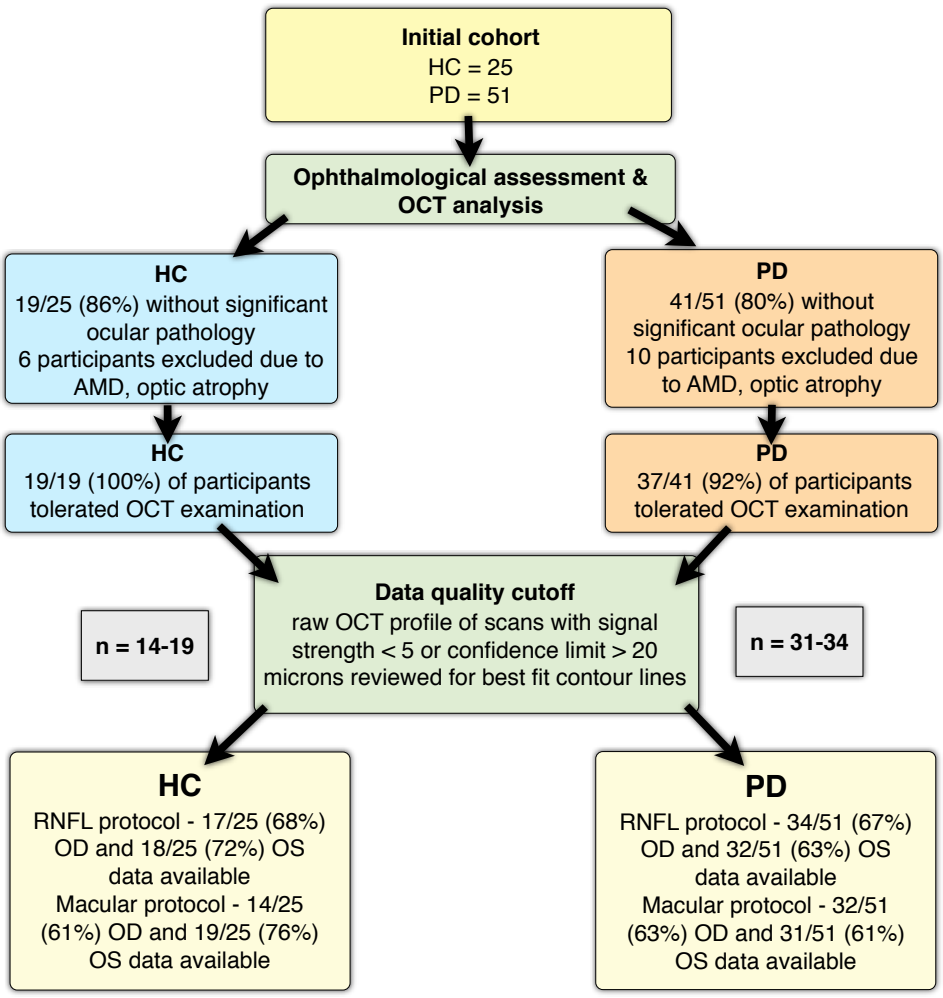
Values expressed as means (+/- SD) (unless otherwise stated)

Statistical tests: † t Test; §Wilcoxon rank sum; **Pearson χ^2 +/- Fisher's exact test where groups frequency < 5

UPDRS = Unified Parkinson's disease rating scale; AMD = Age-related macular degeneration; RIOP = Right intraocular pressure; LIOP = Left intraocular pressure; UCVA = Uncorrected visual acuity; BAPVA = "Best at presentation" visual acuity; CS = Contrast sensitivity

In total, 6/25 (24%) HC were excluded from OCT analysis due to the presence of macular degeneration or optic atrophy; 10/51 (20%) PD subjects were excluded for similar reasons. Two participants with unilateral branch retinal vein occlusion were included in the analysis for the unaffected eye as were participants with retinal drusen not involving the macular region. A further 4 PD patients (8%) were unable to tolerate the OCT protocol due to tremor, dyskinesia or anterocollis. This left a "restricted group" of 19 HC and 37 PD participants for further analysis **(Figure 18)**.

Figure 18. Study flow chart. Note the restriction of group size based upon 1) ocular pathology, 2) scan tolerability, and 3) data quality.



5.3.1 Restricted group analysis

Basic group demographics are shown in **Table 9**. Again, both groups were well matched for age (t-Test (df 54, n = 56) = 0.77, p = 0.447) and gender (Fisher's exact (df 1, n = 56) = 0.74, p = 0.411). Mean PD duration was 8.9 ± 5.6 years. Disease severity was therefore equivalent to the mean scores of the unrestricted cohort (UPDRS II 15.0 ± 7.3; UPDRS III 24.8 ± 11.7).

Table 9. Demographics of the restricted analysis OCT group.

	HC n=19	PD n=37	p
Age	69.4 (6.7)	71.0 (7.8)	†0.447 (ns)
Gender (% male)	47	60	**0.411 (ns)
PD duration	n/a	8.9 (5.6)	
L-dopa dose	n/a	443.2 (305.3)	
Agonist use (%)	n/a	32	
UPDRS II	n/a	15.0 (7.3)	
UPDRS III	n/a	24.8 (11.7)	
Right UCVA	0.35 (0.32)	0.41 (0.27)	§0.525 (ns)
Left UCVA	0.29 (0.25)	0.44 (0.29)	§0.117 (ns)
Binocular UCVA	0.28 (0.20)	0.29 (0.23)	§0.280 (ns)
Right BAPVA	0.05 (0.14)	0.18 (0.22)	§0.073 (ns)
Left BAPVA	0.07 (0.17)	0.19 (0.21)	§0.064 (ns)
Binocular BAPVA	-0.05 (0.10)	0.05 (0.12)	§0.014
Right CS	1.60 (0.12)	1.49 (0.16)	§0.009
Left CS	1.61 (0.11)	1.44 (0.34)	§0.023
Binocular CS	1.71 (0.07)	1.61 (0.12)	§0.003

Values expressed as means (+/- SD) (unless otherwise stated)

Statistical tests: † t Test; §Wilcoxon rank sum; **Pearson χ^2 +/- Fisher's exact test where groups frequency < 5 (ns = non-significant)

UPDRS = Unified Parkinson's disease rating scale; UCVA = Uncorrected visual acuity; BAPVA = "Best at presentation" visual acuity; CS = Contrast sensitivity

There was no difference in UCVA between the HC and PD groups (Right UCVA: Wilcoxon Rank Sum HC = 15, PD = 35, Z = 0.64, p = 0.525; Left UCVA: HC = 15, PD = 35, Z = 1.57, p = 0.117; Binocular UCVA: HC = 15, PD = 35, Z = 1.08, p = 0.280). All measures of BAPVA were lower in the PD group with comparisons for binocular acuity reaching significance (Right BAPVA: Wilcoxon Rank Sum HC = 15, PD = 34, Z = 1.79, p = 0.073; Left BAPVA: HC = 15, PD = 35, Z = 1.86, p = 0.064; Binocular BAPVA: HC = 15, PD = 34 Z = 2.45, p = 0.014). All measures of CS were significantly lower in the PD group (Right CS: Wilcoxon Rank Sum HC = 15, PD = 34, Z = 2.70, p = 0.007; Left CS: HC = 15, PD = 33, Z = 2.26, p = 0.024; Binocular CS: HC = 15, PD = 33, Z = 3.00, p = 0.003).

5.3.2 Scan quality

All OCT scans of questionable quality were examined for “best fit” automated contour lines, excluding those with missing data or “poor fits” from further analysis. For the HC cohort, 5 right macular scans and 3 RNFL scans (2 right; 1 left) failed quality-control assessment and were excluded. For the PD cohort, 5 right and 6 left macular scans along with 3 right and 5 left RNFL scans also failed to meet inclusion criteria for further analysis. We therefore used 14/25 (56%) right and 19/25 (76%) left HC macular scans and 32/51 (63%) right and 31/51 (61%) left PD macular scans for final analysis. Similarly, we utilised data from 17/25 (68%) right and 18/25 (72%) left HC RNFL scans and 34/51 (67%) right and 32/51 (63%) left PD RNFL scans for final analysis.

5.2.3 OCT results

The OCT results are summarized in **Table 10**. Average RNFL thickness was equivalent between HC and PD groups for both the right (OD) and left (OS) eye (OD: Wilcoxon Rank Sum HC = 17, PD = 34, Z = 1.81, p = 0.071; OS: HC = 18, PD = 32, Z = 0.82, p = 0.413). There were no differences in RNFL thickness between HC and PD retina in superior (OD: Wilcoxon Rank Sum HC = 17, PD = 34, Z = 1.82, p = 0.069; OS: HC = 18, PD = 32, Z = 1.26, p = 0.206), inferior (OD: Wilcoxon Rank Sum HC = 17,

PD = 34, Z = 0.40, p = 0.689; OS: HC = 18, PD = 32, Z = 0.34, p = 0.731), temporal (OD: Wilcoxon Rank Sum HC = 17, PD = 34, Z = 0.01, p = 0.992; OS: HC = 18, PD = 32, Z = 0.36, p = 0.716) and nasal quadrants (OD: Wilcoxon Rank Sum HC = 17, PD = 34, Z = 1.54, p = 0.124; OS HC = 18, PD = 32, Z = 1.45, p = 0.148).

Measurements of OD and OS average foveal thickness (OD: Wilcoxon Rank Sum HC = 14, PD = 32, Z = 0.01, p = 0.991; OS: HC = 19, PD = 31, Z = 0.75, p = 0.453) and macular volume (OD: Wilcoxon Rank Sum HC = 14, PD = 32, Z = 0.49, p = 0.625; OS: HC = 19, PD = 31, Z = 0.84, p = 0.401) were also equivalent between HC and PD groups.

Table 10. RNFL and macular thickness measures.

RNFL thickness (microns)	HC	PD	p
Right	n=17	n=34	
average	83.47 (9.4)	89.24 (9.4)	§0.071 (ns)
superior	90.59 (19.6)	102.79 (19.5)	§0.069 (ns)
inferior	116.88 (18.2)	118.03 (17.7)	§0.689 (ns)
temporal	62.94 (13.7)	62.65 (12.4)	§0.992 (ns)
nasal	63.35 (14.6)	73.47 (20.3)	§0.124 (ns)
Left	n=18	n=32	
average	86.62 (8.4)	88.92 (12.5)	§0.413 (ns)
superior	100.28 (12.7)	106.97 (15.2)	§0.206 (ns)
inferior	117.11 (17.0)	112.19 (23.7)	§0.731 (ns)
temporal	61.67 (9.5)	60.09 (12.4)	§0.716 (ns)
nasal	67.61 (17.2)	76.22 (22.9)	§0.148 (ns)
Macular thickness	**HC**	**PD**	**p**
Right	n=14	n=32	
foveal thickness (microns)	179.00 (20.6)	181.34 (29.4)	§0.991 (ns)
macular volume (mm^3)	6.47 (0.4)	6.54 (0.4)	§0.625 (ns)
Left	n=19	n=31	
foveal thickness (microns)	174.26 (20.1)	171.58 (29.5)	§0.453 (ns)
macular volume (mm^3)	6.61 (0.5)	6.47 (0.4)	§0.401 (ns)

Values expressed as means (+/- SD) (unless otherwise stated)
Statistical tests: §Wilcoxon rank sum

5.4 Discussion

Contrary to our expectations, and previous reports, we found neither thinning of the RNFL layer nor a reduction in macular volume or foveal thickness in subjects with PD. There are a number of potential reasons for this finding. First, the mean age of our PD group was significantly greater than in previous studies. Other reports examining the RNFL layer in PD have recruited cohorts with mean ages of between 57 – 59 years (Altintas et al., 2007, Inzelberg et al., 2004, Moschos et al., 2010) while those focusing on macular morphology had mean cohort ages of 64 years (Cubo et al., 2010, Hajee et al., 2009). In contrast, the mean age in our study was 71 years for both HC and PD groups. Measures of RNFL (Kanamori et al., 2003, Alamouti and Funk, 2003) and macular thickness (Kashani et al., 2010, Song et al., 2010) are inversely correlated with age, and overall measures of RNFL and macular thickness were lower in our study than in previously published work. This may have led to a “floor effect”, where retinal thickness measures between groups converge with advancing age, making detection of subtle differences more difficult. The older age of our cohort also makes a direct comparison of other studies with our own difficult. However, the mean age in our study more closely matches that of the PD population as a whole (Lo et al., 2009, Newman et al., 2009), and the inclusion of a well-matched HC group means we feel we are better able to generalize our findings accordingly.

The field of published work on OCT in PD is small. To date, excluding our own study, data for only 74 PD patients is available (n = 43 for RNFL data and n = 31 for macular studies). In several of these publications, both eyes were included in the group analyses, an approach that may not be valid due to the interdependence of measurements in right and left eyes. The small numbers in previous studies also leaves them open to type I error, where significant differences are detected in the absence of a true group difference. Standard deviations from published articles, and our own, vary from ± 10-20 microns for RNFL measurements, ± 10-30 microns for macular thickness and ± 0.3 mm^3 for macular volume measurements.

Power calculations based on a statistical significance level of 0.05 and a predicted power of 0.8 suggest a sample size of between 20-60 would be adequate in each group to detect a 10 micron difference in RNFL and macular thickness (depending on the SD of measurements). It could therefore be argued that several previous studies have been underpowered to detect “true” differences between PD and HC groups. This criticism could, of course, also be applied to our own data, as, although we began with an adequate cohort size (HC 25, PD 51), after exclusions, our sample size was considerably reduced. This leaves our own study prone to type II error – that is, erroneously accepting that there is no difference in HC and PD retinal morphology where one may exist.

No studies published thus far have reported on the number of participants excluded prior to the start of the study; this is potentially important if we are to draw conclusions on external validity of findings. Only one study by Inzelberg et al. (2004) reported specifically on the number of PD participants unable to tolerate the OCT protocol; in this instance 4/16 (25%) were excluded. In contrast, we found OCT to be well tolerated, with only 4/51 (8%) unable to complete the assessment due to tremor, dyskinesia or axial dystonia. More problematic was the loss of data due to poor quality scans. On average, we lost 4/37 (11%) RNFL and 6/37 (16%) macular scans due to data acquisition problems. Most strikingly, 10/51 (20%) PD participants were excluded from final analysis due to co-morbid eye disease (AMD, optic atrophy). In total, therefore, approximately 40% of our original cohort was unavailable for final analysis due one of the three reasons given above.

This places limitations both on interpreting the literature published thus far on retinal morphology in PD and on assessing the potential utility of OCT as a biomarker for disease progression. Results from OCT studies at present are contradictory, suggesting that it is too soon to draw firm conclusions on whether there is a clinically detectable structural change in the retina in PD. One approach likely to resolve the outstanding uncertainty would be an appropriately powered, longitudinal study of incident PD patients using the newer generation of frequency-domain

OCT machines, with better axial resolution (3-5 microns) and shorter data acquisition times. Using an incident cohort may reduce the number of patients excluded from the analysis due to PD-related disability or coincident retinal disease and high-resolution imaging may reduce the amount of data lost for technical reasons. Nevertheless, in terms of the utility of OCT as a biomarker of disease progression, inter-individual variability in measurements and the confounding impact of ocular and retinal pathology suggest that this technique may lack both sensitivity and specificity to inform on disease progression on a case-to-case basis in PD.

6. Visual electrophysiology of Parkinson's disease

6.1 Background

In order to facilitate the gathering and processing of visual information, the retina is laid out in both a laminar and circumferential arrangement. The laminar arrangement allows vertical neurotransmission to take place from photoreceptor to bipolar cell to retinal ganglion cell (RGC), and it is the RGC that acts as the final common pathway in the flow of visual information to the optic nerve. There are two main photoreceptors in the human retina: rods, present in both the parafoveal and peripheral retina and designed for low-light (scotopic) vision, and cones, found predominantly in the macula and specialised for bright-light (photopic) colour vision (*Curcio et al.,* 1990) **(Figure 1)**.

In addition, there are cells mediating horizontal retinal neurotransmission and these are vital in shaping the temporal and spatial qualities of scotopic and photopic vision. Principal players in this horizontal modulation are horizontal cells and amacrine cells. One particular amacrine cell population (dopaminergic A18 neurons) forms a widespread dendritic arborisation throughout the retina (*Dacey,* 1990*, Kolb et al*., 1990*, Pourcho*, 1982*, Voigt and Wassl*e, 1987), directly and indirectly interacting with rod and cone bipolars, and modulating the flow of rod-driven visual information (*Bloomfield and Dacheux,* 2001*, Witkovsky et al*., 1993). In essence, A18 cells help to coordinate the retinal transition from a dark-adapted to light-adapted state (*Cahill,* 1996*, Doyle et al*., 2002b*, Ribelayga et al*., 2008*, Tosini and Menake*r, 1996) and, hence, retinal dopaminergic deficiency may lead to an inappropriately dark-adapted retina under scotopic conditions.

There are also two main types of RGC in the human retina. Those with large cell bodies, prominent in the peripheral retina and known as magnocellular RGCs (M-cells), carry information on movement and contrast. Parvocellular RGCs (P-cells), most prominent in the central retina, signal fine feature and colour information to higher visual centres

(*Ferrera et al.,* 1992*, Ferrera et al*., 1994*, Malpeli et al*., 1996*, Maunsell et al*., 1990*, Nealey and Maunsel*l, 1994). Given the evidence for a dopamine-deficient, rod-primed retina in PD (*Harris et al.,* 1992*, Wink and Harri*s, 2000), one explanation for the high prevalence of peripheral visual disturbances in the condition is that the retinal balance between M- and P-cells is tipped in favour of magnocellular "motion" responses, ultimately manifesting as fleeting, peripheral sensations of passage.

The PERG, by stimulating the retina at an even mean luminance, measures the electrical contribution from cells of the inner retina – predominantly the RGCs (*Maffei et al.,* 1985). The response is highly dependent on the spatial, temporal and contrast characteristics of the pattern stimulus used and previous studies have demonstrated alterations in both PERG latencies and amplitudes in PD (*Gottlob et al.,* 1987*, Langheinrich et al*., 2000*, Nightingale et al*., 1986*, Peppe et al*., 1998*, Peppe et al*., 1992*, Sartucci et al.*, 2006, Biomedecine & Pharmacotherapy, 60, 476, Stanzione et al., 1990). It is possible to manipulate the characteristics of pattern stimuli to bias responses from M- and P-cells (*Tobimatsu et al.,* 1995*, Butler et al*., 2005*, Silva et al*., 2005) and we therefore set out to develop a simultaneous pattern electroretinogram and visual evoked potential protocol in an attempt to answer the following research questions:

1) Is there evidence to support a differential disruption of either magnocellular or parvocellular pathways in PD? and,

2) Do PD subjects experiencing sensations of passage have different electrophysiological responses under magnocellular-biased conditions?

6.2 Specific Methods

See main methods section for full details **(3.5)**. PD subjects were dichotomised into two groups depending upon reported experience of sensations of passage (passage^{+}/passage^{-}) in the visual periphery. The transient PERG responses to magnocellular-biased conditions were analysed using passage^{+}/passage^{-} as the grouping variable to assess the

contribution a potential alteration in retinal magnocellular pathways might make to the this symptom. The relationship between visual acuity (BAPVA) and PERG and PVEP amplitude (P50 PERG and P100 VEP) in both the PD and HC groups was investigated using Pearson product-moment correlation coefficient in order to clarify the role of the retina in impairment of acuity and contrast sensitivity.

6.3 Results

6.3.1 Demographics

Subjects were well matched for age (t-Test (df 65, n = 67) = 0.68, p = 0.502, ns) and gender (Fisher's exact (df 1, n = 67) = 1.20, p = 0.302, ns) **(Table 11)**. The PD group scored lower on the AEMSS (Wilcoxon Rank Sum HC 22, PD 44, Z = 2.43, p = 0.015) and although performance on the MMSE was also impaired, the difference did not reach significance (Wilcoxon Rank Sum HC 22, PD 44, Z = 1.90, p = 0.058, ns). Mean (± SD) PD duration was 8.3 ± 5.2 years and mean UPDRS II and III scores were 14.82 ± 6.77 and 24.16 ± 11.38 respectively, making the group representative of the overall PD cohort recruited to the study (PD duration = 8.4 ± 5.7; UPDRS II = 13.2 ± 6.1; UPDRS III = 23.1 ± 10.0). The overall LED was 638 ± 411 mg/day with 44% of PD subjects taking dopamine agonists, 28% taking COMT inhibitors and 28% using MAO type-B inhibitors.

6.3.2 Visual measures

"Best at presentation" visual acuity (BAPVA) and contrast sensitivity (CS) were both significantly lower in the PD group compared to HC (BAPVA: Wilcoxon Rank Sum HC 21, PD 41, Z = 2.60, p = 0.009; CS: HC 21, PD 41, Z = 2.48, p = 0.013) **(Table 11)**. Right and left intraocular pressures were normal (RIOP: t-Test (df 64, n = 66) = 1.83, p 0.072, ns; LIOP: (df 64, n = 66) = 1.49, p 0.141, ns) and both groups demonstrated equivalent frequencies of moderate/marked cortical and nuclear cataract (Cortical: Fisher's exact (df 1, n = 65) = 0.26, p = 0.737, ns; Nuclear: (df 1, n = 65) =

2.77, p = 0.158, ns). Retinal examination was normal in 73% of HC and 71% of PD subjects (Fisher's exact (df 1, n = 66) = 0.04, p = 1.000, ns) with 5 (12%) of PD and 3 (14%) of HC subjects showing evidence of AMD and 5 (12%) of PD and 1 (5%) of HC subjects showing optic disc cupping on slit lamp examination.

Table 11. Demographics of ERG/VEP study groups.

	HC n = 22	PD n = 44	p
Age	72.4 (7.3)	71.1 (8.0)	†0.502 (ns)
Gender (% Male)	52	66	**0.302 (ns)
AEMSS	12.5 (2.8)	10.1 (3.7)	§0.015
MMSE	29.5 (0.8)	28.7 (2.0)	§0.058 (ns)
PD duration	n/a	8.3 (5.2)	
UPDRS II	n/a	14.8 (6.8)	
UPDRS III	n/a	24.2 (11.4)	
LED mg/day	n/a	638 (411)	
Agonist use (%)	n/a	44	
COMT inhibitor (%)	n/a	28	
MAOI (%)	n/a	28	
BAPVA	-0.01 (0.10)	0.07 (0.13)	§0.009
CS	1.69 (0.09)	1.61 (0.14)	§0.013
RIOP	14.6 (3.4)	13.2 (2.8)	†0.072 (ns)
LIOP	14.9 (2.8)	13.7 (3.0)	†0.141 (ns)
Cortical cataract - moderate/ severe (%)	14	19	**0.737 (ns)
Nuclear cataract - moderate/ severe (%)	0	12	**0.158 (ns)
Retina normal (%)	73	71	**1.000 (ns)

Values expressed as means +/- SD (unless otherwise stated)

Statistical tests: † t Test; §Wilcoxon rank sum; **Pearson $\chi 2$ +/- Fisher's exact test where groups frequency < 5

(ns = non-significant)

AEMSS - Age- and education-adjusted MOANS scaled score; MMSE - Mini-mental state examination; UPDRS - Unified Parkinson's Disease Rating Scale; LED - Levodopa equivalent dose; COMT - Catechol-O-methyl transferase; MAOI - Monoamine oxidase type B inhibitor; BAPVA - BInocular "Best at Presentation" visual acuity; CS - Contrast sensitivity; RIOP - Right intraocular pressure; LIOP - Left intraocular pressure

6.3.3 Transient PERG responses

The transient PERG responses to parvocellular-biased conditions (0.8° check size, high contrast) were equivalent between both groups for right and left P50 and N95 amplitude (μV) and implicit time (msec) **(Table 12)** (Right P50 Amp: t-Test (df 58, n = 60) = 0.49, p = 0.626, ns; Left P50 Amp:

(df 56, n = 58) = 0.09, p = 0.922, ns; Right P50 Imp: (df 56, n = 58) = 1.13, p = 0.263, ns; Left P50 Imp: (df 56, n = 58) = 0.72, p = 0.477, ns; Right N95 Amp: (df 57, n = 59) = 0.21, p = 0.837, ns; Left N95 Amp: (df 56, n = 58) = 0.00, p = 0.998, ns; Right N95 Imp: (df 57, n = 59) = 0.93, p = 0.354, ns; Left N95 Imp: (df 54, n = 56) = 1.44, p = 0.457, ns). Similarly, the transient PERG responses to magnocellular-biased conditions (30^{o} check size, low contrast) showed no group differences (Right P50 Amp: t-Test (df 57, n = 59) = 0.52, p = 0.607, ns; Left P50 Amp: (df 54, n = 56) = 0.03, p = 0.979, ns; Right P50 Imp: (df 57, n = 59) = 0.91, p = 0.368, ns; Left P50 Imp: (df 54, n = 56) = 0.84, p = 0.407, ns; Right N95 Amp: (df 57, n = 59) = 0.53, p = 0.607, ns; Left N95 Amp: (df 54, n = 56) = 0.39, p = 0.697, ns; Right N95 Imp: (df 57, n = 59) = 1.06, p = 0.295, ns; Left N95 Imp: (df 54, n = 56) = 0.74, p = 0.464, ns).

6.3.4 Transient VEP responses

Under parvocellular-biased conditions, both the amplitude (Right: t-Test (df 61, n = 63) = 0.02, p 0.984, ns; Left: (df 60, n = 62) = 0.28, p 0.777, ns; Midline: (df 60, n = 62) = 0.46, p 0.649, ns) and latency (Right: t-Test (df 61, n = 63) = 0.67, p 0.503, ns; Left: (df 60, n = 62) = 0.61, p 0.541, ns; Midline: (df 61, n = 63) = 0.60, p 0.550, ns) of transient VEP responses were equivalent between groups **(Table 12)**. Under magnocellular-biased conditions, no difference was detected in the transient VEP response (Right Amp: t-Test (df 31, n = 61) = 0.76, p 0.453, ns; Left Amp: (df 59, n = 61) = 0.85, p 0.397, ns; Midline Amp: (df 30, n = 61) = 1.31, p 0.199, ns; Right Imp: (df 59, n = 61) = 0.89, p 0.377, ns; Left Imp: (df 59, n = 61) = 0.84, p 0.406, ns; Midline Imp: (df 59, n = 61) = 0.82, p 0.418, ns).

Table 12. Transient PERG and VEP responses.

	HC n = 22	PD n = 38	p
ERG - parvocellular response			
Right P50 Amp	9.93 (5.64)	9.27 (4.67)	†0.626 (ns)
Left P50 Amp	10.41 (6.11)	10.56 (5.82)	†0.922 (ns)
Right P50 Imp	53.32 (2.08)	52.45 (3.24)	†0.263 (ns)
Left P50 Imp	53.14 (2.47)	52.61 (2.84)	†0.477 (ns)
Right N95 Amp	11.43 (5.89)	11.13 (5.00)	†0.837 (ns)
Left N95 Amp	12.15 (6.38)	12.15 (6.22)	†0.998 (ns)
Right N95 Imp	112.09 (8.72)	114.08 (7.41)	†0.354 (ns)
Left N95 Imp	112.10 (9.16)	115.31 (7.29)	†0.457 (ns)
ERG - magnocellular response			
Right P50 Amp	15.37 (5.47)	14.52 (6.31)	†0.607 (ns)
Left P50 Amp	15.63 (6.85)	15.68 (7.08)	†0.979 (ns)
Right P50 Imp	47.10 (4.02)	46.24 (3.14)	†0.368 (ns)
Left P50 Imp	47.05 (3.66)	46.25 (3.30)	†0.407 (ns)
Right N95 Amp	18.30 (6.38)	17.29 (7.44)	†0.607 (ns)
Left N95 Amp	19.28 (6.92)	18.41 (8.50)	†0.697 (ns)
Right N95 Imp	113.38 (9.48)	110.63 (9.60)	†0.295 (ns)
Left N95 Imp	113.40 (10.19)	111.33 (9.98)	†0.464 (ns)
VEP - parvocellular response			
Right Amp	10.79 (5.29)	10.82 (4.89)	†0.984 (ns)
Left Amp	10.42 (5.37)	10.07 (4.28)	†0.777 (ns)
Midline Amp	12.81 (6.07)	12.11 (5.71)	†0.649 (ns)
Right Latency	108.61 (9.92)	110.20 (8.49)	†0.503 (ns)
Left Latency	108.70 (10.16)	110.21 (8.84)	†0.541 (ns)
Midline Latency	108.30 (9.98)	109.73 (8.46)	†0.550 (ns)
VEP - magnocellular response			
Right Amp	7.55 (4.39)	6.74 (3.09)	†0.453 (ns)
Left Amp	7.88 (4.43)	7.03 (3.27)	†0.397 (ns)
Midline Amp	9.26 (5.21)	7.80 (3.57)	†0.199 (ns)
Right Latency	113.14 (11.56)	115.83 (10.99)	†0.377 (ns)
Left Latency	113.24 (11.40)	115.75 (11.00)	†0.406 (ns)
Midline Latency	113.05 (11.42)	115.50 (11.03)	†0.418 (ns)

ERG = Electroretinogram; VEP = Visual evoked potential; Amp = Amplitude (microV); Imp = Implicit time (msec)

Values expressed as means (± SD)

Statistical tests: † t Test

(ns = non-significant)

6.3.5 Steady-state PERG & VEP responses

Steady-state parvocellular-biased responses for right and left PERG (Right: t-Test (df 55, n = 57) = 1.37, p = 0.176, ns; Left: (df 53, n = 55) = 0.45, p = 0.658, ns) and right (t-Test (df 62, n = 64) = 0.01, p = 0.990, ns), left (t-Test (df 62, n = 64) = 1.34, p = 0.185, ns) and midline VEP (t-Test (df 62, n = 64) = 1.45, p = 0.152, ns) recording positions were equivalent in HC and PD subjects **(Table 13)**. Magnocellular-biased responses demonstrated an identical pattern, with no significant differences between HC and PD groups (Right PERG: t-Test (df 54, n = 56) = 0.59, p = 0.556, ns; Left PERG: (df 53, n = 55) = 0.51, p = 0.612, ns; Right VEP: (df 62, n = 64) = 0.80, p = 0.429, ns; Left VEP: (df 62, n = 64) = 0.07, p = 0.946, ns; Midline VEP: (df 62, n = 64) = 0.70, p = 0.484, ns).

Table 13. Steady-state PERG and VEP responses.

	HC n = 22	PD n = 38	p
Parvocellular response			
Right PERG	0.16 (0.06)	0.13 (0.08)	†0.176 (ns)
Left PERG	0.15 (0.02)	0.14 (0.01)	†0.658 (ns)
Right VEP	0.29 (0.21)	0.29 (0.21)	†0.990 (ns)
Left VEP	0.23 (0.14)	0.28 (0.16)	†0.185 (ns)
Midline VEP	0.36 (0.19)	0.29 (0.17)	†0.152 (ns)
Magnocellular response			
Right PERG	0.31 (0.17)	0.34 (0.17)	†0.556 (ns)
Left PERG	0.32 (0.03)	0.34 (0.03)	†0.612 (ns)
Right VEP	0.41 (0.32)	0.35 (0.25)	†0.429 (ns)
Left VEP	0.39 (0.32)	0.40 (0.30)	†0.946 (ns)
Midline VEP	0.44 (0.37)	0.38 (0.27)	†0.484 (ns)

Values expressed as means (+/- SD)
Statistical tests: † t Test
(ns = non-significant)

PERG = Pattern Electroretinogram; VEP = Visual evoked potential

6.3.6 Association between sensations of passage and magnocellular pathway parameters

We detected no difference in P50 and N95 amplitude and implicit time between passage^{+} (n = 25) and passage^{-} (n = 19) subjects **(Table 14)** (Right P50 Amp: t-Test (df 36, n = 38) = 0.10, p = 0.919, ns; Left P50 Amp: (df 34, n = 36) = 0.13, p = 0.900, ns; Right P50 Imp: (df 36, n = 38) = 0.29, p = 0.775, ns; Left P50 Imp: (df 34, n = 36) = 0.58, p = 0.563, ns; Right N95 Amp: (df 36, n = 38) = 0.61, p = 0.549, ns; Left N95 Amp: (df 34, n = 36) = 0.24, p = 0.813, ns; Right N95 Imp: (df 36, n = 38) = 0.23, p = 0.817, ns; Left N95 Imp: (df 34, n = 36) = 0.17, p = 0.868, ns). Likewise, the steady-state PERG and VEP magnocellular-biased responses were equivalent between the two visual symptom groups (Right PERG: t-Test (df 31, n = 33) = 0.30, p = 0.765, ns; Left PERG: (df 31, n = 33) = 0.17, p = 0.865, ns; Right VEP: (df 38, n = 40) = 0.29, p = 0.771, ns; Left VEP: (df 38, n = 40) = 0.08, p = 0.933, ns; Midline VEP: (df 38, n = 40) = 0.32, p = 0.753, ns).

Table 14. Association between "sensations of passage" and ERG and VEP measures.

	Passage^{+} n = 22	Passage^{-} n = 38	p
Transient			
Right P50 Amp	14.43 (6.45)	14.64 (6.33)	†0.919 (ns)
Left P50 Amp	15.55 (7.87)	15.86 (6.06)	†0.900 (ns)
Right P50 Imp	46.36 (3.20)	46.06 (3.15)	†0.775 (ns)
Left P50 Imp	46.52 (3.54)	45.87 (3.00)	†0.563 (ns)
Right N95 Amp	16.66 (7.68)	18.16 (7.23)	†0.549 (ns)
Left N95 Amp	18.70 (8.94)	18.00 (8.14)	†0.813 (ns)
Right N95 Imp	110.32 (9.40)	110.06 (10.16)	†0.817 (ns)
Left N95 Imp	111.10 (8.67)	111.67 (11.89)	†0.868 (ns)
Steady-state			
Right PERG	0.33 (0.19)	0.35 (0.15)	†0.765 (ns)
Left PERG	0.33 (0.15)	0.34 (0.17)	†0.865 (ns)
Right VEP	0.32 (0.22)	0.34 (0.23)	†0.771 (ns)
Left VEP	0.37 (0.23)	0.36 (0.19)	†0.933 (ns)
Midline VEP	0.37 (0.25)	0.35 (0.20)	†0.753 (ns)

Values expressed as means (± SD)
Statistical tests: † t Test (ns = non-significant)

Amp = Amplitude (microV); Imp = Implicit time (msec); PERG = Pattern electroretinogram; VEP = Visual evoked potential

6.3.7 Correlation between visual acuity, contrast sensitivity and ERG/ VEP responses

The PD group had significantly lower visual acuity and contrast sensitivity than the HC group. Under parvocellular conditions, despite not detecting group differences in terms of PERG P50 or VEP P100 amplitudes, there was a strong negative correlation between P50 Amp and BAPVA in the PD group ($r = -.56$, $n = 36$, $p = <0.001$) that was not evident in controls ($r = -.26$, $n = 20$, $p = 0.253$, ns). Controlling for age and disease severity, the correlation between VA and parvocellular P50 amplitude remained significant ($r = -.41$). There was also a similar, but non-significant, trend for the PERG P50 amplitude under magnocellular conditions in the PD group (PD: $r = -.31$, $n = 36$, $p = 0.069$, ns; HC: $r = -.17$, $n = 20$, $p = 0.467$, ns). There was no significant correlation between VEP P100 amplitude and BAPVA under either parvo- or magnocellular stimulation. Similarly, there was a positive correlation between P50 Amp and CS, more striking under parvocellular than magnocellular conditions (parvocellular: $r = .59$, $n = 36$, $p = <0.001$; magnocellular: $r = .37$, $n = 36$, $p = 0.019$), that was absent in controls (parvocellular: $r = .27$, $n = 20$, $p = 0.266$, ns; magnocellular: $r = .33$, $n = 20$, $p = 0.132$, ns).

6.4 Discussion

We found no evidence to support the notion that the PD retina and subcortical visual system responds differently under magnocellular- and parvocellular-biased conditions. Nor did we find a difference in the predominantly peripheral retinal response in those PD subjects experiencing sensations of passage compared to those without. However, the correlation between PERG responses and visual impairment suggests that retinal dysfunction might be responsible for the reductions in acuity and contrast sensitivity in the PD group. The lack of correlation between VEP recordings and both VA and CS would support this notion and, taken together, our results provide a *tentative* link between *retinal* neurophysiological dysfunction and visual symptoms such as blurred

vision and difficulty reading, which remain poorly defined and understood in PD.

There are a number of possible explanations for some of our “negative” results. The first is that the spatial and temporal characteristics of our stimuli were in the wrong range to pick up group differences between HC and PD subjects. Although previous studies have demonstrated alterations in PERG and VEP amplitudes and latencies in PD, the alterations have been restricted to mid-spatial frequencies using alternating gratings as stimuli. This is very different from our experimental setup, utilising checkerboard stimuli with an entirely different range of spatial and temporal characteristics. Our principal aim was to develop an experimental protocol that enabled simultaneous recording of ERG and VEP responses, and this placed limitations on the format of stimuli used. As our primary hypothesis was that M-pathway dysfunction contributes to passage symptoms in PD, we did not explore the mid-spatial frequency stimuli used in previous studies in PD.

A second potential problem is the possibility that our experimental protocol was not sufficiently specific in its activation of M- and P-pathways to detect differences between passage^{+} and passage^{-} subjects. Although similar protocols have been studied in schizophrenia, the unique nature of our experimental setup makes direct comparisons of the protocols problematic (Butler et al., 2007, Butler and Javitt, 2005). Although there is good evidence for the existence of two separate pathways within the retina and subcortical visual system, due to shared spatio-temporal properties it is unlikely to be possible to specifically activate the M- or P-pathways in isolation (Blakemore and Vital-Durand, 1986, Levitt et al., 2001, Skottun and Skoyles, 2007, Skottun and Skoyles, 2007). Nonetheless, the pilot results of patching either the central or peripheral field during recordings suggests that we did achieve stimulation of the rod-driven, peripheral retina with our M-biased conditions and stimulation of the cone-driven, central retina under P-biased conditions **(see section 3.5.4)**.

Another key confounder of this study is the possible effect of medication in the PD group. Due to practicalities of the study, we did not request that patients discontinue their medication prior to the recording session and, inevitably, patients were tested in a variety of clinical states (medication response “on”, “wearing off” etc.). The PD-specific changes in the PERG are responsive to treatment with levodopa, an important factor that we were unable to control for in our study (Peppe et al., 1998, Peppe et al., 1995).

We feel our cohort of patients is representative of a typical PD clinic population but, as a group, are substantially older than those in other studies. In addition, we did not specifically exclude subjects with minor ocular disease (cataract, retinal drusen) from the study as these are common in elderly populations. This is important if our results are to be widely applicable, but introduces potential confounders into the analyses. However, the frequency of such ocular features was identical in both groups, and we do not feel that the results would have been different if these individuals were excluded from the analysis. As with all studies in PD, tremor, dyskinesia and somnolence did interfere with some of the recording sessions, although most subjects completed the ERG/VEP session without any problems.

Finally, the failure to detect differences in peripheral retinal responses between passage^{+} and passage^{-} PD subjects may suggest that this symptom either does not have a retinal origin, or simply that the study design was inadequate to detect such a change. Although the protocol did succeed in isolating the peripheral retinal response, this is not necessarily synonymous with activation of the magnocellular pathway. Nonetheless, our results suggest that there are no striking differences in a representative, treated PD cohort when checkerboard pattern stimuli are used to drive central and peripheral retinal responses. Future studies are clearly feasible given the tolerability of procedure but modifications would be required to our protocol. In particular, the use of a younger cohort, assessed on- and off-treatment, at identical times of the day would circumvent issues of medication effects. In addition, further work on the

design of our pattern stimuli in patients with, for example, specific rod and cone dystrophies may provide stronger evidence for our assertion that by varying the spatio-temporal characteristics of checkerboard stimuli, it is possible to bias responses from M- and P-cells in the human retina.

7. Visual exploration in Parkinson's disease and PD dementia

7.1 Background

Prominent among the non-motor complications of PD is cognitive impairment both in the form of a dementia syndrome (*Aarsland et al.,* 2003*, Hobson and Mear*a, 2004) and mild cognitive impairment (MCI) (*Foltynie et al.,* 2004*, Muslimovic et al*., 2005). Cognitive impairment in the context of PD is characterised by impairments in visuospatial and visuoperceptual function, attention (*Cormack et al.,* 2004*, Mosimann et al*., 2004b*, Uc et al*., 2005*, Williams-Gray et al*., 2007), executive function and memory (*Muslimovic et al.,* 2005), a combination that may play an integral role in the development of CVH (*Collerton et al.,* 2005*, Diederich et al*., 2005*, Barnes and Boubert*, 2008).

Selection of visual information in a complex scene is achieved by deploying sequences of saccades and fixations in a goal-directed fashion (*Noton and Stark,* 1971*, Rayner and Pollatse*k, 1992*, Henderson and Hollingwort*h, 1999). Important cortical areas that contribute to saccade generation include the frontal eye field (*Rivaud et al.,* 1994*, Pierrot-Deseilligny et al*., 1995, *Pierrot-Deseilligny et al.,* 1991a*, Pierrot-Deseilligny et al*., 1995*, Muri et al*., 1996), the supplementary eye field and the parietal eye field (*Pierrot-Deseilligny et al.,* 1991b*, Muri et al*., 1996). In addition, the prefrontal and posterior parietal cortices are also vital in the programming of spatially accurate saccades (*Pierrot-Deseilligny et al.,* 1995*, Pierrot-Deseilligny et al*., 2005). These areas project, via the superior colliculus, thalamus and basal ganglia to lower brainstem structures concerned with saccadic eye movements (*Hikosaka et al.,* 2000).

Eye movement abnormalities are well recognised in patients with PD, both in terms of deficient smooth pursuit, restricted vergence, reduced range of eye movements and alterations in saccadic output (*Corin et al.,* 1972*, White et al*., 1983*, Rascol et al*., 1989*, Repka et al*., 1996*, Bares et al*.,

2003). Evidence for disease-specific disruption of saccades in PD is contradictory. Whereas some studies have demonstrated increases in saccadic latency, reductions in amplitude and increased error rates (*Rascol et al.,* 1989*, Kennard and Lueck*, 1989*, Briand et al*., 1999*, Hood et al*., 2007*, MacAskill et al*., 2002*, van Stockum et al*., 2008), others have not replicated these findings (*Vidailhet et al.,* 1994*, Briand et al*., 1999*, Briand et al*., 2001*, Lueck et al*., 1990*, Vidailhet et al*., 1999*, Mosimann et al*., 2005).

Both the properties of the stimulus used, medication effects and cognitive heterogeneity of study cohorts are important determinants of saccadic metrics and may help explain some of the inconsistencies in the reported literature (*Chambers and Prescott,* 2010*, Michell et al*., 2006*, Hood et al*., 2007*, Hodgson et al*., 1999*, Mosimann et al*., 2005). Indeed, patients with AD, PDD and DLB show longer fixation durations, increased saccadic latencies and more saccadic errors than controls (*Lueck et al.,* 2000*, Ogrocki et al*., 2000*, Abel et al*., 2002*, Mosimann et al*., 2005) suggesting cortical neurodegeneration can impair oculomotor function. Aside from the absolute metrics of saccades and fixations, visual exploration strategies can be used to provide insights into the cognitive processes required for more “real-world” tasks such as emotion recognition, text- and clock-reading (Hodgson et al., 2002, *Mosimann et* al., 2004a*, Lueck et al.,* 2000, Ogrocki et al., 2000).

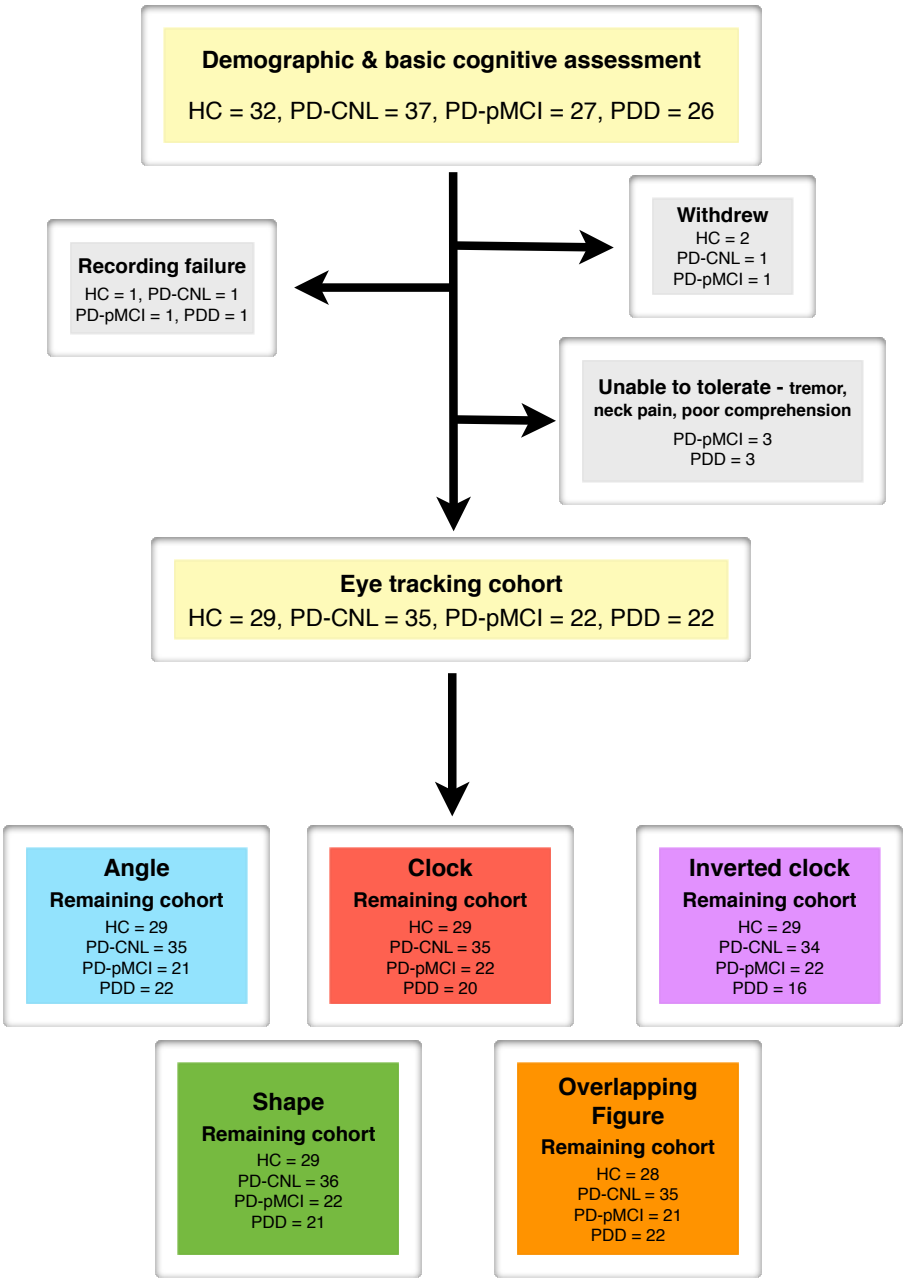
Saccadic characteristics, and hence visual exploration strategies, are therefore influenced by a variety of factors - frontal and parietal eye fields, ventral and dorsal visual streams, attentional, executive and basal ganglia networks and the effect of medications. Many of these visual, cognitive and oculomotor functions co-localize to neuroanatomically linked cortical regions targeted by the degenerative process of PD and PDD. It follows that measurements of visual exploration behaviour might provide novel insights into the contribution various cognitive domains make to the neuropsychological deficits evident in PD and PDD, and may even act as a surrogate biomarker for those at risk of cognitive impairment. Given that cortical saccade programming and integration of visuospatial input with

motoric output are achieved in contiguous cortical regions, disruption of efficient visual exploration strategies may contribute to motor complications such as visually-induced gait freezing. Similarly, there may be a similar association between impaired visual exploration, visuoperceptual impairment and the development of visual hallucinations.

7.2 Specific methods

For the eye-tracking study, the non-demented PD cohort was subdivided into a group with normal cognition (PD-CNL) and a group with possible mild cognitive impairment (PD-pMCI) using performance on measures of global cognition (MMSE, AEMSS) and the DRS-2 cognitive sub-scale scores. This gave four study groups - HC = 32, PD-CNL = 37, PD-pMCI = 27 and PDD = 26. Not all subjects contributed to the final eye tracking data set due to a variety of reasons outlined in the flow chart **(Figure 19)**. Reasons for data loss included withdrawal from the study, inability to tolerate the test or failure of the eye tracking equipment. The recruitment figures for this part of the study were therefore - HC = 29, PD-CNL = 35, PD-pMCI = 22 and PDD = 22. In addition, a proportion of participants completed only part of the eye tracking battery due to poor comprehension, fatigue, drowsiness etc. As expected, the group most affected by data loss was the PDD cohort. When comparison was made between the demographic features of those PDD subjects completing the battery (PDD-c, n = 16) and those failing to do so (PDD-i, n = 10), there were no differences in age (Wilcoxon Rank Sum; PDD-c 16, PDD-i 10, $z = 0.40$, $p = 0.692$, ns), education (Wilcoxon Rank Sum; PDD-c 16, PDD-i 10, $z = 0.08$, $p = 0.934$, ns), UPDRS III (Wilcoxon Rank Sum; PDD-c 16, PDD-i 10, $z = 0.77$, $p = 0.444$, ns) or global cognition (AEMSS: Wilcoxon Rank Sum; PDD-c 16, PDD-i 10, $z = 0.64$, $p = 0.507$, ns). Subjects failing to complete the eye tracking battery did, however, have significantly longer PD and dementia durations (PD duration: Wilcoxon Rank Sum; PDD-c 16, PDD-i 10, $z = 2.27$, $p = 0.023$; dementia duration: Wilcoxon Rank Sum; PDD-c 16, PDD-i 10, $z = 2.68$, $p = 0.007$).

Figure 19. Flow chart for eye tracking study.



Visual exploration strategies were defined by 1) time to first fixation in the correct interest area (IA), 2) Run count (RC) into the central stimulus, and 3) RC ratio. The RC ratio is generated from the mean RC into the 3 incorrect IAs vs. the RC into the correct IA. As such, low RC ratios are likely to reflect a strategy where the correct IA is explored in preference to incorrect regions and a RC ratio of 0.5 reflects a strategy where exploration of the correct IA is twice as frequent as that of the incorrect IAs. High RC ratios suggest either a less structured strategy, where incorrect IAs are re-visited repeatedly, or a cautious approach aimed at minimising errors.

In addition to assessing these strategies across the four diagnostic groups, we defined subjects as “effective” or “ineffective” explorers based on error rates during the eye tracking battery. We reasoned that this would provide insight into which factors predicted visual exploration efficiency and how deficient visual exploration might impact on visual and motor symptoms. We therefore dichotomised our PD subjects (n = 81) into low-error (LE) and high-error (HE) groups on a task-by-task basis. The median error rates were between 0 and 1 for all five eye tracking tasks, and “high-error” was defined as ≥ 2 errors (out of a possible 16) in a particular task. For the simplest task (clock), the HE group was very small (n = 5) whereas for the overlapping figure task, the HE group consisted of 29 subjects (of a possible 81). This resulted in two relatively heterogeneous groups, with a mix of PD-CNL, PD-pMCI and PDD subjects in each. Over 95% of the PD-CNL and PD-pMCI and 85% of the PDD group fell into the LE group for clock reading (i.e. “effective explorers”), whereas 17% of the PD-CNL, 43% of the PD-pMCI and 68% of the PDD group were classified as high-error makers on the overlapping figures task (i.e. “ineffective explorers”). We omitted the clock task from further analysis due to the small numbers in the LE group.

7.2.1 Statistics

Planned group comparisons for the eye tracking analysis were a) HC vs. PD-CNL, b) PD-CNL vs. PD-pMCI, c) PD-CNL vs. PDD and d) PD-pMCI

vs. PDD. In addition to standard statistical tests, stepwise linear regression was conducted using a standard least squares approach with backward elimination to identify which cognitive sub-scale scores best predicted RC ratio in the overlapping figure task. We entered attention (ATT), initiation/ perseveration (IP), conceptualization (CONCEPT), memory (MEM) and clock drawing (CDT) scores into the initial model. We examined the potential link between CVH and exploration strategy by performing logistic regression, with presence of CVH as the dependent variable and time to first fixation in the correct IA, central RC and RC ratio on the overlapping figures task as the predictors. We also performed a regression analysis using freezing of gait (FOG) as the dependent variable and time to first fixation in the correct IA, central RC and RC ratio on the angle task as the predictors. The relationship between global cognition (AEMSS), disease severity (UPDRS III), levodopa equivalent dose (LED) and fixation duration was investigated using Pearson product-moment correlation coefficient. Overlapping figures task fixation duration was selected as the dependent variable as this was the task with the highest error rates in all three PD groups.

7.3 Results

7.3.1 Demographic characteristics

All four groups were well matched for age (ANOVA (df 3, n = 108) = 0.97, p = 0.409; ns) and education (Kruskal Wallis (df 3, n = 108) = 3.21, p = 0.361; ns) **(Table 15)**. Males were over represented in the PDD and PD-pMCI groups compared to HC (HC vs. PDD: Fisher's exact (df 1, n = 51) = 7.95, p = 0.007; HC vs. PD-pMCI: (df 1, n = 54) = 4.41, p = 0.046) and there was also a significant gender difference between PD-CNL and PDD groups (Fisher's exact (df 1, n = 57) = 4.49, p = 0.042). PD duration was longer for PDD than PD-CNL patients (t-Test (df 55, n = 57) = 2.52, p = 0.015). Estimated dementia duration was 1.7 years (range 0-3 years, where 0 = newly diagnosed at study entry). There was a strong trend to higher LED in PD-pMCI and PDD subjects compared to PD-CNL although

this only reached significance for comparison between PD-CNL and PDD groups (t-Test (df 55, n = 57) = 2.94, p = 0.005). PD-CNL and PD-pMCI subjects were well matched for disease severity (UPDRS II: Wilcoxon Rank Sum PD-CNL 35, PD-MCI 22, Z = 1.65, p = 0.099, ns; UPDRS III: Wilcoxon Rank Sum PD-CNL 35, PD-MCI 22, Z = 1.32, p = 0.187, ns) but there were significant differences in UPDRS II and UPDRS III scores between PD-CNL/PD-pMCI subjects and those in the PDD cohort (UPDRS II: Wilcoxon Rank Sum PD-CNL 35, PDD 22, Z = 4.62, p = <0.001; PD-pMCI 22, PDD 22, Z = 3.50, p = < 0.001; UPDRS III: PD-CNL 35, PDD 22, Z = 3.27, p = <0.001; PD-pMCI 22, PDD 22, Z = 2.28, p = 0.023).

7.3.2 Cognitive features

When the global cognitive ability of the PD-CNL group was compared to HC, both MMSE (Wilcoxon Rank Sum HC 29, PD-CNL 35, Z = 1.23, p = 0.219, ns) and AEMSS (Wilcoxon Rank Sum HC 29, PD-CNL 35, Z = 0.70, p = 0.487, ns) scores were equivalent **(Table 15)**. In contrast, the PD-CNL and HC groups differed significantly in these measures when compared to the PD-pMCI group (MMSE: Wilcoxon Rank Sum HC 29, PD-pMCI 22, Z = 3.43, p = <0.001; PD-CNL 35, PD-pMCI 22, Z = 2.95, p = 0.003; AEMSS: HC 29, PD-pMCI 22, Z = 4.99, p = <0.001; PD-CNL 35, PD-pMCI 22, Z = 5.56, p = <0.001). PDD subjects differed from all three groups both for MMSE (Wilcoxon Rank Sum HC 29, PDD 22, Z = 6.14, p = <0.001; PD-CNL 35, PDD 22, Z = 6.39, p = <0.001; PD-pMCI 35, PDD 22, Z = 4.55, p = <0.001) and AEMSS scores (Wilcoxon Rank Sum HC 29, PDD 22, Z = 6.08, p = <0.001; PD-CNL 35, PDD 22, Z = 6.33, p = <0.001; PD-pMCI 35, PDD 22, Z = 4.34, p = <0.001).

PD-CNL subjects matched HC subjects on all cognitive sub-scale scores of the DRS-2 (ATT: Wilcoxon Rank Sum HC 29, PD-CNL 35, Z = 0.24, p = 0.813, ns; IP: HC 29, PD-CNL 35, Z = 0.27, p = 0.785, ns; CONCEPT: HC 29, PD-CNL 35, Z = 1.44, p = 0.149, ns; MEM: HC 29, PD-CNL 35, Z = 0.34, p = 0.734, ns; CONST: n/a – identical results) and although there

was a strong trend to poorer scores on the CDT, the difference was not significant (Wilcoxon Rank Sum: HC 29, PD-CNL 35, Z = 1.96, p = 0.050, ns). PD-pMCI subjects scored lower than PD-CNL and HC subjects on all cognitive sub-scale scores of the DRS-2 (ATT: Wilcoxon Rank Sum HC 29, PD-pMCI 22, Z = 2.51, p = 0.012; PD-CNL 35, PD-pMCI 22, Z = 2.52, p = 0.012; IP: HC 29, PD-pMCI 22, Z = 5.34, p = <0.001; PD-CNL 35, PD-pMCI 22, Z = 5.61, p = <0.001; CONCEPT: HC 29, PD-pMCI 22, Z = 3.06, p = 0.002; PD-CNL 35, PD-pMCI 22, Z = 2.31, p = 0.021; MEM: HC 29, PD-pMCI 22, Z = 2.05, p = 0.040; PD-CNL 35, PD-pMCI 22, Z = 3.16, p = 0.002; CDT: HC 29, PD-pMCI 22, Z = 3.64, p = <0.001; PD-CNL 35, PD-pMCI 22, Z = 2.32, p = 0.020) apart from the CONST scale, previously noted to discriminate poorly between cognitively normal and cognitively impaired individuals (Wilcoxon Rank Sum HC 29, PD-pMCI 22, Z = 1.61, p = 0.107, ns; PD-CNL 35, PD-pMCI 22, Z = 1.77, p = 0.072, ns). PDD subjects preformed worse on IP (Wilcoxon Rank Sum PD-pMCI 22, PDD 22, Z = 3.51, p = <0.001), MEM (Wilcoxon Rank Sum PD-pMCI 22, PDD 22, Z = 3.57, p = <0.001) and CDT (Wilcoxon Rank Sum PD-pMCI 22, PDD 22, Z = 3.19, p = 0.001) than the PD-pMCI subjects but there was no difference in measures of ATT (Wilcoxon Rank Sum PD-pMCI 22, PDD 22, Z = 1.20, p = 0.231, ns), CONCEPT (Wilcoxon Rank Sum PD-pMCI 22, PDD 22, Z = 1.11, p = 0.267, ns) and CONST (Wilcoxon Rank Sum PD-pMCI 22, PDD 22, Z = 1.66, p = 0.097, ns).

Table 15. Demographics and cognitive features of eye tracking study groups.

	HC n=29	PD-CNL n=35	PD-pMCI n=22	PDD n=22	p value
Age (years)	72.3 (7.8)	69.4 (9.0)	70.8 (7.1)	72.3 (6.0)	‡0.409 (ns)
Education (years)	11.6 (2.7)	12.3 (3.1)	12.0 (3.4)	11.2 (3.0)	*0.361 (ns)
Gender (%Male)	48	60	77	86	**0.451[a] (ns), 0.046[b], 0.007[c], 0.025[d] (ns), 0.042[e], 0.698[f] (ns)
PD duration (years)	n/a	7.6 (5.6)	8.8 (5.4)	11.6 (6.1)	†0.426[d] (ns), 0.015[e], 0.118[f] (ns)
Estimated dementia duration (years)	n/a	n/a	n/a	1.7 (0.9)	
UPDRS II	n/a	11.9 (6.4)	14.9 (5.4)	28.8 (5.8)	§0.099[d] (ns), <0.001[e,f]
UPDRS III	n/a	21.3 (10.5)	25.6 (8.8)	35.4 (14.7)	§0.187[d] (ns), 0.001[e], 0.023[f]
LED	n/a	579 (406)	774 (479)	917 (450)	†0.105[d] (ns), 0.005[e], 0.312[f] (ns)
Global cognition					
MMSE	29.6 (0.8)	29.5 (0.7)	28.3 (1.6)	24.5 (2.7)	§0.219[a] (ns), <0.001[b,c,e,f] 0.003[d]
AEMSS (DRS)	12.8 (2.9)	12.4 (2.1)	7.6 (2.5)	3.9 (1.7)	§0.487[a] (ns), <0.001[b,c,d,e,f]
Cognitive sub-scale scores (DRS)					
ATT	12.2 (1.3)	12.1 (1.2)	10.9 (1.9)	9.9 (2.6)	§0.813[a] (ns), 0.012[b], <0.001[c], 0.012[d], <0.001[e], 0.231[f] (ns)
I/P	11.0 (1.4)	11.0 (1.3)	6.8 (2.5)	4.1 (2.0)	§0.785[a] (ns), <0.001[b,c,d,e,f]
CONST	10.0 (0.0)	10.0 (0.0)	9.7 (0.9)	8.7 (2.3)	§n/a[a] , 0.107[b] (ns), 0.003[c], 0.072[d], 0.001[e], 0.097[f] (ns)
CDT (Shulman)	4.9 (0.3)	4.7 (0.4)	4.2 (0.9)	2.9 (1.5)	§0.050[a] (ns), <0.001[b,c], 0.020[d], <0.001[e], 0.001[f]
CONCEPT	11.5 (1.5)	10.9 (1.6)	9.2 (2.8)	8.1 (3.2)	§0.149[a] (ns), 0.002[b], <0.001[c], 0.021[d], <0.001[e], 0.267[f] (ns)
MEM	10.0 (3.2)	10.6 (1.9)	8.1 (3.1)	4.6 (2.5)	§0.734[a] (ns), 0.040[b], <0.001[c], 0.002[d], <0.001[e,f]

Values expressed as means (+/- SD) (unless otherwise stated)

Statistical tests: ‡ANOVA; † t Test; *Kruskal-Wallis; §Wilcoxon rank sum; **Pearson χ^2 +/- Fisher's exact test where groups frequency < 5

(ns = non-significant)

a = HC vs. PD-CNL; b = HC vs. PD-pMCI; c = HC vs. PDD; d = PD-CNL vs. PD-pMCI; e = PD-CNL vs. PDD; f = PD-pMCI vs. PDD

UPDRS - Unified Parkinson's Disease Rating Scale; LED - Levodopa equivalent dose; MMSE - Mini-mental state examination; CDT - Clock drawing test (Shulman scoring method); AEMSS - Age and education-adjusted MOANS scaled score (from DRS); ATT - Attention; I/P - Initiation/perseveration; CONST - Construction; CONCEPT - Conceptualization; MEM - Memory.

7.3.3 Eye tracking battery performance

Error rates, expressed as a percentage of the total trials, illustrate the types of visual task found most challenging by the study subjects **(Table 16 & Figure 20).** For all groups, fewest errors were made on the clock task, followed by the angle, shape, inverted clock and overlapping figures task. Error rate percentage between HC and PD-CNL subjects was equivalent across all tasks (Angle: Wilcoxon Rank Sum HC 29, PD-CNL, Z = 0.35, p = 0.727; Clock: HC 29, PD-CNL 35, Z = 0.42, p = 0.672, ns; Inverted clock: HC 29, PD-CNL 34, Z = 0.32, p = 0.747, ns; Shape: HC 29, PD-CNL 35, Z = 0.1.12, p = 0.265, ns; Overlap: HC 28, PD-CNL 35, Z = 1.09, p = 0.275, ns). Error rate percentages on angle and overlapping figures tasks were significantly higher in the PD-pMCI group compared to PD-CNL (Angle: Wilcoxon Rank Sum PD-CNL 35, PD-pMCI 22, Z = 2.50, p = 0.012; Overlap: PD-CNL 35, PD-pMCI 22, Z = 3.00, p = 0.003) and there was a trend toward significance for the inverted clock task (Inverted clock: Wilcoxon Rank Sum PD-CNL 34, PD-pMCI 22, Z = 1.76, p = 0.079, ns). Both the clock and shape tasks were performed equally well by both PD-CNL and PD-pMCI subjects (Clock: PD-CNL 35, PD-pMCI 22, Z = 0.99, p = 0.324, ns; Shape: PD-CNL 35, PD-pMCI 22, Z = 0.52, p = 0.602, ns). Comparison of error rates between PD-CNL and PDD groups reached significance for all five tasks (Angle: Wilcoxon Rank Sum PD-CNL 35, PDD 22, Z = 5.18, p = <0.001; Clock: PD-CNL 35, PDD 20, Z = 4.01, p = <0.001; Inverted clock: PD-CNL 34, PDD 17, Z = 3.12, p = 0.002; Shape: PD-CNL 35, PDD 21, Z = 3.18, p = 0.002; Overlap: PD-CNL 35, PDD 22, Z = 5.03, p = <0.001). All comparisons between PD-pMCI and PDD reached significance (Angle: Wilcoxon Rank Sum PD-pMCI 22, PDD 22, Z = 3.15, p = 0.002; Clock: PD-pMCI 22, PDD 20, Z = 2.73, p = 0.006; Shape: PD-pMCI 22, PDD 21, Z = 2.59, p = 0.002; Overlap: PD-pMCI 22, PDD 22, Z = 2.09, p = 0.037) with the exception of performance on the inverted clock task, where PD-pMCI subjects' performance closely resembled that of the PDD group (Inverted clock: PD-pMCI 22, PDD 17, Z = 1.09, p = 0.277, ns).

Table 16. Error rates and response times for the eye tracking battery.

	HC n=29	PD-CNL n=35	PD-MCI n=22	PDD n=22	p value
Error rate (%)					
Angle	1.7 (2.8)	1.6 (3.1)	4.9 (6.0)	13.1 (10.0)	§0.727[a] (ns), 0.012[b], <0.001[c], 0.002[d]
Clock	0.2 (1.1)	0.5 (2.3)	1.4 (3.2)	5.3 (7.4)	§0.672[a] (ns), 0.324[b] (ns), <0.001[c], 0.006[d]
Inverted Clock	3.8 (6.3)	3.4 (5.3)	12.2 (19.8)	19.5 (26.0)	§0.747[a] (ns), 0.079[b] (ns), 0.002[c], 0.277[d] (ns)
Shape	2.7 (6.3)	3.6 (5.3)	3.5 (3.7)	16.4 (16.9)	§0.265[a] (ns), 0.602[b] (ns), 0.002[c], 0.010[d]
Overlap	5.0 (6.1)	3.3 (4.4)	10.9 (11.8)	20.2 (16.9)	§0.275[a] (ns), 0.003[b], <0.001[c], 0.037[d]
Response time (msec)					
Angle	2404 (532)	2523 (593)	3251 (1018)	4719 (1824)	†0.406[a] (ns), 0.006[b], <0.001[c], 0.002[d]
Clock	2741 (627)	3114 (826)	3830 (1240)	5054 (1697)	†0.050[a] (ns), 0.023[b], <0.001[c], 0.010[d]
Inverted Clock	4419 (933)	4590 (804)	6895 (3052)	8170 (2586)	†0.439[a] (ns), 0.002[b], <0.001[c], 0.184[d] (ns)
Shape	3642 (955)	3960 (1126)	4616 (1631)	7672 (4084)	†0.234[a] (ns), 0.106[b] (ns), <0.001[c], 0.004[d]
Overlap	4886 (1409)	5221 (1232)	7121 (2365)	9921 (4031)	†0.319[a] (ns), 0.002[b], <0.001[c], 0.009[d]

Values expressed as means (± SD)

Statistical tests: † t Test; *Kruskal-Wallis; §Wilcoxon rank sum

(ns = non-significant)

a = HC vs. PD-CNL; b = PD-CNL vs. PD-pMCI; c = PD-CNL vs. PDD; d = PD-pMCI vs. PDD

Figure 20. Error rates for the eye tracking battery.

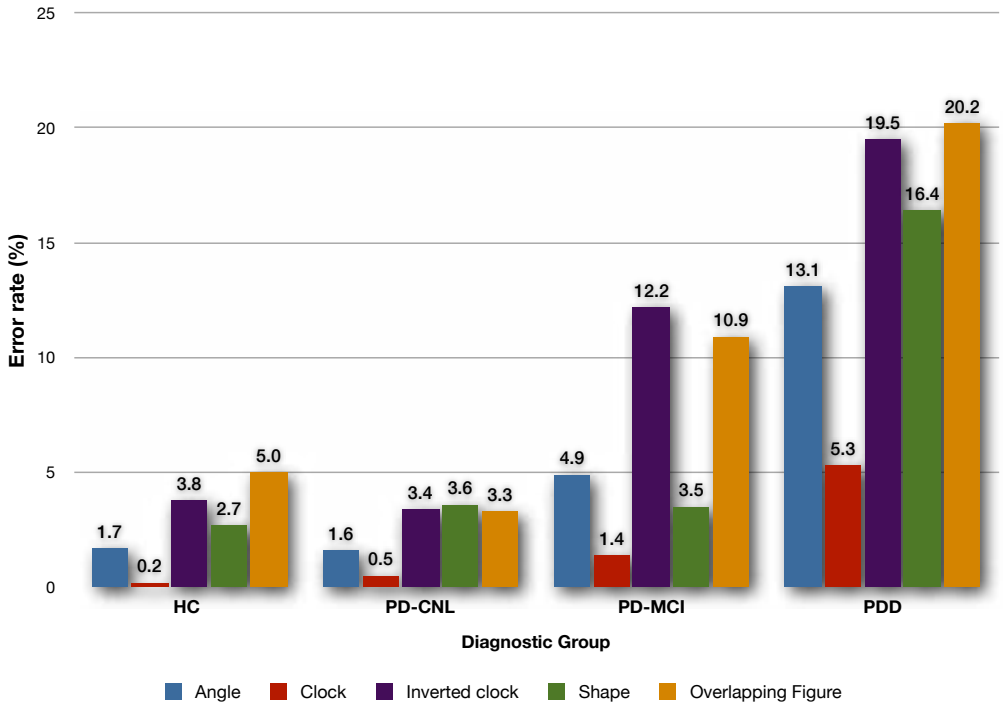
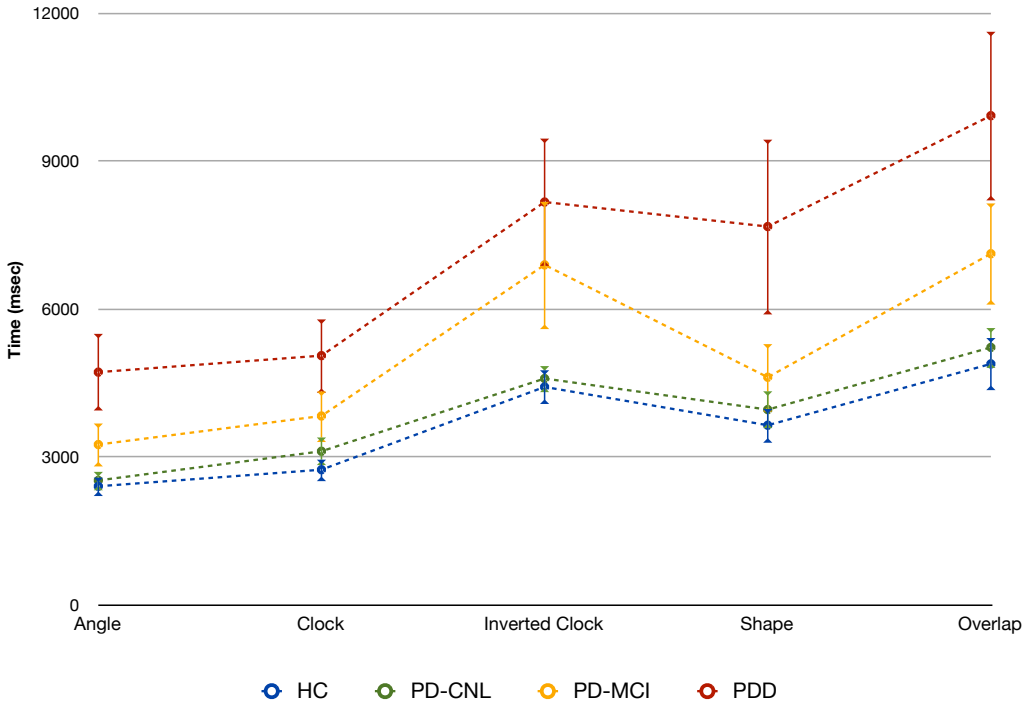


Figure 21. Response time for the eye tracking battery.



7.3.4 Response times

Response times (RT) for the eye tracking battery were shortest for the angle task, followed by clock, shape position, inverted clock and overlapping figures tasks respectively **(Table 16 & Figure 21)**. HC subjects had the shortest RT across all tasks with a trend to progressively longer RT moving from PD-CNL, through PD-pMCI to PDD groups. The RT comparison between HC and PD-CNL subjects failed to reach significance for any of the tasks, although there was a strong trend to significance for clock matching (Angle: t-Test (df 62, n = 64) = 0.84, p = 0.406, ns; Clock: (df 62, n = 64) = 2.00, p = 0.050, ns; Inverted clock: (df 61, n = 63) = 0.78, p = 0.439, ns; Shape: (df 63, n = 65) = 1.20, p = 0.234, ns; Overlap: (df 61, n = 63) = 1.01, p = 0.319, ns). RT differences between PD-CNL and PD-pMCI on the shape position task demonstrated a trend to significance (t-Test (df 33, n = 58) = 1.66, p = 0.106, ns) and comparisons for all other visual battery tasks were significant (Angle: t-Test (df 28, n = 56) = 2.98, p = 0.006; Clock: (df 33, n = 57) = 2.39, p = 0.023; Inverted clock: (df 23, n = 56) = 3.47, p = 0.002; Overlap: (df 27, n = 56) = 3.41, p = 0.002). RT was significantly longer for PDD subjects when compared to both PD-CNL (Angle: t-Test (df 24, n = 57) = 5.47, p = <0.001; Clock: (df 24, n = 55) = 4.80, p = <0.001; Inverted clock: (df 16, n = 50) = 5.42, p = <0.001; Shape: (df 22, n = 57) = 4.08, p = <0.001; Overlap: (df 23, n = 57) = 5.31, p = <0.001) and PD-pMCI (Angle: t-Test (df 33, n = 43) = 3.28, p = 0.002; Clock: (df 40, n = 42) = 2.69, p = 0.010; Shape: (df 26, n = 43) = 3.19, p = 0.004; Overlap: (df 34, n = 43) = 2.79, p = 0.009) with the exception of the RT between PD-pMCI and PDD for the inverted clock task (t-Test (df 36, n = 38) = 1.35, p = 0.184, ns).

7.3.5 Exploration strategy by diagnostic group

In general, HC subjects were first to fixate the correct IA, with PD-CNL, PD-pMCI and PDD subjects taking progressively longer **(Table 17 & Figure 22)**. The comparison between HC and PD-CNL reached significance only for the clock task (Angle: t-Test (df 62, n = 64) = 1.58, p = 0.120, ns; Clock: (df 62, n = 64) = 2.38, p = 0.021; Inverted clock: (df 61, n = 62) = 0.92, p = 0.362, ns; Shape: (df 63, n = 65) = 1.60, p = 0.114, ns; Overlap: (df 61, n = 63) = 1.59, p = 0.118, ns) and there was a strong trend to significance when comparing PD-CNL and PD-pMCI subjects (Angle: t-Test (df 54, n = 56) = 1.80, p = 0.078, ns; Clock: (df 55, n = 57) = 2.00, p = 0.051, ns; Inverted clock: (df 26, n = 56) = 3.62, p = 0.054, ns; Shape: Angle: (df 29, n = 57) = 1.35, p = 0.187, ns; Overlap: (df 28, n = 56) = 1.65, p = 0.110, ns). There were, however, significant differences between both PD-CNL and PDD groups for all five tasks (Angle: t-Test (df 29, n = 56) = 5.56, p = <0.001; Clock: (df 25, n = 55) = 4.85, p = <0.001; Inverted clock: (df 18, n = 50) = 3.62, p = 0.002; Shape: (df 24, n = 57) = 4.33, p = <0.001; Overlap: (df 27, n = 57) = 3.36, p = 0.002) and PD-pMCI and PDD groups for angle, clock and shape position tasks (Angle: t-Test (df 41, n = 43) = 3.00, p = 0.005; Clock: (df 40, n = 42) = 2.75, p = 0.001; Inverted clock: (df 36, n = 40) = 1.39, p = 0.174, ns; Shape: (df 42, n = 43) = 2.87, p = 0.007; Overlap: (df 41, n = 43) = 1.61, p = 0.116, ns).

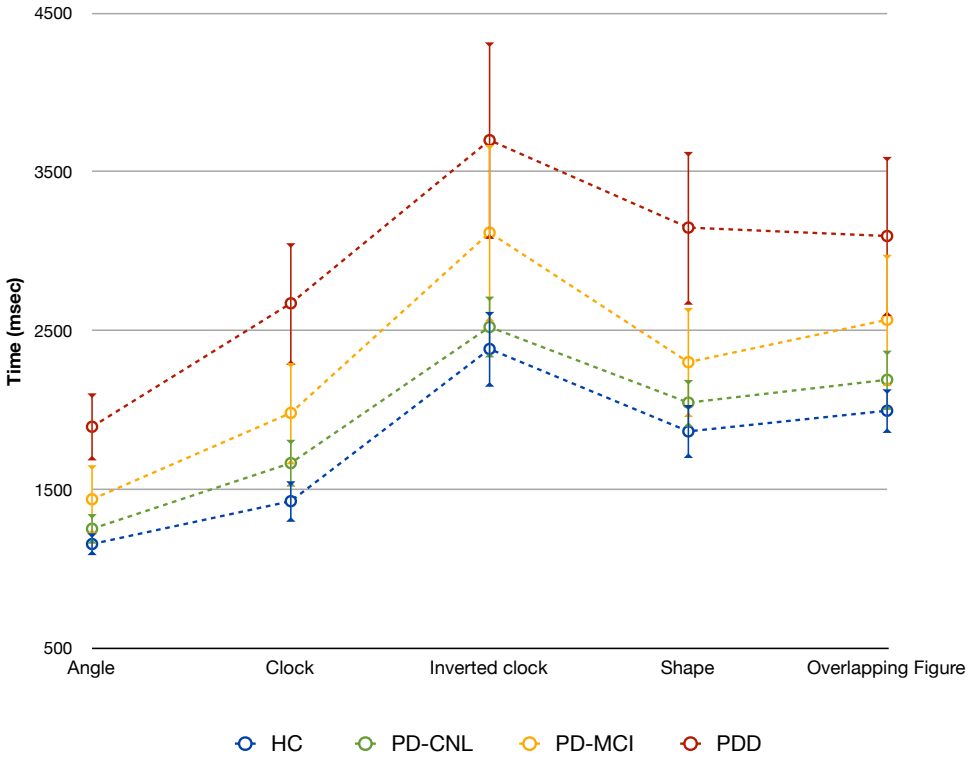
Table 17. Exploration strategy by study groups.

	HC n = 29	PD-CNL n = 35	PD-MCI n = 22	PDD n = 22	p
Fixation duration (msec)					
Angle	185 (24)	201 (33)	218 (36)	239 (40)	†0.033[a], 0.066[b] (ns), <0.001[c], 0.077[d] (ns)
Clock	180 (24)	198 (35)	209 (35)	237 (37)	†0.022[a], 0.252[b] (ns), <0.001[c], 0.016[d]
Inverted Clock	191 (23)	208 (33)	236 (47)	254 (47)	†0.021[a], 0.013[b], <0.001[c], 0.236[d] (ns)
Shape	170 (26)	185 (32)	204 (26)	226 (38)	†0.035[a], 0.031[b], <0.001[c], 0.026[d]
Overlap	201 (25)	217 (29)	238 (39)	267 (40)	†0.022[a], 0.027[b], <0.001[c], 0.022[d]
Time to first fixation in correct interest area (msec)					
Angle	1155 (189)	1251 (275)	1437 (501)	1894 (496)	†0.120[a] (ns), 0.078[b] (ns), <0.001[c], 0.005[d]
Clock	1425 (351)	1665 (439)	1981 (758)	2672 (867)	†0.021[a], 0.051[b] (ns), <0.001[c], 0.001[d]
Inverted Clock	2384 (640)	2523 (558)	3117 (1307)	3700 (1244)	†0.362[a] (ns), 0.054[b] (ns), 0.002[c],0.174[d] (ns)
Shape	1865 (450)	2046 (454)	2301 (809)	3149 (1115)	†0.114[a] (ns), 0.187[b] (ns), <0.001[c], 0.007[d]
Overlap	1995 (371)	2190 (561)	2568 (955)	3096 (1182)	†0.118[a] (ns), 0.110[b] (ns), 0.002[c],0.116[d] (ns)
Run count (central)					
Angle	2.58 (0.44)	2.47 (0.52)	2.69 (0.43)	3.26 (0.98)	†0.354[a] (ns), 0.096[b] (ns), <0.001[c], 0.019[d]
Clock	2.16 (0.37)	1.94 (0.50)	2.28 (0.59)	2.33 (0.44)	†0.053[a] (ns), 0.025[b], 0.006[c], 0.757[d] (ns)
Inverted Clock	2.05 (0.53)	1.83 (0.54)	2.53 (1.06)	2.61 (0.79)	†0.097[a] (ns), 0.007[b], <0.001[c], 0.794[d] (ns)
Shape	3.78 (0.73)	3.56 (0.66)	3.56 (0.58)	4.44 (1.21)	†0.195[a] (ns), 0.999[b] (ns), <0.001[c], 0.005[d]
Overlap	4.63 (0.70)	4.52 (0.66)	4.63 (0.83)	5.08 (0.77)	†0.529[a] (ns), 0.604[b] (ns), 0.005[c], 0.072[d] (ns)
Run count ratio					
Angle	0.51 (0.13)	0.51 (0.10)	0.55 (0.12)	0.61 (0.12)	†0.975[a] (ns), 0.156[b] (ns), <0.001[c], 0.087[d] (ns)
Clock	0.39 (0.11)	0.41 (0.11)	0.44 (0.12)	0.43 (0.10)	‡0.508 (ns)
Inverted Clock	0.47 (0.09)	0.48 (0.12)	0.61 (0.18)	0.64 (0.24)	†0.786[a] (ns), 0.001[b], 0.020[c], 0.678[d] (ns)
Shape	0.35 (0.11)	0.34 (0.09)	0.33 (0.09)	0.47 (0.19)	†0.727[a] (ns), 0.693[b] (ns), 0.010[c], 0.008[d]
Overlap	0.59 (0.11)	0.53 (0.09)	0.63 (0.12)	0.66 (0.12)	†0.038[a], <0.001[b], <0.001[c], 0.391[d] (ns)

Values expressed as means (±SD)
Statistical tests: ‡ANOVA; † t Test
(ns = non-significant)

a = HC vs. PD-CNL, b = PD-CNL vs. PD-MCI, c = PD-CNL vs. PDD, d = PD-MCI vs. PDD

Figure 22. Time to first fixation in the correct interest area by study group.

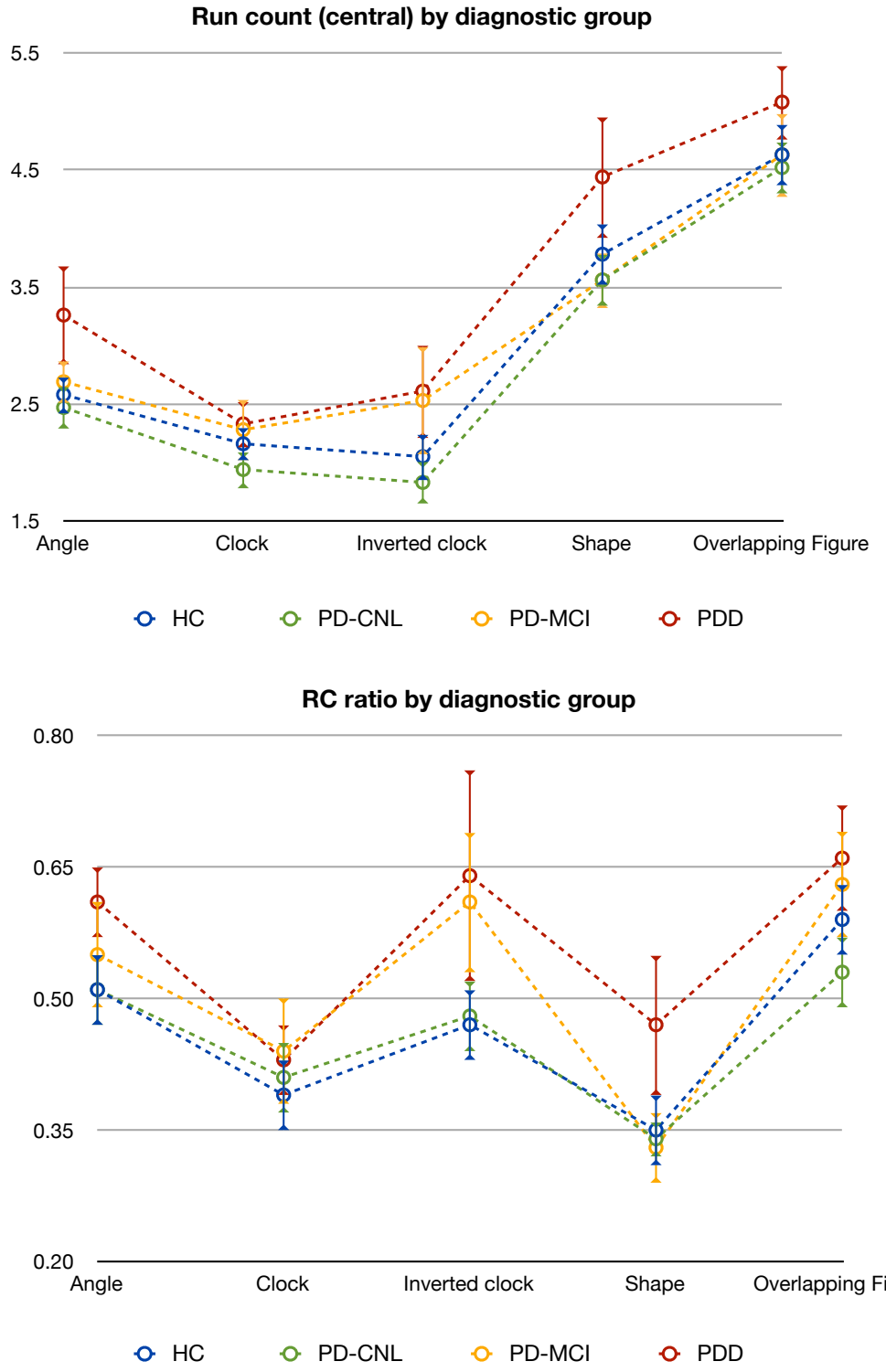


There was a trend to lower central RC in PD-CNL than HC for both clock and inverted clock tasks (clock: t-Test (df 62, n = 64) = 1.98, p = 0.053, ns; inverted clock: (df 61, n = 63) = 1.69, p = 0.097, ns) but in other respects, the PD-CNL subjects' RC strategy matched that of HC subjects (angle: t-Test (df 62, n = 64) = 0.93, p = 0.354, ns; shape: (df 63, n = 65) = 1.31, p = 0.195, ns; overlap: (df 61, n = 63) = 0.63, p = 0.529, ns). Similarly, the clock and inverted clock central RC was significantly lower for PD-CNL than PD-pMCI subjects, with other aspects of the eye tracking battery failing to show such striking differences (clock: t-Test (df 55, n = 57) = 2.30, p = 0.025; inverted clock: (df 28, n = 56) = 2.88, p = 0.007; angle: (df 54, n = 56) = 1.69, p = 0.096, ns; shape: (df 56, n = 58) = 0.00, p = 0.999, ns; overlap: (df 54, n = 56) = 0.52, p = 0.604, ns). As with time to first correct fixation, there were significant differences in central RC between both PD-CNL and PDD for all five tasks (Angle: t-Test (df 55, n = 57) = 4.02, p = <0.001; Clock: (df 53, n = 55) = 2.88, p = 0.006; Inverted clock: (df 48, n = 50) = 4.16, p = <0.001; Shape: (df 55, n = 57) = 3.57, p =

<0.001; Overlap: (df 55, n = 57) = 2.91, p = 0.005). PD-pMCI and PDD groups had similar central RCs for clock and inverted clock tasks but PDD subjects revisited the central angle, shape and overlapping figures stimuli more frequently than their PD-pMCI counterparts (Angle: t-Test (df 29, n = 43) = 2.49, p = 0.019; Clock: (df 40, n = 42) = 0.31, p = 0.757, ns; Inverted clock:(df 36, n = 38) = 0.26, p = 0.794, ns; Shape: (df 28, n = 43) = 3.02, p = 0.005; Overlap: (df 41, n = 43) = 1.85, p = 0.072, ns) **(Figure 23)**.

The RC ratio for the clock task was equivalent for all four diagnostic groups (ANOVA (df 3, n = 106) = 0.78, p = 0.508, ns). HC and PD-CNL groups demonstrated similar strategies as defined by the RC ratio, with the exception of a lower RC ratio in the PD-CNL group for the overlapping figures task (angle: t-Test (df 62, n = 64) = 0.03, p = 0.975, ns; inverted clock: (df 61, n = 62) = 0.27, p = 0.786, ns; shape: (df 63, n = 65) = 0.35, p = 0.727, ns; overlap: (df 61, n = 63) = 2.13, p = 0.038). RC ratio for the two most challenging tasks (inverted clock, overlapping figures) was significantly higher in PD-pMCI than PD-CNL (inverted clock: t-Test (df 54, n = 56) = 2.55, p = 0.020; overlap: (df 54, n = 56) = 3.50, p = <0.001) but strategy on the other two tasks was equivalent (angle: t-Test (df 54, n = 56) = 1.44, p = 0.156, ns; shape: (df 56, n = 58) = 0.693, ns). PDD subjects differed from PD-CNL subjects in RC ratio for all tasks except the aforementioned clock task (angle: t-Test (df 55, n = 57) = 3.65, p = <0.001; inverted clock: (df 18, n = 50) = 2.55, p = 0.020; shape: (df 25, n = 57) = 2.77, p = 0.010; overlap: (df 55, n = 57) = 4.62, p = <0.001). A comparison between PD-pMCI and PDD subjects demonstrated that PD-pMCI subjects had similar RC ratios for the inverted clock and overlapping figures tasks (inverted clock: t-Test (df 36, n = 38) = 0.42, p = 0.678, ns; overlap: (df 41, n = 43) = 0.87, p = 0.391, ns) and lower RC ratios for angle and shape tasks, although the former failed to reach significance (angle: t-Test (df 41, n = 43) = 1.75, p = 0.087, ns; shape: (df 29, n = 43) = 2.86, p = 0.008) (**Figure 23)**.

Figure 23. Central run count and run count ratio by diagnostic group.



7.3.6 Exploration strategy by error groups

The time for first fixation in the correct IA was significantly longer in the high error (HE) group for angle, inverted clock, shape and overlapping figures tasks **(Table 18 & Figure 24)** (Angle: t-Test (df 20, n = 78) = 3.19, p = 0.005; Inverted clock: (df 19, n = 72) = 2.65, p = 0.016; Shape: (df 21, n = 79) = 3.10, p = 0.005; Overlap: (df 36, n = 77) = 3.41, p = 0.002). Central RC, reflecting the frequency with which subjects re-checked the central stimulus against the comparators, was significantly greater in HE subjects for angle, inverted clock, shape and overlapping figures tasks **(Figure 25)** (Angle: t-Test (df 19, n = 77) = 3.15, p = 0.005; Inverted clock: (df 70, n = 72) = 2.62, p = 0.011; Shape: (df 22, n = 79) = 2.55, p = 0.012; Overlap: (df 76, n = 78) = 3.11, p = 0.003). The task requiring least “re-checking” was the inverted clock, followed by the angle, shape and overlapping figures tasks. The RC ratio, a reflection of the degree with which subjects compare correct and incorrect comparators, was also significantly higher for HE subjects in the angle, inverted clock, shape and overlapping figures tasks **(Figure 25)** (Angle: t-Test (df 76, n = 78) = 2.78, p = 0.007; Inverted clock: (df 70, n = 72) = 5.16, p = <0.001; Shape: (df 21, n = 79) = 4.59, p = <0.001; Overlap: (df 76, n = 78) = 8.31, p = <0.001). For the overlapping figures task, regression analysis identified only the IP sub-scale score as an independent predictor of inefficient visual exploration, suggesting a “dysexecutive” component to the breakdown of exploration strategy. The model predicted only 16% of the variance in RC ratio, however, suggesting other unmeasured factors are also important ((df 1, n = 77) = 14.60, p = < 0.001). In an identical approach, using the angle task RC ratio, IP also emerged as the only cognitive sub-scale score predictive of RC ratio. Again, although the model was significant ((df 1, n = 77) = 9.09, p = 0.004), it predicted only 11% of the variance in the RC ratio.

Table 18. Exploration strategy by error group.

	Low error	High error	p
Fixation duration (msec)			
Angle	n = 61 211 (34)	n = 17 237 (48)	†0.046
Inverted Clock	n = 54 215 (32)	n = 18 264 (56)	†0.002
Shape	n = 60 195 (32)	n = 19 212 (43)	†0.068 (ns)
Overlap	n = 49 226 (34)	n = 29 256 (46)	†0.015
Time to first correct fixation (msec)			
Angle	1372 (384)	1878 (622)	†0.005
Inverted Clock	2700 (655)	3765 (1665)	†0.016
Shape	2194 (643)	3092 (1210)	†0.005
Overlap	2238 (526)	2928 (1000)	†0.002
RC central			
Angle	2.58 (0.50)	3.19 (0.74)	†0.005
Inverted Clock	2.07 (0.80)	2.66 (0.90)	†0.011
Shape	3.61 (0.67)	4.37 (1.26)	†0.012
Overlap	4.51 (0.66)	5.04 (0.82)	†0.003
RC ratio			
Angle	0.53 (0.11)	0.61 (0.13)	†0.007
Inverted Clock	0.50 (0.13)	0.72 (0.21)	†<0.001
Shape	0.33 (0.08)	0.52 (0.17)	†<0.001
Overlap	0.53 (0.08)	0.71 (0.10)	†<0.001

Values expressed as means (± SD)
Statistical tests: † t Test
(ns = non-significant)

Figure 24. Time to first fixation in the correct interest area by error group.

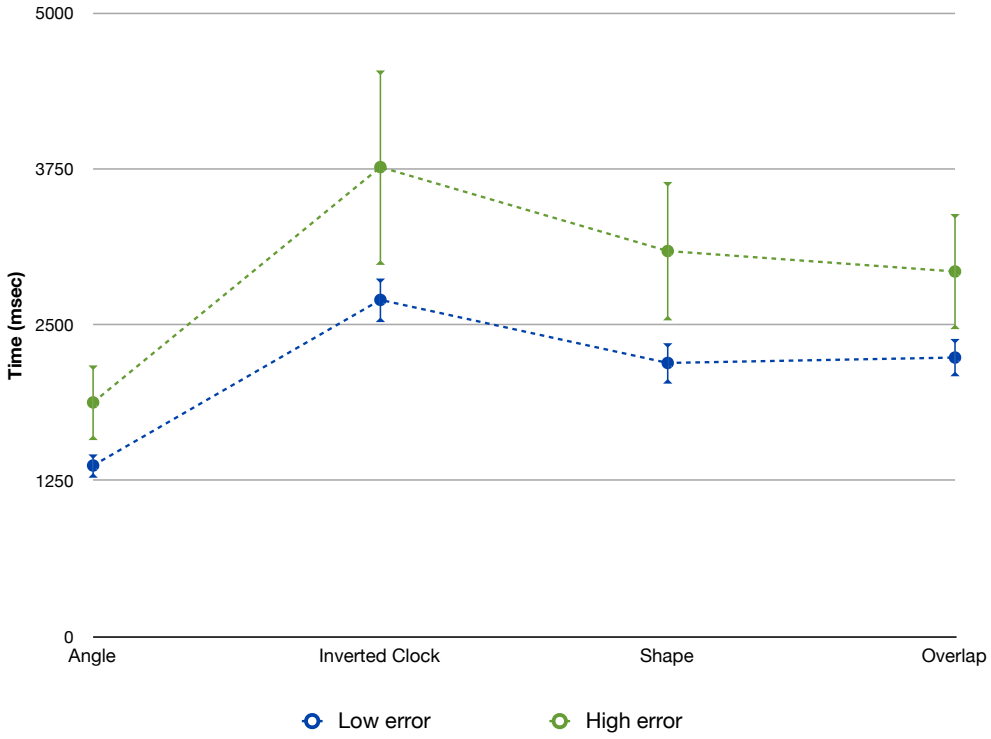
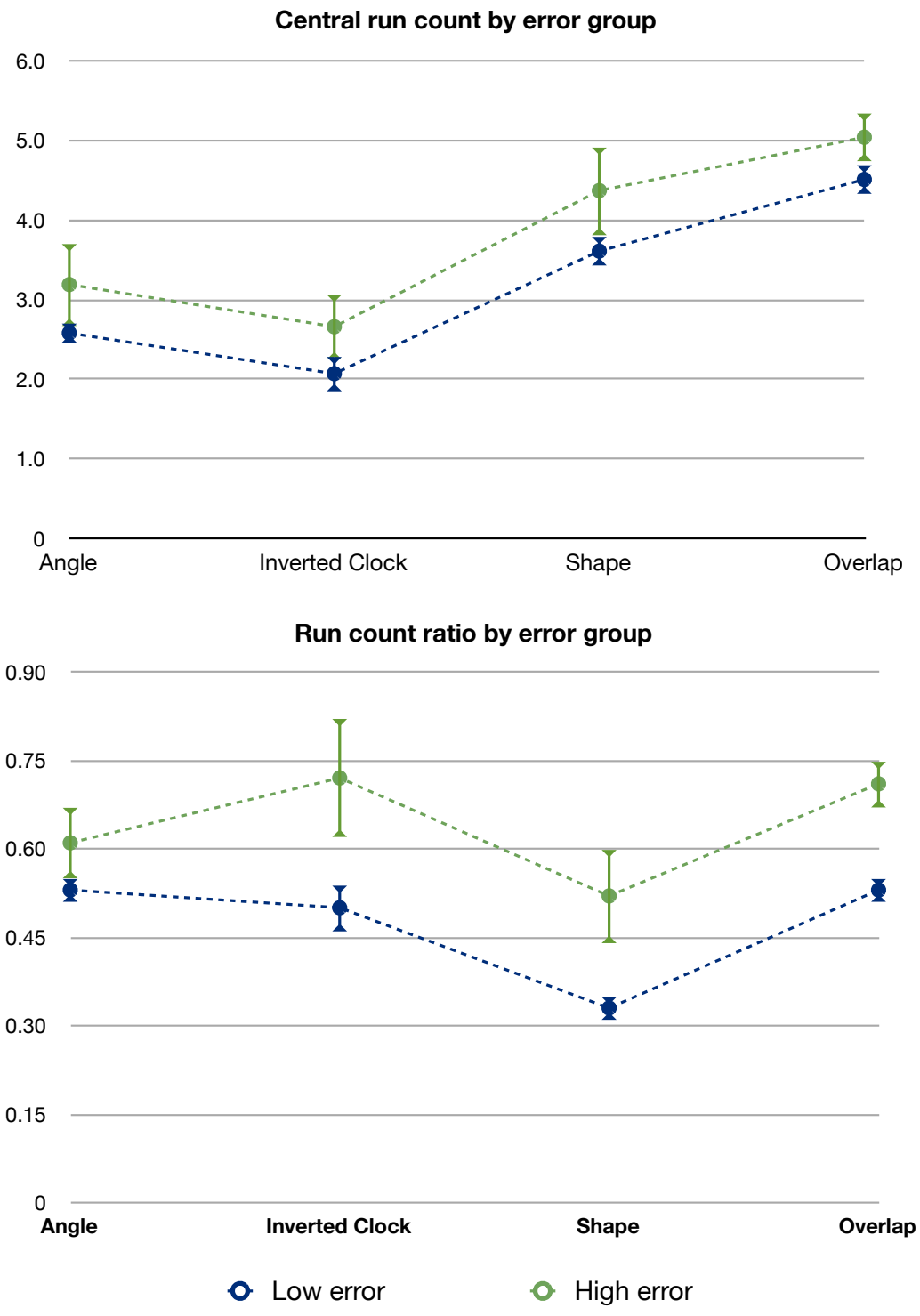


Figure 25. Central run count and run count ratio by error group.



7.3.7 Association between exploration strategy, CVH and gait freezing

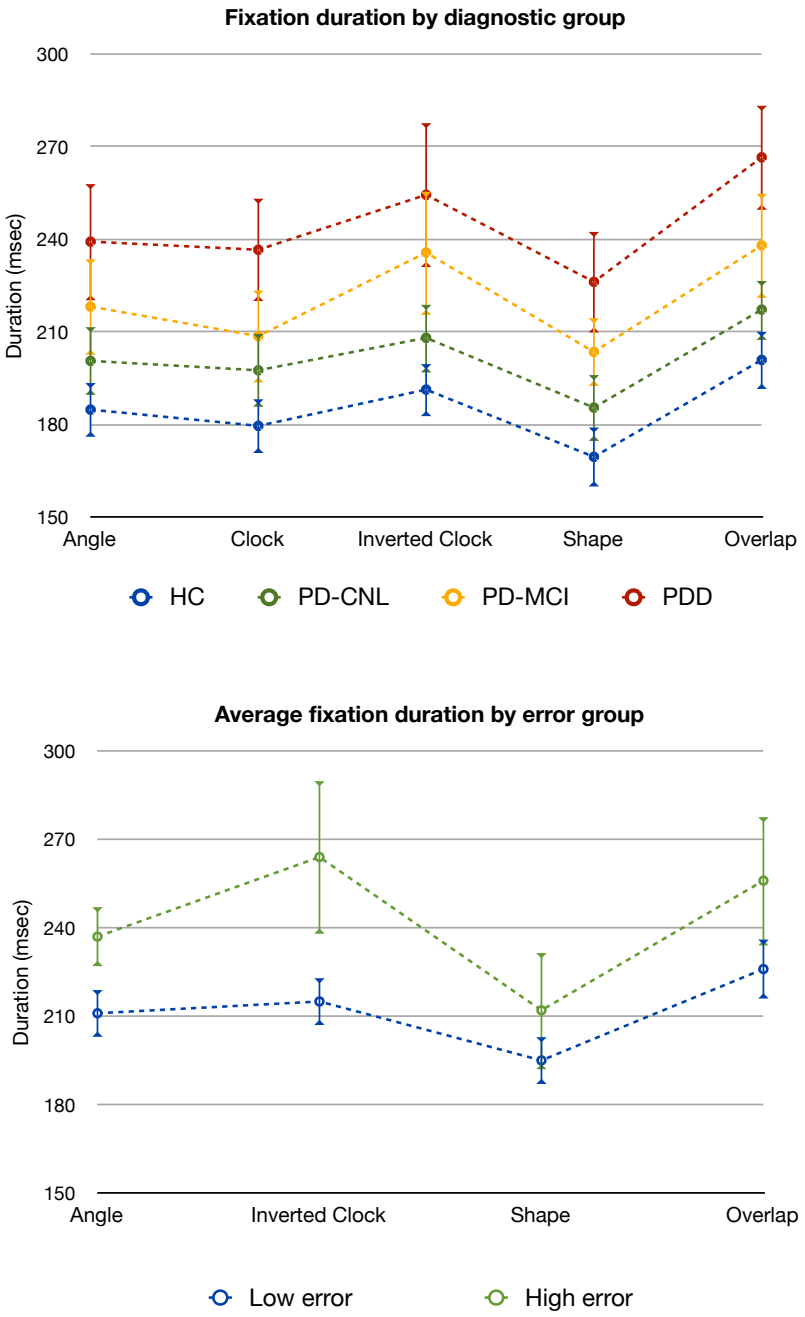
We examined the association between CVH and exploration strategy, as defined by time to first fixation in the correct IA, central RC and RC ratio. by performing logistic regression analysis. The overall model was significant ((df 1, n = 77) = 9.96, p = 0.019), but explained only 10% of the variance in frequency of CVH in the PD/PDD cohort. No single strategy measure made a uniquely significant contribution to the model (time to first fixation in the correct IA, p = 0.150, ns; central RC, p = 0.312, ns; RC ratio, p = 0.196, ns). We also performed a regression analysis using FOG as the dependent variable. On this occasion, the full model was not significant (df 3, n = 77) = 1.57, p = 204, ns).

7.3.8 Fixation duration

The average duration of fixations during the visual battery was shorter in HC than PD-CNL subjects regardless of task (Angle: t-Test (df 62, n = 64) = 2.18, p = 0.033; Clock: (df 62, n = 64) = 2.34, p = 0.022; Inverted clock: (df 59, n = 62) = 2.37, p = 0.021; Shape: (df 63, n = 65) = 2.16, p = 0.035; Overlap: (df 61, n = 63) = 2.34, p = 0.022) **(Table 17 & Figure 26)**. A similar trend was seen when comparing PD-CNL and PD-pMCI subjects, although this only reached significance for the shape, inverted clock and overlapping figures tasks (Angle: t-Test (df 54, n = 56) = 1.88, p = 0.066, ns; Clock: (df 55, n = 57) = 1.16, p = 0.252, ns; Inverted clock: (df 54, n = 56) = 2.58, p = 0.013; Shape: (df 56, n = 58) = 2.21, p = 0.031; Overlap: (df 54, n = 56) = 2.27, p = 0.027). This trend to prolonged fixation durations was replicated when comparing PD-pMCI and PDD subjects although the angle and inverted clock task comparisons did not reach significance (Angle: t-Test (df 41, n = 43) = 1.82, p = 0.077, ns; Clock: (df 40, n = 42) = 2.51, p = 0.016; Inverted clock: (df 36, n = 38) = 1.20, p = 0.236, ns; Shape: (df 41, n = 43) = 2.30, p = 0.026; Overlap: (df 41, n = 43) = 2.38, p = 0.022). The comparison between fixation duration in cognitively normal PD subjects and those with dementia was the most

striking, with fixations in the PDD group lasting, on average, 38-50 msec longer than the PD-CNL group (Angle: t-Test (df 55, n = 57) = 4.00, p = <0.001; Clock: (df 53, n = 55) = 3.89, p = <0.001; Inverted clock: (df 48, n = 50) = 4.05, p = <0.001; Shape: (df 55, n = 57) = 4.31, p = <0.001; Overlap: (df 55, n = 57) = 5.39, p = <0.001).

Figure 26. Average fixation duration by diagnostic and error groups.



When fixation duration was examined in the LE and HE groups, there were significantly longer fixation durations for angle, inverted clock and overlapping figures tasks (angle: t-Test (df 21, n = 78) = 2.12, p = 0.046; inverted clock: (df 21, n = 72) = 3.50, p = 0.002; overlap: (df 25, n = 72) = 2.62, p = 0.015) and a strong trend to significance for the shape position task (t-Test (df 72, n = 74) = 1.85, p = 0.068, ns) in the HE group **(Table 18)**. There was a significant negative correlation between AEMSS and fixation duration (r = -.44, n = 76, p = <0.001) and a strong positive correlation between UPDRS III and fixation duration (r = .55, n = 76, p = <0.001). There was a weak, and non-significant, correlation between fixation duration and LED (r = .18, n = 78, p = 0.098, ns). Controlling for UPDRS III scores, the relationship between cognition and fixation duration was weakened (r = -.29) whereas the correlation between UPDRS III and fixation duration was less affected by controlling for cognition (r = .46). Multiple regression was used to assess the contribution that AEMSS and UPDRS III made to duration of fixations during the overlapping figures task. A model containing both measures was significant (df 2, n = 76) = 12.52, p = <0.001, predicting 34% of the variance in fixation duration. As suggested by the correlation analysis, UPDRS III positively correlated with fixation duration (Std Beta 0.44, p = <0.001) and contributed most to the model, whereas AEMSS was negatively correlated with fixation duration and made a weaker, but still significant, contribution to the overall predictive value of the model (Std Beta -0.27, p = 0.013).

7.4 Discussion

To the best of our knowledge, this is the first study to report on visual cognition and visual exploration strategy in a variety of PD cognitive sub-groups. We have shown eye tracking to be a viable technique for analysing the complex interplay between visual exploration strategies, cognitive sub-domain function and performance on a visual assessment battery.

Our results highlight the cognitive heterogeneity present in a cross-sectional cohort of PD and PDD patients. This is particularly true of non-demented PD cohorts, where a significant proportion of subjects are likely to have cognitive impairment (*Foltynie et al.,* 2004). In particular, non-demented PD patients are reported to have impairments in executive function, memory and visuospatial and visuoperceptual abilities (*Muslimovic et al.,* 2005; *Mosimann et al.,* 2004b*, Uc et al*., 2005*, Williams-Gray et al*., 2007). In the absence of published criteria, we relied upon global and sub-scale cognitive scores to identify those PD subjects who, although not fulfilling diagnostic criteria for PDD, clearly did not score in the normal range – a group we defined as “possible MCI”. Although we did not perform detailed neuropsychological assessments used in some previous studies of PD-MCI (*Caviness et al., 2007; Janvin et al., 2006a; Petersen et al., 2009*), our analyses would suggest that our approach did indeed generate an group with a cognitive phenotype very different from the PD-CNL group.

With respect to performance on the eye tracking battery, we found very similar, low error rates for both HC and PD-CNL groups, and no evidence to suggest a specific visuospatial or visuoperceptual deficit in PD subjects with normal cognition. In contrast, the performance of the PD-pMCI subjects was strikingly different, with higher error rates on visuospatial (angle, inverted clock) and visuoperceptual (overlapping figures) tasks than the cognitively normal PD subjects. PDD subjects exhibited a similar, albeit more marked, pattern of deficits but were additionally impaired on the shape position task. Interestingly, clock reading and matching was not

markedly impaired in the PDD group (5% error rate), perhaps reflecting the over-learned nature of the task.

The RT of PD-CNL subjects was marginally longer for all tasks when compared to the HC subjects, although the comparison failed to reach significance. In general, PD-CNL subjects offered a verbal response to the onset of the stimulus 120 – 370 msecs later than HC, depending on task complexity. This prolongation of RT may reflect a more cautious and measured approach to the assessment battery in PD or impairments in cognitive function too subtle to be picked up by our screening methods. In comparison to the PD-CNL group, those subjects with PD-pMCI showed much longer delays between stimulus onset and response, between 700 – 2300 msecs, depending on task. As one might expect from the error rates, inverted clock and overlapping figures tasks generated the longest RT, providing further objective evidence that PD subjects with possible MCI found these visuospatial and visuoperceptual measures more difficult than their cognitively normal counterparts.

Exploration strategy, as defined by time to first correct fixation, central run count and run count ratio, was identical for controls and cognitively normal PD subjects. PD-CNL and PDD subjects differed markedly in all strategy measures across all tasks (except the clock task RC ratio). The comparison between PD-pMCI and the two other PD groups is more complex. Although the comparisons were not always significant at the $p < 0.05$ level, in general, the time to first correct fixation increased steadily as cognitive function worsened. For some of the tasks (clock, inverted clock) the tendency to revisit the central stimulus (central RC) in PD-pMCI more closely matched that of PDD subjects, whereas in the angle, shape and overlapping figures tasks, the strategy better matched that of the PD-CNL group. In contrast, the PD-pMCI and PDD subjects showed similar RC ratios for all tasks apart from the shape task, where PD-pMCI strategy resembled that of cognitively normal subjects.

An alternative approach to the analysis of exploration strategy would have been to split the total recorded trials into those where correct and incorrect

responses were given. Due to the experimental design, this information was not readily available for analysis and, for HC and PD-CNL groups, the number of error trials would naturally be very low. We therefore opted to dichotomise the entire PD cohort into high- and low-error makers based on task-by-task performance on the visual battery. We reasoned that this would provide insight into how visual exploration proceeds in those most effective at solving the visual tasks in the eye tracking battery and validate our choice of strategy measures. One of the strengths of this approach is the inclusion of multiple correct trials even in the “high-error” group, meaning that, where significant differences are observed, these are likely to be a more robust finding. As expected, we were unable to run this analysis for the clock task due to the low number of errors made even by those subjects with PDD.

For the remaining four tasks, the HE group took longer to fixate the correct interest area, suggesting that visual exploration proceeds in a non-stochastic fashion and those prone to errors are more likely be drawn to irrelevant comparators than those in the LE group. High-error makers were also compelled to revisit the central stimulus more frequently than the LE group. Similarly, the RC ratio, reflecting the requirement to check correct and incorrect comparators against each other, was higher for angle, shape, inverted clock and overlapping figures tasks. Of note, the RC ratio was lowest for the shape task, reflecting the visual simplicity of the component parts (triangle, square) and a strategy favouring more checking against the central stimulus. In contrast, the RC ratio was highest (i.e. worst) for overlapping figures and inverted clock tasks, highlighting a strategy of comparator-to-comparator, as well as comparator-to-stimulus checking. Our regression model suggested that frontal executive dysfunction, as measured by the DRS IP score, is associated with increased the RC ratio. A more detailed neuropsychological assessment is necessary to confirm this finding in future work. We found no relationship between strategic performance on a putative ventral stream task (overlapping figures) and the presence of CVH. Similarly, we examined the strategic performance of a putative dorsal stream task (angle matching) as

a predictor of gait freezing and found no association. We had hypothesised that gaze strategies on ventral and dorsal stream tasks would be predictive of visual and motor symptoms. Our failure to confirm this hypothesis may, in part, be due to the small number of iterations within each task and further work with a larger battery may prove more revealing.

Despite being well matched for error rates, PD-CNL subjects made consistently longer fixations on all tasks than did the HC subjects. In general, the prolongation of fixation duration was of the magnitude of 15 – 18 msecs, and was relatively independent of task complexity. One potential explanation for this would be a PD-specific oculomotor deficit, resulting from disruption of basal ganglia or cortical saccadic circuitry, leading to an inability to disengage fixations and initiate subsequent saccades in an efficient manner. Saccadic latency may be prolonged in PD both for reflexive-biased and cognitively-biased saccades (*Rascol et al.,* 1989*, Kennard and Luec*k, 1989*, Briand et al*., 1999*, Hood et al*., 2007), although other studies have not demonstrated such changes (*Vidailhet et al.,* 1994*, Briand et al*., 1999*, Briand et al*., 2001*, Mosimann et al*., 2005*, Lueck et al*., 1990*, Vidailhet et al*., 1999*, Mosimann et al*., 2005). There is little information on the metrics of fixations and saccades during more “naturalistic” scene viewing in PD. One study reported prolonged fixations during reading in PD (*Gottlob et al.,* 2004) but in a study of visual exploration duration the Tower of London task, Hodgson et al. (2002) showed that despite strategic differences between PD and HC subjects, fixation durations were identical. Fixation duration during facial emotion viewing is influenced by executive function in PD (*Clark et al.,* 2010) and the impact of cognitive impairment on fixation characteristics is therefore an important factor in interpreting our results.

In the absence of specific measurements of the temporal characteristics of the saccades of our subjects, we can only speculate that greater saccadic latencies result in longer fixation durations for the PD cohort. An alternative explanation would be that impairment of visual cognition, executive function or attention, too subtle to be picked up by cognitive screening, is influencing the characteristics of the fixations and saccades

even in PD-CNL subjects. Such impairment could result in small changes both in RT and fixation duration without necessarily causing higher error rates on the visual battery itself. Both PD severity and global cognition, reflected by UPDRS III and AEMSS scores respectively, were important predictors of fixation duration in our regression modelling. What is clear is that, as cognition declines, fixation duration becomes significantly longer, with more demanding tasks showing the most dramatic changes. The longer fixation duration is therefore a potential reflection not just of subcortical oculomotor deficits, but may also serve to highlight the involvement of fronto-parietal eye fields and/or dorsal and ventral streams in PD. It has been argued that saccadic measurements may act as a surrogate biomarker for disease progression in clinical trials of PD although the interaction between medication effects and the influence of both cortical and subcortical structures on saccadic metrics makes such an approach potentially challenging (*Barker and Michell,* 2009).

There are limitations to our study in terms of recruitment and sample size. We effectively excluded patients under the age of 50 years in order to allow adequate age matching of the study groups but, as the average age of the PD population in clinic and community-based studies is 70-72 years (*Lo et al.,* 2009*, Newman et al*., 2009), we feel our results are likely to have considerable external validity. We employed consecutive recruitment for the PD group to minimise potential bias but the PDD cohort was a convenience sample. Our sample sizes were relatively small compared to other studies of cognition in PD and withdrawals from the study, technical issues and an inability to complete the protocol resulted in a degree of data loss, most evident in the PDD group. We chose tasks of differing complexity to avoid a ceiling effect in the results from the PDD subjects but found instead a floor effect in terms of clock reading that made further analysis of strategy impossible. In addition, concerns over deteriorating performance and drop-outs associated with a longer assessment battery dictated that we use a relatively small number of images within each task category. Refinement of the battery to those tasks most likely to discriminate cognitive sub-groups, would allow a greater number of

iterations to be run. Despite these limitations, we feel our results have been achieved in a representative sample of PD patients, that the normative data from the HC group is reliable and the conclusions from our results are robust.

In summary, we have demonstrated that impairments on putative tests of visuospatial and visuoperceptual function can be demonstrated in both PD-pMCI and PDD patients, distinct from the cognitive performance of either a control or PD-CNL cohort. Visual exploration strategies are less efficient in cognitively impaired PD subjects, with the most striking impairment seen in the PDD cohort. In addition, the strategy employed by high-error makers may reflect the interaction between visuocognitive and frontal executive impairments in PD. Finally, we have demonstrated a disease-specific prolongation of fixation duration in PD subjects, possibly due to disruption of subcortical and/or cortical oculomotor regions in cognitively normal PD subjects, but amplified by the cortical neurodegeneration that is the hallmark of PDD.

Further studies are warranted to confirm these findings a larger cohort, perhaps incorporating assessment of reflexive and cognitively-biased saccades in addition to more naturalistic scene/object viewing. A more detailed cognitive examination would also be helpful in defining the domains most closely associated with changes in exploration strategy. Finally, how strategic impairments in visual exploration correlate with important day-to-day clinical symptoms and outcome measures, such as visual hallucinations and gait freezing, remains to be clarified.

8. Conclusions and Future Studies

Parkinson's disease, with its ever widening clinical phenotype, and range of both motor and non-motor symptoms, poses considerable challenges not just for patients and carers, but also for medical staff involved in their care. In an ageing population, and with advancing age the key risk factor for the development of PD, the impact on society is likely to increase. Non-motor symptoms such as dementia and visual hallucinations are important determinants of long-term outcome and quality of life. Attempting to better understand these issues was the primary motivation behind the study.

What has emerged from the first part of the thesis is a more complete appreciation both of the wide range of visual symptoms experienced by patients with PD, and their rising frequency as cognitive impairment develops. This is the first study to have examined visual symptoms and impairments in a systematic fashion, whilst attempting to correlate these with demographic, cognitive and ocular features. Our study has taken the first steps towards understanding common, but under-appreciated, visual problems in PD such as diplopia and difficulty reading. It also provides justification for future work in defining their impact on quality of life and the therapeutic approaches most likely to alleviate them. We have also highlighted the need to consider the four main "hallucinatory" experiences in PD - illusory misperception, sensations of presence and passage and complex visual hallucinations - as pathophysiologically separate entities. We hope that our findings will be incorporated into the methodology of future studies, ultimately leading to a better understanding, not only of "hallucinatory" experiences in PD and PDD, but also in other conditions such as Alzheimer's disease, dementia with Lewy bodies and narcolepsy.

We attempted to set up a study that would avoid one of the common pitfalls of research in PD, namely how to localise visual impairments and symptoms to a specific region of the visual pathway. For example, reported reductions in visual acuity in PD could be accounted for by a disease-specific effect on the retina, damage to the early visual cortex or even poor test performance. One of the *a priori* hypotheses of the study

was that cognitive performance would have a significant impact on measures of visual acuity. However, when we correlated measures of basic visual function with global cognition, controlling for disease severity, we failed to detect a significant interaction. This led us to to an alternative hypothesis, namely that the seeds of visual impairment in PD may be sown in the retina itself.

Previously published OCT and electroretinogram data argue strongly in favour of PD-related neurodegeneration in the retina. Therefore, we hypothesised that we would detect differences between PD and control groups both in terms of retinal morphology and electrophysiological response, that could subsequently be correlated with impairments in visual acuity and contrast sensitivity. Our results challenge previous OCT evidence in two key ways. First, we did not see evidence of retinal thinning either in the macula itself or in the peri-papillary region. This somewhat surprising finding suggests that a well-designed, appropriately powered longitudinal study is the only way to address questions over whether disease progression in PD leads to detectable changes in retinal morphology and what, if any, impact this might have both in terms of visual function and visual symptoms. Our results also challenge the assertion that OCT may be a useful biomarker for disease progression, not only due to the lack of difference between the study groups, but also because of the number of individuals excluded from the final analysis due to co-morbid ocular disease.

The PERG and VEP study was challenging in terms of protocol development and data acquisition and the lack of group differences rendered interpretation of the results difficult. Our experimental hypothesis, surrounding a potential magnocellular pathway basis for sensations of passage, remains theoretically sound. However, with a novel and largely unvalidated methodology it is difficult to reject this hypothesis on the basis of our results. Peripheral retinal responses between HC and PD subjects, and between PD subjects with and without passage symptoms, did not differ to pattern stimuli but further work is required to

validate this experimental protocol before “peripheral retinal” can be equated with “magnocellular” responses.

We did find PERG evidence correlating retinal dysfunction with the intriguing and robust reductions in visual acuity and contrast sensitivity that we, and many others, have noted in PD. However, association is not causation and further work is needed before we can assert with confidence that acuity and contrast sensitivity are not merely serving as markers of early visual cortex dysfunction in PD.

The final part of the thesis focused on visual cognition in PD, with particular respect to visual exploration strategies employed when interacting with visually-presented information. Ours is the first study to report on visual cognition in a variety of PD cognitive sub-groups and, despite the limitations in our definition of “possible mild cognitive impairment” and the fact that we did not use a validated battery of perceptual tests, the results are noteworthy. In addition to significant differences in memory, attentional and frontal-executive abilities, PD-pMCI subjects performed worse on tasks with a putative visuospatial and visuoperceptual basis (angle, inverted clock and overlapping figures). The extent of these deficits was intermediate between the PD-CNL group, who performed as controls, and the PDD group, with the highest error rates.

Visual exploration strategy is an important marker of error rates, as evidenced by the clear separation in strategic measures between low-error and high-error rate subjects. Although the tasks in the eye tracking battery have previously been used to study visuospatial and visuoperceptual function, it is clear from the “goal-directed” nature of visual exploration that other cognitive domains, not least executive function, are also involved. A much more detailed cognitive assessment battery is needed in future studies to better define the interaction between attention, executive function, working memory and the perceptual and spatial abilities required to efficiently dissect out these visual tasks. Such an approach might also help to define how such strategic differences contribute to functional impairments such as visual symptoms and gait freezing. Finally, visual

exploration strategies, in conjunction with measures such as fixation duration, might provide an alternative means not only of assessing and quantifying cognitive impairment in PD, but also of monitoring response to novel disease-modifying agents and cognitive-enhancers as and when they become available.

9. References

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10. Appendix A - Publications arising from the thesis

Published

1. Archibald NK, Clarke MP, Mosimann UP, Burn DJ. The retina in Parkinson's disease. Brain. 2009;132:1128-45.
2. Archibald NK, Clarke MP, Mosimann UP, Burn DJ. Retinal morphology in Parkinson's disease. *Parkinsonism and Related Disorders (in press).*

Under review

3. Archibald NK, Clarke MP, Mosimann UP, Burn DJ. Visual symptoms in Parkinson's disease and Parkinson's disease dementia. *Movement Disorders (submitted).*

In preparation

4. Archibald NK, Mosimann UP, Burn DJ, Clarke MP. Retinal neurophysiology in Parkinson's disease - association with visual impairment and symptoms.
5. Archibald NK, Hutton SB, Clarke MP, Mosimann UP, Burn DJ. Visual exploration in Parkinson's disease and Parkinson's disease dementia.

11. Appendix B - Questionnaires

UPDRS II. ACTIVITIES OF DAILY LIVING

1. Speech:
    0 = Normal
    1 = Mildly affected. No difficulty being understood
    2 = Moderately affected. Sometimes asked to repeat statements
    3 = Severely affected. Frequently asked to repeat statements
    4 = Unintelligible most of the time

2. Salivation:
    0 = Normal
    1 = Slight but definite excess of saliva in mouth; may have nighttime drooling
    2 = Moderately excessive saliva; may have minimal drooling
    3 = Marked excess of saliva with some drooling
    4 = Marked drooling; requires constant use of tissue or handkerchief

3. Swallowing:
    0 = Normal
    1 = Rare choking
    2 = Occasional choking
    3 = Requires soft food
    4 = Requires nasogastric (NG) tube or gastrostomy tube

4. Handwriting:
    0 = Normal
    1 = Slightly slow or small
    2 = Moderately slow or small; all words are legible
    3 = Severely affected; not all words are legible
    4 = The majority of words are not legible

5. Cutting food and handling utensils
    0 = Normal
    1 = Somewhat slow and clumsy, but no help needed
    2 = Can cut most foods, although clumsy and slow; some help needed
    3 = Food must be cut by someone, but can still feed slowly
    4 = Needs to be fed

6. Dressing
    0 = Normal
    1 = Somewhat slow, but no help needed
    2 = Occasional assistance with buttoning, getting arms into sleeves
    3 = Considerable help required, but can do some things alone
    4 = Helpless

7. Hygiene
    0 = Normal
    1 = Somewhat slow, but no help needed
    2 = Needs help to shower or bathe; or very slow in hygienic cares
    3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom
    4 = Foley catheter or other mechanical aids

8. Turning in bed / Adjusting bed clothes
    0 = Normal
    1 = Somewhat slow and clumsy, but no help needed
    2 = Can turn alone or adjust sheets, but with great difficulty
    3 = Can initiate attempt, but not turn or adjust sheets alone
    4 = Helpless

9. Falling – unrelated to freezing
    0 = None
    1 = Rare falling
    2 = Occasionally falls, less than once daily
    3 = Falls on average of once daily
    4 = Falls more than once daily

10. Freezing when walking
    0 = None
    1 = Rare freezing when walking; may have start hesitation
    2 = Occasional freezing when walking
    3 = Frequent freezing. Occasional falls from freezing
    4 = Frequent falls from freezing

11. Walking
    0 = Normal
    1 = Mild difficulty. May not swing arms or may tend to drag leg
    2 = Moderate difficulty, but requires little or no assistance
    3 = Severe disturbance of walking, requiring assistance
    4 = Cannot walk at all, even with assistance

12. Tremor (symptomatic complaint of tremor in any part of body)
    0 = Absent
    1 = Slight and infrequently present
    2 = Moderate; bothersome to patient
    3 = Severe; interferes with many activities
    4 = Marked; interferes with most activities

13. Sensory complaints related to parkinsonism
    0 = None
    1 = Occasionally has numbness, tingling or mild aching
    2 = Frequently has numbness, tingling or aching; not distressing
    3 = Frequent painful sensations
    4 = Excruciating pain

Total UPDRS II Score:

UPDRS III. MOTOR EXAMINATION

14. Speech:
    0 = Normal
    1 = Slight loss of expression, diction and/or volume
    2 = Monotone, slurred but understandable; moderately impaired
    3 = Marked impairment, difficult to understand
    4 = Unintelligible

15. Facial expression
    0 = Normal
    1 = Minimal hypomimia; could be normal ‘ poker face’
    2 = Slight but definitely abnormal diminution of facial expression
    3 = Moderate hypomimia; lips parted some of the time
    4 = Masked or fixed faces, with severe or complete loss of facial expression; lips parted 1/4 inch or more

16. Tremor at rest
    0 = Absent
    1 = Slight and infrequently present
    2 = Mild in amplitude and persistent, or moderate in amplitude but only intermittently present
    3 = Moderate in amplitude and present most of the time
    4 = Marked in amplitude and present most of the time

Face / chin	_____		
Left arm	_____	Right arm	_____
Left leg	_____	Right leg	_____

17. Action or postural tremor of hands
    0 = Absent
    1 = Slight: present with action
    2 = Moderate in amplitude; present with action
    3 = Moderate in amplitude ; present with posture holding as well as with action
    4 = Marked in amplitude ; interferes with feeding

Left	_____	Right	_____

18. Rigidity (judged on passive movement of major joints with patient relaxed in sitting position: ‘ cog wheeling’ to be ignored):

0 = Absent
1 = Slight or detectable only when activated by mirror or other movements
2 = Mild to moderate
3 = Marked, but full range of motion easily achieved
4 = Severe ; range of motion achieved with difficulty

Neck _____

Left arm _____ Right arm _____

Left leg _____ Right leg _____

19. Finger taps (patient taps thumb with index finger in rapid succession with widest amplitude possible, each hand separately):

0 = Normal (> 15 / 5 s)
1 = Mild slowing and / or reduction in amplitude (11 - 14 / 5 s)
2 = Moderately impaired : definite and early fatiguing: may have occasional arrests in movement (3 -6 / 5s)
3 = Severely impaired; frequent hesitation in initiating movements or arrests in ongoing movements
4 = Can barely perform the task (0-2 / 5 s)

Left _____ Right _____

20. Hand movements (patient opens and closes hands in rapid succession with widest amplitude possible, each hand separately) :

0 = Normal
1 = Mild slowing and or reduction in amplitude
2 = Moderately impaired ; definite and early fatiguing; may have occasional arrests in movement
3 = Severely impaired; frequent hesitation in initiating movements or arrests in ongoing movement
4 = Can barely perform the task

Left _____ Right _____

21. Rapid alternating movements of hand (pronation- supination movements of hands, vertically or horizontally, with as large an amplitude as possible, both hands simultaneously):

0 = Normal
1 = Mild slowing and or reduction in amplitude
2 = Moderately impaired ; definite and early fatiguing; may have occasional arrests in movement
3 = Severely impaired; frequent hesitation in initiating movements or arrests in ongoing movement
4 = Can barely perform the task

Left _____ Right _____

22. Leg agility (patient taps heel on ground in rapid succession, picking up entire leg; amplitude should be about 3 inches):

0 = Normal
1 = Mild slowing and or reduction in amplitude
2 = Moderately impaired ; definite and early fatiguing; may have occasional arrests in movement
3 = Severely impaired; frequent hesitation in initiating movements or arrests in ongoing movement
4 = Can barely perform the task

Left _____ Right _____

23. Arising from chair (patient attempts to arise from a straight-backed wood or metal chair, with arms folded across chest):

0 = Normal
1 = Slow, or may need more than one attempt
2 = Pushes self up from arms of seat
3 = Tends to fall back and may have to try more than one time but can get up without help
4 = Unable to arise without help

24. Posture:

0 = Normal erect
1 = Not quite erect, slightly stooped posture; could be normal for older person
2 = Moderately stooped posture, definitely abnormal; can be leaning to one side
3 = Severely stooped posture with kyphosis; can be moderately leaning to one side
4 = Marked flexion, with extreme abnormality of posture

25. Gait :

0 = Normal
1 = Walks slowly; may shuffle with short steps, but no festination or propulsion
2 = Walks with difficulty but requires little or no assistance; may have some festination, short steps or propulsion
3 = Severe disturbance of gait; requires assistance
4 = Cannot walk at all, even with assistance

26. Postural stability (response to sudden posterior displacement produced by pull on shoulders while patient is erect, with eyes open and feet slightly apart; patient is prepared):

0 = Normal
1 = Retropulsion, but recovers unaided
2 = Absence of postural response; would fall if not caught by examiner
3 = Very unstable; tends to lose balance spontaneously
4 = Unable to stand without assistance

27. Body bradykinesia and hypokinesia (combining slowness, hesitancy, decreased arm swing, small amplitude, and poverty of movement in general):
    0 = None
    1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons; possibly reduced amplitude
    2 = Mild degree of slowness and poverty of movement that is definitely abnormal; alternatively, some reduced amplitude
    3 = Moderate slowness; poverty or small amplitude of movement
    4 = Marked slowness; poverty or small amplitude of movement

Total UPDRS III Score :

FREEZING OF GAIT QUESTIONNAIRE (FOGQ)

1.1. During your worst state—Do you walk:

0 Normally

1 Almost normally—somewhat slow

2 Slow but fully independent

3 Need assistance or walking aid

4 Unable to walk

1.2. Are your gait difficulties affecting your daily activities and independence?

0 Not at all

1 Mildly

2 Moderately

3 Severely

4 Unable to walk

1.3. Do you feel that your feet get glued to the floor while walking, making a turn or when trying to initiate walking (freezing)?

0 Never

1 Very rarely—about once a month

2 Rarely—about once a week

3 Often—about once a day

4 Always—whenever walking

1.4. How long is your longest freezing episode?

0 Never happened

1 1–2 s

2 3–10 s

3 11–30 s

4 Unable to walk for more than 30 s

1.5. How long is your typical start hesitation episode (freezing when initiating the first step)?

0 None

1 Takes longer than 1 s to start walking

2 Takes longer than 3 s to start walking

3 Takes longer than 10 s to start walking

4 Takes longer than 30 s to start walking

1.6. How long is your typical turning hesitation: (freezing when turning)

0 None

1 Resume turning in 1–2 s

2 Resume turning in 3–10 s

3 Resume turning in 11–30 s

4 Unable to resume turning for more than 30 s

TOTAL

EPWORTH SLEEPINESS SCORE

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the most appropriate number for each situation:

0 = no chance of dozing
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

Situation	Chance Of Dozing
Sitting and reading	
Watching TV	
Sitting inactive in a public place (e.g. a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in traffic	

REM SLEEP BEHAVIOR DISORDER SCREENING QUESTIONS

1. Have you ever seen the patient appear to "act out his/her dreams" while sleeping? (punched or flailed arms in the air; shouted or screamed)

   YES NO

2. Has the patient told you about dreams of being chased, attacked, or that involve defending himself or herself?

   YES NO

(Adapted from Mayo Sleep Questionnaire – informant. "Yes" response to both of these questions: **SN 85% & SP 100%)**

PARKINSON'S DISEASE QUALITY OF LIFE QUESTIONNAIRE (PDQ 8)

Due to having Parkinson's disease, how often have you experienced the following, *during the last month?* Please circle the number beside the statement you picked. If several statements in the group seem to apply equally well, circle each one. Be sure to read all the statements in each group before making your choice.

1. Had difficulty getting around in public?

Never
Occasionally
Sometimes
Often
Always (or cannot do at all)

2. Had difficulty dressing yourself?

Never
Occasionally
Sometimes
Often
Always (or cannot do at all)

3. Felt depressed?

Never
Occasionally
Sometimes
Often
Always (or cannot do at all)

4. Had problems with your close personal relationships?

Never
Occasionally
Sometimes
Often
Always (or cannot do at all)

5. Had problems with your concentration, e.g. when reading or watching TV?

Never
Occasionally
Sometimes
Often
Always (or cannot do at all)

Felt unable to communicate with people properly?

Never
Occasionally
Sometimes
Often
Always (or cannot do at all)

7. Had painful muscle cramps or spasms?

Never
Occasionally
Sometimes
Often
Always (or cannot do at all)

8. Felt embarrassed in public due to having Parkinson's disease?

Never
Occasionally
Sometimes
Often
Always (or cannot do at all)

THE BRISTOL ACTIVITIES OF DAILY LIVING SCALE (BADLS)

This questionnaire is designed to reveal the everyday ability of people who have memory difficulties of one form or another. For each activity (Nos. 1-20), statements a-e refer to a different level of ability.

Thinking of the last 2 weeks, circle the letter that represents your relative's/friend's ability. Only 1 letter should be circled for each activity.

(If in doubt about which letter to circle, choose the level of ability which represents their *average* performance over the last 2 weeks)

FOOD

a. Selects and prepares food as required
b. Able to prepare food if ingredients set out
c. Can prepare food if prompted step by step
d. Unable to prepare food even with prompting and supervision
e. Not applicable

EATING

a. Eats appropriately using correct cutlery
b. Eats appropriately if food made manageable and/or uses spoon
c. Uses fingers to eat food
d. Needs to be fed
e. Not applicable

DRINK

a. Selects and prepares drinks as required
b. Can prepare drinks if ingredients left available
c. Can prepare drinks if prompted step by step
d. Unable to make a drink even with prompting and supervision
e. Not applicable

DRINKING

a. Drinks appropriately
b. Drinks appropriately with aids, beaker/straw etc.
c. Does not drink appropriately even with aids but attempts to

d. Has to have drinks administered (fed)
e. Not applicable

DRESSING

a. Selects appropriate clothing and dresses self
b. Puts clothes on in wrong order and/or back to front and/or dirty clothing
c. Unable to dress self but moves limbs to assist
d. Unable to assist and requires total dressing
e. Not applicable

HYGIENE

a. Washes regularly and independently
b. Can wash if given soap, flannel, towel
c. Can wash self is prompted and supervised
d. Unable to wash self and needs full assistance
e. Not applicable

TEETH

a. Cleans own teeth/dentures regularly and independently
b. Cleans teeth/dentures if given appropriate items
c. Requires some assistance, toothpaste on brush, brush to mouth, etc.
d. Full assistance given
e. Not applicable

BATH/SHOWER

a. Bathes regularly and independently
b. Needs bath to be drawn/shower turned on but washes independently
c. Needs supervision and prompting to wash
d. Totally dependent needs full assistance
e. Not applicable

TOILET/COMMODE

a. Uses toilet appropriately when required
b. Needs to be taken to the toilet and given assistance
c. Incontient of urine or faeces
d. Incontinent of urine and faeces

e. not applicable

TRANSFERS

a. Can get in/out of chair unaided
b. Can get into a chair but needs help to get out
c. Needs help getting in and out of a chair
d. Totally dependent on being put onto and lifted from chair
e. Not applicable

MOBILITY

a. Walks independently
b. Walks with assistance, i.e. furniture, arm for support
c. Uses aids to mobilize, i.e. frame, sticks etc.
d. Unable to walk
e. Not applicable

ORIENTATION - TIME

a. Fully orientated to time/day/date etc
b. Unaware of time/day etc but seems unconcerned
c. Repeatedly asks the time/day/date
d. Mixes up night and day
e. Not applicable

ORIENTATION—SPACE

a. Fully orientated to surroundings
b. Orientated to familiar surroundings only
c. Gets lost in home, needs reminding where bathroom is
d. Does not recognise home as own and attempts to leave
e. Not applicable

COMMUNICATION

a. Able to hold appropriate conversation
b. Shows understanding and attempts to respond verbally with gestures
c. Can make self understood but difficulty understanding others
d. Does not respond to or communicate with others
e. Not applicable

TELEPHONE

a. Uses telephone appropriately, including obtaining correct number
b. Uses telephone if number given verbally/visually or pre-dialed
c. Answers telephone but does not make calls
d. Unable/unwilling to use telephone at all
e. Not applicable

HOUSEWORK/GARDENING

a. Able to do housework/gardening to previous standard
b. Able to do housework/gardening but not to previous standard
c. Limited participation even with a lot of supervision
d. Unwilling/unable to participate in previous activities
e. Not applicable

SHOPPING

a. Shops to previous standard
b. Only able to shop for 1 or 2 items without a list
c. Unable to shop alone, but participates when accompanied
d. Unable to participate in shopping even when accompanied
e. Not applicable

FINANCES

a. Responsible for own finances at previous level
b. Unable to write cheque but can sign name and recognizes money values
c. Can sign name but unable to recognize money values
d. Unable to sign name or recognize money values
e. Not applicable

GAMES/HOBBIES

a. Participates in pastimes/activities to previous standard
b. Participates but needs instruction/ supervision
c. Reluctant to join in, very slow, needs coaxing
d. No longer able or willing to join in
e. Not applicable

TRANSPORT

a. Able to drive, cycle or use public transport independently
b. Unable to drive but uses public transport or bike etc
c. Unable to use public transport alone
d. Unable/unwilling to use transport even when accompanied
e. Not applicable

NEUROPSYCHIATRIC INVENTORY QUESTIONNAIRE (NPI-Q)

Informant: Spouse / Child / Other : _____

Please ask the following questions based upon changes. Indicate "yes" only if the symptom has been present in the past month; otherwise, indicate "no".

For each item marked "Yes":

Rate the **SEVERITY** of the symptom (how it affects the patient):

1 = Mild (noticeable, but not a significant change)
2 = Moderate (significant, but not a dramatic change)
3 = Severe (very marked or prominent; a dramatic change)

AND ALSO

Rate the **DISTRESS** you experience because of the symptom (how it affects you):

0 = Not distressing at all
1 = Minimal (slightly distressing, not a problem to cope with)
2 = Mild (not very distressing, generally easy to cope with)
3 = Moderate (fairly distressing, not always easy to cope with)
4 = Severe (very distressing, difficult to cope with)
5 = Extreme or very severe (extremely distressing, unable to cope with)

Please answer each question honestly and carefully. Ask for assistance if you are not sure how to answer any question.

DELUSIONS: Does the patient believe that others are stealing from him or her, or planning to harm him or her in some way?

Yes No (circle)

if "Yes"

Severity? 1 2 3 (circle)

Distress? 1 2 3 4 5 (circle)

HALLUCINATIONS: Does the patient act as if he or she hears voices? Does he or she talk to people who are not there?

Yes No (circle)

if "Yes"

Severity? 1 2 3 (circle)

Distress? 1 2 3 4 5 (circle)

AGITATION OR AGGRESSION: Is the patient stubborn and resistive to help from others?

Yes No (circle)

if "Yes"

Severity? 1 2 3 (circle)

Distress? 1 2 3 4 5 (circle)

DEPRESSION OR DYSPHORIA: Does the patient act as if he or she is sad or in low spirits? Does he or she cry?

Yes No (circle)

if "Yes"

Severity? 1 2 3 (circle)

Distress? 1 2 3 4 5 (circle)

ANXIETY: Does the patient become upset when separated from you? Does he or she have any other signs of nervousness, such as shortness of breath, sighing, being unable to relax, or feeling excessively tense?

Yes No (circle)

if "Yes"

Severity? 1 2 3 (circle)

Distress? 1 2 3 4 5 (circle)

ELATION OR EUPHORIA: Does the patient appear to feel too good or act excessively happy?

Yes No (circle)

if "Yes"

Severity? 1 2 3 (circle)

Distress? 1 2 3 4 5 (circle)

APATHY OR INDIFFERENCE: Does the patient seem less interested in his or her usual activities and in the activities and plans of others?

Yes No (circle)

if "Yes"

Severity? 1 2 3 (circle)

Distress? 1 2 3 4 5 (circle)

DISINHIBITION: Does the patient seem to act impulsively? For example, does the patient talk to strangers as if he or she knows them, or does the patient say things that may hurt people's feelings?

Yes No (circle)

if "Yes"

Severity? 1 2 3 (circle)

Distress? 1 2 3 4 5 (circle)

IRRITABILITY OR LABILITY: Is the patient impatient or cranky? Does he or she have difficulty coping with delays or waiting for planned activities?

Yes No (circle)

if "Yes"

Severity? 1 2 3 (circle)

Distress? 1 2 3 4 5 (circle)

MOTOR DISTURBANCE: Does the patient engage in repetitive activities, such as pacing around the house, handling buttons, wrapping string, or doing other things repeatedly?

Yes No (circle)

if “Yes”

Severity? 1 2 3 (circle)

Distress? 1 2 3 4 5 (circle)

NIGHTTIME BEHAVIORS: Does the patient awaken you during the night, rise too early in the morning, or take excessive naps during the day?

Yes No (circle)

if “Yes”

Severity? 1 2 3 (circle)

Distress? 1 2 3 4 5 (circle)

APPETITE AND EATING: Has the patient lost or gained weight, or had a change in the food he or she likes?

Yes No (circle)

if “Yes”

Severity? 1 2 3 (circle)

Distress? 1 2 3 4 5 (circle)

NORTH EAST VISUAL HALLUCINATIONS INVENTORY III - PATIENT VERSION

Please ask about any visual hallucinations or unusual visual experiences. Questions (i-iv) should be asked, where a positive answer is given, record as much as possible of what is said in the box below.

Where descriptions are given please ask about motion, colour, size, contour, 2D/ 3D and whether what is seen is life like. *(If information is lacking, encourage the patient to give more detail)*

Section A - screening questions

(i) “Do you feel like your eyes ever play tricks on you? Have you ever seen something (or things) that other people could not see?” Y / N

(ii) “Have you ever looked at an object or pattern and something else suddenly appeared or disappeared?” Y / N

(iii) a “Have you ever had the feeling of the presence of somebody or something, in the corner of your eye?” Y / N

(iii) b “Have you ever seen somebody or something, like a shadow, in the corner of your eye?” Y / N

(iv) “Have you ever had other visual experiences?” Y / N

2) “Have you experienced seeing dots, flashes, patterns of light or similar that were not there?” Y / N

Please gather as much information as possible and please do the frequency ratings for each question answered with yes.

Section B - Frequency rating

Frequency ratings for questions 1 i) - 1 iv) and 2:

Rating refers to question	i	ii	iii	iv	2
3. When did your hallucinations first start?					
About one month ago					
Between one month and one year ago					
More than one year ago					
4. When was the last time you experienced any of the things we have spoken about?					
Within the last month					
Between one month and one year ago					
More than one year ago					
5. How often have you had hallucinations in the last month?					
Less than once a week					
1-6 times per week					
Every day					

Where there have been no hallucinations experienced within the last month please stop here
The following questions all relate to hallucinations experienced within the last month.

Please indicate whether the ratings refer to - i / ii / iii a / iii b / iv or 2

6. Approximately how long do your hallucinations usually last?
1 Less than 5 minutes
2 5 minutes to 2 hours
3 Longer than two hours

7. At what time of the day do your hallucinations usually occur?
1 Night time
2 Day time
3 They can occur at anytime

8. Are your hallucinations associated with falling asleep or waking up?
1 Never
2 Sometimes
3 Always

9. Do you find your hallucinations irritating or frustrating?
0 Not at all
1 Somewhat
2 Very

10. Do you find your hallucinations frightening or distressing?
0 Not at all
1 Somewhat
2 Very

11. Do the hallucinations ever speak or make noises?
0 Never
1 Sometimes
2 Always

12. Are your hallucinations associated with an odd smell or taste?
0 Never
1 Sometimes
2 Always

13. **Does it ever feel like the hallucinations are touching you?**
0 Never
1 Sometimes
2 Always

14. Do your hallucinations make you worry that you are losing your mind?
0 Not at all
1 Somewhat
2 A lot

15. Do you find your close relationships (e.g. with family) difficult because of your hallucinations?
0 Not at all
1 Somewhat
2 Very

16. Whilst you are having a hallucination do you ever believe it is real?
0 Never
1 Sometimes
2 Always

17. **Do you ever act out your hallucinations?**
0 Never
1 Sometimes
2 Always

18. Are you able to ignore your hallucinations?
0 Always
1 Sometimes
2 Never

19. Have you stopped doing things you used to because of your hallucinations?
0 Not at all
1 Somewhat
2 A lot

20. Do your hallucinations go together with beliefs that others say are not true?
0 Never
1 Sometimes
2 Always

“Is there anything else you can tell me about your hallucinations that we have not spoken about?”
Please record any comments made by the participant