HALLUCINATIONS IN PARKINSON'S DISEASE: A PSYCHOLOGICAL MODEL

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor of Philosophy by Daisy Whitehead

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To Sue, Dorothy, Ivan and Stan

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ABSTRACT

This thesis attempts to apply a psychological model of hallucinations to a Parkinson's Disease (PD) population, using theories and paradigms derived from studies of hallucinations in other populations; namely visually impaired, dementing, narcoleptic and schizophrenic populations, with the aim of comparing the strength of an integrated model to the existing medical model of hallucinations in PD .

Chapter one characterises the motor and cognitive effects of PD, and also the neuropsychiatric symptoms experienced by PD patients. Methodological approaches to assessing and classifying neuropsychiatric symptoms are discussed. Hypotheses are made concerning the multi-dimensional nature of hallucinatory phenomena, sleep-related phenomena and motor signs, and the presence of distinct patterns of association for each "cluster" of symptoms.

Chapter two reviews findings from existing studies of concomitants of hallucinations in PD. The evidence for a medical model which emphasises the role of generalised cognitive decline, disease and medication-related factors is assessed, and the weaknesses of the medical model discussed. Hypotheses of increased disease severity and reduced cognitive function in hallucinating PD patients are made. Alternative models of hallucinations in PD are presented, which have been derived from other populations.

Chapter three reviews investigations of sleep-related phenomena in PD, and their association with hallucinations. Theories concerning shared underlying mechanisms are discussed, and predictions of increased levels of altered dream phenomena and daytime sleepiness in hallucinating patients are made.

Chapter four reviews studies of perceptual and cognitive deficits in hallucinating PD patients, and criticises them for their lack of application of model-derived hypotheses. Paradigms to detect cognitive biases and intrusions used in the schizophrenia literature are described. Hypotheses are made, predicting greater deficits in executive, visual perceptual and attentional function in hallucinating patients. In addition, greater levels of cognitive intrusions on tests of mnemonic and executive function, and greater levels of *mis*perception on tests of visual object perception are hypothesised in hallucinating patients.

The present study investigated the presence of hallucinatory and sleep-related phenomena, used objective and subjective indices to measure sleep pattern, and neuropsychological battery to test cognitive and visual perceptual function in 78 PD patients.

Chapters six to nine review the results of the present study finding (i) multiple factors amongst sleep-related, hallucinatory and motor symptoms, (ii) increased levels of pathological motor activity and daytime sleepiness in hallucinators, and evidence of abnormal circadian rhythm (iii) an impairment on tests of object recognition, but no evidence for greater executive or attentional dysfunction in hallucinating patients and (iv) greater levels of verbal cognitive intrusions on mnemonic and executive tests, and a greater number of visual errors and object misidentifications in hallucinators. Chapter nine presents a linear regression model of hallucinations in PD, with the addition of sleep and cognitive variables explaining significantly more variance in a hallucinations score, than the medical model alone.

Chapter ten reviews findings, and discusses methodological weaknesses of the present study. A model of perceptual processes and errors that arise from them in delusional misidentification syndromes in schizophrenia is presented, and adapted to fit the findings of the current study, incorporating the role of sleep disruption. Limitations and implications of the model are discussed.

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LIST OF ABBREVIATIONS

5HT	5-hydroxy-tryptophan
A	Anomia
AADC	L-amino acid decarboxylase
AD	Alzheimer's Disease
ADE	Altered dream experiences
ADL	Activities of daily living
AH	Auditory hallucinations
AMP	Amplitude
BDS	Blessed Dementia rating Scale
CAMCOG	Cambridge Cognition
CANTAB	Cambridge Neuropsychological Test Automated Battery
CBS	Charles Bonnet Syndrome
ChAT	Choline Acetyltransferase
CG	Caregiver
CNS	Central nervous system
COMT	Catechol-o-methyl transferase
COV	Coefficient of variation
CR	Controlled release
CTE	Cross-trial errors
CTI	Cross-trial intrusions
DA	Dopamine
DLB	Dementia with Lewy Bodies

DMS	Delusional misidentification
DRT	Dopamine replacement therapy
DSM	Diagnostic and Statistical Manual for mental disorders
EDS	Excessive daytime sleepiness
EEG	Electroencephalogram
ERP	Early receptor potential
EDS	Excessive daytime sleepiness
ESS	Epworth Sleepiness Scale
GDS	Geriatric Depression Scale
HADS	Hospital Anxiety and Depression Scale
HLA	Human leukocyte antigens
I	Intrusions
IS	Interdaily stability
IV	Intradaily variability
L5	Activity during the least active 5 hours
LC	Locus coeruleus
LM	Logical memory
M	Misidentifications
M10	Activity during the most active 10 hours
MID	Multi-infarct dementia
MMPI	Minnesota Multiphasic Personality Inventory
MMSE	Mini mental-state examination
MSA	Multi-system atrophy

MSLT	Multiple sleep latency test
NART	National Adult Reading Test
NI	Novel intrusions
NPCRA	Non-parametric Circadian Rhythm Analysis
NPI	Neuropsychiatric Inventory
OH	Olfactory hallucinations
P	Perseverations
PAF	Pure autonomic failure
PD	Parkinson's Disease
PDD	Parkinson's Disease with Dementia
PET	Positron emission tomography
PIGD	Postural instability-gait-dominant
PLMS	Periodic leg movements of sleep
PPN	Pedunculopontine nucleus
PSG	Polysomnography
PSP	Progressive supranuclear palsy
QUE	Questionnaire on Unusual Experiences
R	Repetitions
RA	Relative amplitude
RAS	Reticular activating system
RBD	REM sleep Behavioural Disorder
REM	Rapid eye movement
RI	Recall Inaccuracies

RLS	Restless legs syndrome
RT	Reaction-time
SA	Sleep activity
SAS	Supervisory attentional system
SCN	Suprachiasmatic nucleus
SOREM	Sleep onset rapid eye movement episode
SPECT	Single photon emission computerised tomography
SR	Self-reported
STAI	State Trait Anxiety Inventory
SWS	Slow-wave sleep
TD	Tremor dominant
TH	Tactile hallucinations
TST	Total sleep time
UPE	Unusual perceptual experiences
UPDRS	Unified Parkinson's Disease Rating Scale
VF	Verbal fluency
VH	Visual hallucinations
VOSP	Visual Object and Space Perception battery
WAIS	Wechsler Adult Intelligence Scale
WASO	Wake after sleep onset
α7nAChR	a 7-type nicotinic acetylcholine receptor

OVERVIEW OF THESIS

This introduction charts the progression over time of the literature concerning hallucinations in Parkinson's Disease (PD), and describes the development of current models of hallucinations in PD. It will demonstrate the shift in emphasis from both pharmacological and clinicomedical approaches defining PD as a 'movement disorder', to an integrated neuropsychological and neurobiological approach, where the impact on motor, neuropsychological and neuropsychiatric function is considered.

James Parkinson's (1817) Essay on the shaking palsy describes "Involuntary tremolous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forewards [sic], and to pass from a walking to a running pace: [and critically] the senses and intellect being uninjured."

Characterised primarily as a 'movement disorder' for the large part of the 20th century, in recent years attention has turned to the broad spectrum of cognitive, psychological and neuropsychiatric symptoms experienced by many Parkinson's Disease patients.

The introduction of levodopa therapy in the 1960s, though a huge breakthrough in the treatment of motor symptoms, brought with it problems of progressive motor side-effects over time and other unwanted cognitive and psychiatric side-effects, including hallucinations, psychosis, impaired alertness and sleep disruption (Celesia & Barr, 1970). More recent pharmacological advances such as the development of dopaminergic agonists and COMT inhibitors have improved long-term treatment of motor symptoms, but have failed to resolve the problem of neuropsychiatric effects. Initially neuropsychiatric symptoms were thought to be due to the progressive effects of dopaminergic therapies, as dopaminergic receptors became 'hypersensitive' to medication. Experience of distressing and disruptive side-effects was looked upon as an unfortunate problem which necessitated

careful pharmacological management to balance the benefits of improved motor functioning with the cost of upsetting symptoms for both patients and caregivers. Crucially then such psychiatric symptoms were thought to be largely due to medication and neural adaptation to it over time, rather than being a fundamental effect of Parkinson's pathology or the disease process itself (Moskowitz et al, 1978). Moreover, case reports of hallucinations in unmedicated PD patients have emerged from time to time, (Konig, 1912; Jackson, 1923; Mjones, 1949). however, these earlier studies however, may have suffered from a lack of diagnostic specificity and it is certainly possible that some cases involved concurrent PD and dementia (PDD), Dementia with Lewy Bodies (DLB) or PD and psychosis in the same individual. Advances in brain scanning techniques and knowledge of the complexities of neurotransmitter systems and their interactions have demonstrated the extent to which dopaminergic loss in the basal ganglia has 'upstream' effects, implicating functions in many higher cortical processes, and also the disruption to other neurotransmitter systems such as acetylcholine, serotonin and noradrenalin. Subtle deficits in perception, executive function and attention without gross changes in global cognitive ability have been described in both medicated and unmedicated Parkinson's patients. Therefore, if these neuropathological changes underlie cognitive change independently of medication, then neuropsychiatric symptoms may also arise from changes endemic to the disease process.

Dementia with Lewy Bodies (DLB) with its cortical distribution of Lewy bodies was first described as a histopathological phenomenon in 1913 and as a clinical entity in 1996. This disease which encorporates the pathological and clinical aspects of Parkinson's Disease, as well as those of a cortical dementia, may first present as a movement disorder with later widespread cognitive decline and prominent psychiatric symptoms, particularly visual hallucinations. These 'positive' neuropsychiatric symptoms including Rapid-eye-movement

(REM) behaviour disorder, vivid dreams, hallucinations, delusions and psychosis bear such a close resemblance phenomenologically to those experienced by Parkinson's patients that distinguishing the two diseases in the presence of mild cognitive impairment is often very difficult. Whether PD with dementia and DLB are two distinct pathologies or essentially at an overlapping point in the spectrum of α-synucleinopathies is a matter of keen debate, and will be discussed later in this chapter. It is also possible that subtypes exist within the diagnosis of PD which have yet to be fully delineated. Critically, in DLB neuropsychiatric symptoms can emerge without the presence of dopaminergic medication, and so in such cases these symptoms clearly have an anatomical pathological basis rather than a medication-related one. The range of motor, cognitive and neuropsychiatric symptoms in PD, PDD and DLB are reviewed in Chapter 1.

Prior to the beginning of the current study, the majority of research into the phenomena of hallucinations in Parkinson's Disease had used a clinicomedical approach with a focus on the pharmacological and disease-related concomitants of hallucinations. These studies can be considered as the first and second generation within the hallucinations in PD literature. Though disease severity and mild cognitive decline were found to be robust predictors of hallucinations in PD, what these studies largely neglected to address was the specific cognitive profile of hallucinators, driven by theoretically derived hypotheses. Chapter 2 reviews this literature and considers the methodological issues and flaws raised by these studies.

Other 'concomitants' had included poor eyesight, disruption to sleep and presence of vivid dreams and daytime sleepiness, prompting later researchers, a 'third generation', to draw on models of hallucinations in narcolepsy, schizophrenia, other dementias and Charles Bonnet Syndrome to examine hallucinations using specific paradigms, and moving away from a purely pharmacological model. Arnulf et al (2001) used objective polysomnographic

measures of daytime sleepiness to examine the changes in consciousness that are typical of hallucinators, and drew parallels with hypnopompic hallucinations experienced in narcolepsy. The way in which PD impacts upon sleep, and the role sleep-related mechanisms play in hallucinations will be reviewed in Chapter 3. Most recently Barnes et al (2003) examined the cognitive profile of hallucinators using a battery of visual tests and also a reality monitoring paradigm taken from research into auditory hallucinations in schizophrenia. These approaches which have set out to test specific a priori hypotheses about the nature of hallucinations and the mechanism producing them on a functional level rather than focusing solely on clinical measures of severity and non-specific global cognition have proved fruitful in advancing theoretical models of hallucinations in a Parkinsonian population. Chapter 4 reviews the development of studies which have examined cognitive function in PD hallucinators and in other hallucinators in a systematic manner, and draws on experimental paradigms from other literatures to set out the current study's hypotheses.

In recent years some excellent theoretical reviews have appeared which have attempted to draw together literature both concerning hallucinations in PD and in other dementias and diseases (Manford & Andermann, 1998; Collerton et al, unpublished). In summary, emphasis has shifted over the past 40 years from considering hallucinations amongst a range of L-dopa side effects, to considering hallucinations as a single symptom for which specific correlates or 'predictors' were identified, and finally to a more integrated approach drawing on a rich experimental literature on hallucinations in other populations and adopting a theory-driven experimental approach. This thesis aims to test specific *a priori* hypotheses, utilising paradigms and methods drawn from the wider literature to build an integrated model of hallucinations in Parkinson's Disease.

CHAPTER 1

RANGE OF PSYCHOLOGICAL AND NEUROPSYCHIATRIC DISTURBANCE IN PARKINSON'S DISEASE

1.1 Parkinson's Disease - population characteristics

The following section characterises the Parkinson's Disease (PD) population in the UK, as well as Europe and the US, and outlines the motor aspects of the disease to familiarise the reader with concepts of disease severity and with clinical terms which will be used throughout the thesis.

1.1.1 Incidence and Prevalence of Parkinson's Disease in the UK

Parkinson's Disease typically emerges in the later decades of life with a lifetime prevalence of 2 (95% CI 1, 3) per 1000, and an incidence of 19 (95% CI 12, 27) per 100,000 in the UK (MacDonald et al, 2000). The bulk of these cases lie within age ranges 60 to 90 (MacDonald et al, 2000), although there is increasing recognition and diagnosis of early-onset cases, which are defined as beginning before the age of 40. A subgroup of juvenile onset cases, though even rarer have been reported in patients aged under 21. Given this age-related demographic pattern prevalence and incidence vary across age and a recent collaborative study of seven European population based cohorts gave the following prevalences: for ages 65-69, 6 per 1000; 70-74, 10 per 1000; 75-79, 24 per 1000; 80-84, 30 per 1000; 85-89, 26 per 1000; and for the 90+ range, 25 per 1000. It can therefore be seen that prevalence peaks during the 70-90+ age range and although age at onset can vary widely the typical PD population is an elderly group, many of whom have retired. Suggestions have been made as to different phenotypes and possibly aetiologies of Parkinsonism occurring in early versus late onset

cases (Riderer & Foley, 2002). However, the current study included only late onset cases in order to achieve a more homogeneous sample.

1.1.2 Gender, race and PD epidemiology

Despite the fact that PD tends to occur later in life, it affects a greater proportion of men, with a typically quoted male:female ratio of 2:1. A recent review of incidence studies calculated an increased relative risk for men, with males being 1.5 times more at risk than women (Wooten et al, 2004). Reasons for this gender difference are unclear, but studies have suggested that oestrogen may have a neuroprotective role, that nitrergic systems are more active in men leading to increased glutamate neurotoxicity, that exposure to toxins and head trauma may be more likely in men or that a PD susceptibility gene may be localised to the X chromosome (Kompioliti, 2003; Taskiran et al, 2003; Tanner & Goldman, 1996; Pankratz et al, 2002). The current study's sample replicates this 2:1 sex ratio and therefore reflects the current epidemiological trends of Parkinson's Disease. Prevalence and incidence of PD in non-white UK citizens is controversial and there are suggestions of a greater number of atypical presentations of Parkinsonism in Afro-Caribbean and South Asian patients living in the UK (Chaudhuri et al, 2000). The participants in the present study were exclusively White European, reflecting both the demographic mix in some parts of the North West, and perhaps reflecting lower prevalence rates or lower diagnosis rates in Asian and Afro-Caribbean patients.

1.1.3. Prognosis of PD patients in the UK and Europe

Prognosis for European patients with PD is significantly worse than for age and sex matched noncases, with increases in relative risk of death and of institutionalisation for all age groups from 55 onwards (Berger et al, 2000), and a mortality rate ratio of 1.6 (95% CI 1.3-1.8) across all ages in a Swedish community-based study (Fall et al, 2003) However the actual difference in mean age at death was only one year; 81.9 (95% CI 80.3-83.0) for cases and 82.9 (95% CI 82.0-83.7) for non-cases (Fall et al, 2003). Striking differences emerge in terms of risk of mortality and of institutionalisation between the sexes, with men having a greater relative risk of death (OR 3.08; 95% CI 2.14-4.42) than women (OR 1.78; 95% CI 1.25-2.54), and women having a five-fold increased risk of institutionalisation (OR 7.94; 95% CI 4.87-12.96) than men (OR 1.67; 95% CI 0.69-4.05) (Berger et al, 2000). This latter finding is likely to reflect the fact that older men are less likely to have lost their spouse and caregiver than older women, as well as female spouses being more prepared to take on the role of caregiver.

1.2 Motor aspects of Parkinson's Disease

1.2.1 Clinical symptoms and diagnosis

Autopsy confirmation of basal ganglia pathology is necessary for a definite diagnosis of PD, and basal ganglia Lewy bodies (eosinophilic inlcusion bodies) are the histopathological hallmark of PD (Jellinger 2003). In the absence of widely available techniques for assessing in vivo dopaminergic function, diagnosis is usually made according to clinical criteria suggesting 'possible' or 'probable' PD (Calne et al, 1992). Parkinson's Disease is characterised clinically by three cardinal signs; tremor, bradykinesia (or poverty of movement), and rigidity, and for a diagnosis of 'probable' PD 2 of the 3 signs must be present (Calne et al, 1992). Postural

instability has also been classed as a cardinal sign according to some diagnostic schemes, although it may be absent in early PD. Other symptoms include a shuffling gait, problems with speech, a mask-like face (hypomimia), and hypersalivation. In a functional sense, PD patients may have problems with standing up from sitting, walking, any tasks which require manual dexterity and a firm grip such as dressing and grooming, turning around, maintaining balance, turning over in bed, painful paraestheias and 'freezing' (problems with hesitation or initiation of gait) when walking over thresholds. Autonomic dysfunction may also be present with orthostatic hypotension, constipation and urinary frequency (Jost, 2003; Kaufmann & Biaggioni, 2003). Other diseases affecting basal ganglia function, in particular diseases involving histopathological changes consistent with Lewy bodies (the α-synucleinopathies) may be difficult to differentiate from PD in their early stages. Responsivity to dopaminergic replacement therapy is another sign that is supportive of a diagnosis of PD, as patients with progressive supranuclear palsy (PSP), multiple-system atrophy (MSA) and dementia with Lewy bodies (DLB) show limited motor response to levodopa. Hughes et al (2002) demonstrated an improvement in diagnostic accuracy of PD in the UK compared to a study 10 years previously (Hughes et al, 1992), with a greater frequency of autopsy confirmation of PD clinical diagnosis.

1.2.2 Pathology of PD - mechanisms of motor disorder

The underlying mechanism of motor dysfunction in PD is loss of function in the dopaminergic pathway from the substantia nigra to the caudate nucleus and putamen, which are together known as the 'striatum'. The striatum, pallidum, subthalamic nucleus and substantia nigra pars compacta together comprise the 'basal ganglia', which is responsible primarily for motor

control. As can be seen from Figure 1.1 below, loss of dopaminergic cells in the nigrostriatal pathway impacts upon structures and pathways within the basal ganglia, and also has implications for ascending pathways to the cerebral cortex.

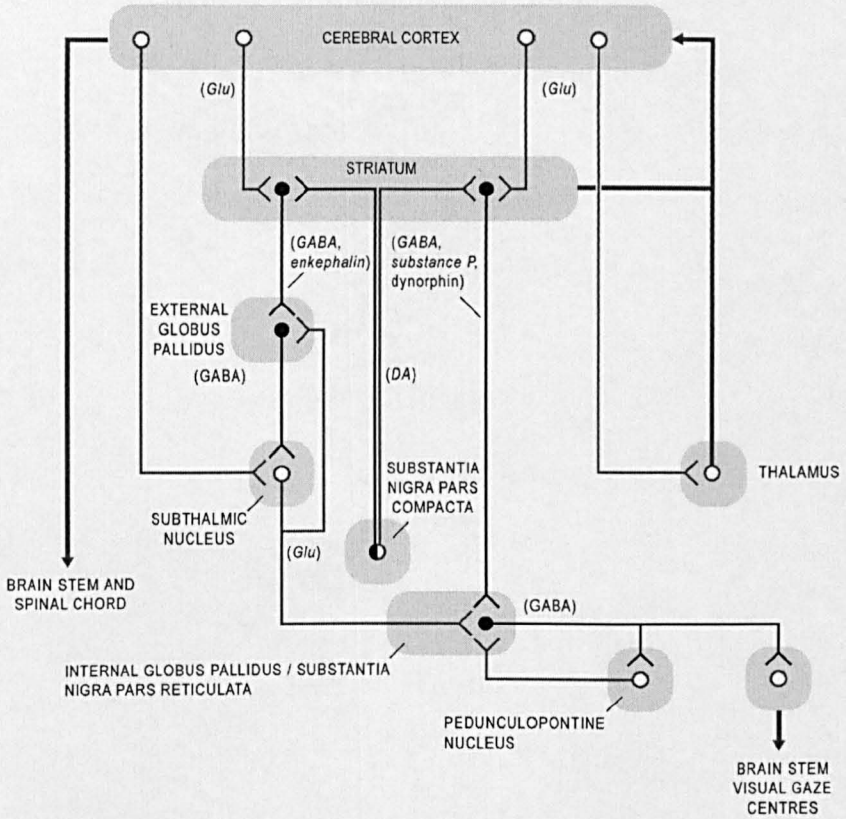


Figure 1.1 Diagram of basal ganglia-thalamocortical circuitry and neurotransmitters (adapted from Feldman et al, 1997). DA = dopamine; GABA = gamma-amino butyric acid; Glu = glutamate.

Autopsy studies have found that 70-80% of striatal dopamine and 50% of nigral neurons are typically lost before the motor symptoms of PD reach clinically detectable levels (Agid et al, 1987; Fearnley et al, 1991). Therefore dopaminergic loss may have been developing, although at subclinical levels, for several years prior to the emergence of motor signs. Figure

1.1 shows the complexity of the basal ganglia pathways, and the impact that loss of striatal dopamine may have on other pathways and neurotransmitters within the system. Some Parkinsonian symptoms, such as hypersalivation, are thought to result from an imbalance between cholinergic and dopaminergic function.

'Lewy bodies', abnormal cytoplasmic inclusions, are found in degenerating brain stem neurons, and are the pathological hallmarks of Parkinson's Disease and the wider α-synucleinopathies (Jellinger, 2003). Lewy bodies are not confined to the striatum, and have also have been found in the amygdala, locus coeruleus and cortex in PD patients, with implications for non-motor symptoms such as changes in the sleep/wake cycle, sensory and cognitive deficits (Braak et al, 2003). Extrastiatal pathology, and changes in dopaminergic projections to other areas of the brain may affect other neurotransmitter systems in localised areas. Reduced cholinergic function has been observed in the hippocampus and cortex, noradrenergic cell loss in the locus coeruleus which has implications for function in the cortex, hippocampus, amygdala, thalamus and hypothalamus, and serotonergic activity is also affected by Parkinson's Disease (Agid et al, 1987; Gerlach et al, 1994). Such widespread change has important implications for cognitive, perceptual, affective and neuropsychiatric function in PD (Ring & Serra-Mestres, 2002; Aarsland & Ehrt, 2003).

To summarise, changes in dopaminergic function in the motor pathways of the basal ganglia may have been developing before disease diagnosis, with subtle effects on CNS processes other than movement (Prunztek et al, 2004). As PD progresses, dopaminergic loss and more widespread pathology may impact upon perception, cognition, affect and the sleep/wake cycle.

1.2.3 α-synucleinopathies - PD within a wider range of movement disorders

As has been mentioned Lewy bodies are found at autopsy in a range of CNS disease known as the α-synucleinopathies, including PD, PD with dementia, DLB, Pure Autonomic Failure (PAF) and Multiple System Atrophy (MSA) (Marti et al, 2003; Jellinger, 2003). All display Parkinsonian-type motor symptoms, though these may vary according to the extent and location of Lewy bodies. DLB in particular is difficult to differentiate from PD in the early stages, and is characterised by cognitive loss, hallucinations, extrapyramidal motor symptoms and fluctuations in cognition (McKeith et al, 1996; Klatka et al, 1996; Ferman et al, 2004), and less frequently REM behaviour disorder, repeated falls and systematised delusions (McKeith et al, 1999; Del Ser et al, 2000; Ferman et al, 2004) . The overlap in symptomatology has meant that DLB may be currently underdiagnosed, and PD overdiagnosed by clinicians (Litvan et al, 1998). Current diagnostic criteria recommend that if cognitive decline is apparent prior to or within one year of the onset of motor symptoms, then DLB should be diagnosed (McKeith et al, 1996). PD with dementia is arguably highly similar in terms of clinical symptoms and pathology, but is diagnosed if dementia emerges more than one year after onset of motor symptoms (McKeith et al, 1996). Therefore the distinction between the two diseases is somewhat arbitrary, and patients may be indistinguishable from one another several years into the disease process. Similarities and differences between PD, PDD and DLB are discussed later, though whether they in fact lie on the same disease trajectory is still unresolved.

1.2.4 Concepts of disease severity and its assessment

The concept of disease severity in PD can be defined in a number of ways, demanding different means of assessment. Disease duration is perhaps the most simple measure, but in

practice this usually means duration since diagnosis, as motor symptoms are insidious and slow to develop. Disease duration though fails to take into account the rapidity of decline. Therefore, one patient who has had the disease for only three years may show the same degree of motor impairment as another who has a disease duration of ten years. Disease severity has also been conceptualised as a series stages through which the patient progresses, leading to more severe motor symptoms. Perhaps the most widely used is Hoehn & Yahr's five stage scale (Hoehn & Yahr, 1967). The scale assumes a unilateral onset, which then progresses to involve both sides of the body and affects postural stability in the later stages. Disadvantages of this scheme are that it assumes a specific order of diseases progression, that it has a small range of scores, and that it does not assess atypical symptoms which may be problematic to the patient, nor take into account overall level of disability. Measuring disability in terms of impairment in carrying out everyday functions is a useful way of measuring the impact of symptoms upon an individual and can be an easy way for informants or patients themselves to rate their own disease severity. Non-specific activities of daily living (ADL) scales, for example the Schwab-England Scale , can be used to assess functional disability, allowing comparisons across different disease population but a scale specific to PD which has been developed as part of the Unified Parkinson's Disease Rating Scale (Fahn & Elton, 1987) may provide the clinician with more information about problems specific to PD such as hypersalivation, 'freezing' or dyskinesias. The UPDRS also contains a motor examination scale which is a clinical examination of specific motor abilities. This scale provides a large range on which the patient can score, and measures both upper and lower body involvement and left and right body functioning. Specific motor examinations such as these may provide the closest measure of dopaminergic function beyond pharmacological

challenges or Positron Emission Tomography (PET) scanning, and indeed UPDRS score has been shown to correlate with central dopaminergic function as quantified by PET (Otsuka et al 1996). However, a number of studies have indicated that the scale also takes into account motor features mediated by non-dopaminergic systems, which may be less responsive to levodopa therapy, but have important implications for prognosis (Jankovic et al, 1990; Levy et al, 2000).

1.2.5 Progression of movement disorder in PD

Motor presentation at onset and rate and degree of disease progression can vary enormously between patients, and it has been suggested that different phenotypes of the disease exist, perhaps with different aetiologies, complications and prognoses (Jankovic et al, 1990; Levy et al, 2000). Jankovic et al (1990) propose two clusters of motor symptoms characterising two groups of patients; those with a tremor-dominant (TD) presentation, and those with a postural-instability-gait dominant (PIGD) profile. Jankovic and colleagues as well as other groups found a different prognosis in terms of rapidity of disease progression, and likelihood of intellectual impairment for these groups, with PIGD patients showing worse outcome in both aspects (Burn et al, 2003). Levy et al (2000) using a similar approach characterised two groups of motor symptoms - Group A including bradykinesia, rigidity, tremor and facial expression and Group B speech and axial impairment (posture, postural stability and gait) resembling a PIGD subtype, which displayed a greater susceptibility to dementia. It has been suggested that so-called axial signs arise from more widespread central nervous system (CNS) dysfunction beyond the confines of the basal ganglia and nigrostriatal tracts, and may reflect deficits in non-dopaminergic systems, possibly the cholinergic system, which are therefore less

responsive to L-dopa treatment (Levy et al, 2000). Accordingly, in a comparison of motor symptoms in patients with Parkinson's Disease without dementia, Parkinson's Disease with dementia and Dementia with Lewy Bodies, Burns and colleagues (2003) found that PDD and DLB patients were more likely to show a PIGD pattern of symptoms. Therefore different combinations of motor symptoms at presentation can imply different prognoses and likelihood of cognitive changes, and may also suggest a greater likelihood of neuropsychiatric symptoms such as hallucinations.

1.2.6 Management of PD - Dopamine Replacement Therapy and its side-effects

The following section will briefly review the range of medication used to treat Parkinson's Disease to familiarise the reader with the different categories, to highlight the range of side-effects and to describe motor-related complications that can arise from treatment with L-dopa.

1.2.6.1 Levodopa

Levodopa is the natural precursor of dopamine in the human brain, and is the most potent of dopamine replacement therapies (DRT). It is converted to dopamine by the enzyme L-amino acid decarboxylase (AADC) in the brain, and the addition of benserazide and carbidopa to levodopa preparations reduces breakdown of levodopa peripherally by AADC. In the UK current preparations of levodopa are Sinemet and Madopar and PD patients are typically started on a low dose, which is increased to maximise motor benefits. As with all DRT, pharmacological and pharmacokinetic factors reduce efficacy over time, and dosage and frequency of dose are usually increased over the years, as further cell loss occurs in the substantia nigra.

1.2.6.2 Catechol-o-methyl-transferase (COMT) inhibitors

COMT inhibitors block the central breakdown of levodopa and so are used in conjunction with levodopa therapy to avoid early wearing-off, but without the need to increase the dose or frequency of levodopa itself.

1.2.6.3 Dopamine agonists

Dopamine agonists such as ropinirole, pramipexole and cabergoline act directly on post-synaptic dopamine receptors. They provide a longer duration of action than levodopa, and may be use to 'smooth out' fluctuations in patients who have been on levodopa for some time. Some dopamine agonists have been implicated in excessive daytime sleepiness, and "sleep attacks", and ergoline dopamine agonists such as pergolide may present an elevated risk for hallucinations.

1.2.6.4 Anticholinergics

Dopamine and acetylcholine work in tandem in the motor system by counteracting each other's effects. Anticholinergic drugs are therefore used to counteract the effects, such as hypersalivation, of increasing levels of endogenous acetylcholine when endogenous dopamine declines. Although anticholinergics are useful in younger patients with pronounced tremor, they are contra-indicated in patients with confusion or cogntive decline, as they can exacerbate both these problems. Dubois et al (1990) compared neuropsychological performance in PD patients with anticholinergic treatment as an adjunct to levodopa and those without, and found that those using anticholinergics showed significantly poorer performance on WAIS verbal tests, digit span and on several measures indicating frontal function. There is also evidence of reduced choline-acetyl-transferase (ChAT) activity in PD, and even more markedly in PDD and DLB (Tiraboschi et al, 2000), and some studies have suggested that

anticholinergics are associated with increased tendency to hallucinate in PD (Goetz & Stebbins, 1995) and thus there appears to be good theoretical and clinical evidence that anticholinergics have serious side-effects in PD.

1.2.7 DRT induced complications - dyskinesias, the on-off phenomena and freezing

As discussed, treatment using dopamine replacement therapies (DRT) may reduce certain motor signs, whilst having little impact on others, but may also cause complications over time which result in increased motor problems, albeit of a different nature to the core symptoms of tremor, rigidity etc. Chronic use of L-dopa leads to a gradual 'wearing-off' of the drug, where fluctuations in response became apparent (Nutt, 2001). These fluctuations typically start after a 'honeymoon' period of 3-5 years, and increase as the drugs wear off more quickly towards the end of the dose, eventually resulting in 'off' periods where tremor, rigidity and bradykinesia return, and sometimes in periods of complete akinesia (Marsden et al, 1981; Riley & Lang, 1993; Quinn, 1998). Fluctuations become more frequent over time, and patients may switch between 'on' and 'off' motor states several times within the duration of a single dose. In addition, 'dyskinesias' (abnormal involuntary movements) emerge in some patients which can be just as disabling as the initial motor symptoms (Luquin et al, 1992). Reasons for the development of motor fluctuations may reflect a combination of pharmacokinetic factors, progression of the disease itself with loss of central dopaminergic function, and pharmacodynamic factors possibly the development of 'hypersensitivity' of dopamine receptors (Nutt et al, 1988; Quinn, 1998). These drawbacks have prompted the development of soluble preparation of levodopa to 'rescue' patients in off periods, sustained release tablets to reduce wearing off, COMT inhibitors to prolong the effect of levodopa and the concurrent

use of agonists which carry a far smaller risk of dyskinesias (Olanow et al, 2000). In addition, many younger patients, for whom a longer disease duration is likely, are now started on an agonist as the initial drug therapy which provides a 'smoother' action over the course of the day and allows the introduction of levodopa and its inherent problems to be delayed (Rascol et al, 2002).

However, agonist medications have been found to present greater risks of side-effects such as psychosis, are used more cautiously in elderly patients, and are contra-indicated in those with some degree of dementia (Saint-Cyr, 1995; Goetz & Stebbins, 1993). To summarise motor fluctuations may be just as disabling for a patient as the initial motor symptoms, and reflect changes in receptor sensitivity in the nigrostriatal pathway following chronic stimulation.

1.2.8 Management of motor and mental symptoms - the clinician's dilemma

Management of PD typically involves regular assessment of motor symptoms, and gradual increases in dose and frequency of medication, addition of agents to prolong release such as the controlled-release (CR) preparations or COMT inhibitors, and often introduction of other medications (Quinn et al, 1998; Rascol et al, 2002). Increases or changes in dose and type of medication are therefore an ongoing process in PD, which may act as triggers for the emergence of neuropsychiatric side-effects such as hallucinations or psychosis (Goetz et al, 1993; 1995; 1998; Saint-Cyr et al, 1993). In such cases management becomes a process of maximising the motor benefits of therapy whilst minimising the side-effects, and the distress caused to both patient and caregiver from both aspects needs to be weighed up. To summarise, in order to manage a patients motor symptoms and maximise mobility, medication must be regularly reviewed. However, good motor function may only be achieved at the

expense of distressing neuropsychiatric symptoms, a problem which has emerged as a key therapeutic dilemma (Damecour & Turcotte, 1995; Doraiswamy et al, 1995).

1.3.Cognitive effects of Parkinson's Disease

The following section will briefly describe prevalence of cognitive decline in PD and outline the range of cognitive deficits found in Parkinson's Disease patients. A more in depth discussion of cognitive deficits in PD, PDD and DLB will be found in chapter 4. At this point though a brief outline will serve to characterise the nature and prevalence of cognitive change in the PD population.

1.3.1 Overview of cognitive deficits in PD

As mentioned previously, the character of cognitive decline does not typically fall into a model of cortical dementia such as described in the DSM criteria. Changes are often subtle and insidious and may not be severe enough to impair daily functioning (Emre, 2003). (A subclinical decline in global functioning may be found in many PD patients, but reaches levels compatible with a diagnosis of dementia in only a subgroup). Perhaps the most prominent feature of PD cognitive change is a dysexecutive function (Dubois & Pillon, 1997; Emre, 2003). Dubois and Pillon (1997) argue that all cognitive deficits in PD can be explained by an underlying dysexecutive syndrome which impacts on other cognitive domains such as attention, memory, visuospatial ability and construction, which are in effect secondary deficits resulting from inability to perform a wide range of tasks due to deficits in planning, initiation of an appropriate response, shifting attention and loss of ability to monitor responses adequately.

Deficits in other domains are well-documented, although it could be argued that many paradigms used to examine these domains require in tact executive abilities. Deficits truly reflecting impairment in other domains would require that they were independent from executive function statistically. If present, such deficits would imply either that subcortical damage exerted a wider effect on cognitive function, or that neocortical or cortical damage was present.

Memory deficits in PD and PDD differ from the widespread and profound loss of both recall and recognition in Alzheimer's (Pillon et al, 1991; Stern et al, 1993). Deficits in attention have been well-documented, in terms of reaction-time, vigilance and ability to carry out continuous performance tasks (Litvan et al, 1991). Visuospatial deficits appear relatively early in the disease trajectory, though they may be exaggerated by peripheral and central visual perceptual deficits in contrast sensitivity, colour discrimination, loss of acuity due to retinal dopamine loss and double vision (Cummings, 1992; Harris, 1998). Language functions in PD do not display the gross deficits found in Alzheimer's Disease.

1.3.2 α-synucleinopathies and dementia - the problem of diagnostic specificity

As mentioned in the outline advances in scanning and histopathological techniques have shown that damage to the basal ganglia has implications for cognitive processes mediated by projections from the striatum. It has been demonstrated that deficits in cognitive performance correlate with certain motor symptoms (Burn et al, 2003; Levy et al, 2000) yet cognitive loss certainly cannot be explained by motor or speech impairment alone, nor entirely by concepts of 'bradyphrenia' or 'psychic slowing' (Naville, 1922). However, changes in cortical function arising from subcortical projections cannot alone explain the full range of neuropsychological

found in PD patients, and administration of dopaminergic therapy can not significantly reverse deficits. Given the elevated risk of dementia in the α-synucleinopathies, it is clear that some cortical damage or atrophy may underlie impairment in some higher functions such as memory, visual function and attention.

Consideration of cognitive change in PD and PDD is complicated by the existence of DLB and its similarity to PDD, and also the fact that it is a relatively recent clinical entity. Therefore, earlier studies of dementia and cognitive deficits in PD may well have included patients who would now be diagnosed as having DLB, and so estimates of prevalence and descriptions of the typical pattern of impairment may have changed over time. As discussed below, the existence of DLB and lack of a definitive clinical test for either PD, PDD or DLB until autopsy, with histopathological criteria also, raises a number of methodological issues that must be taken into consideration when interpreting studies of cognitive change or other neuropsychiatric features in PD.

1.3.2 Exploring dementia in the α-synucleinopathies - methodological considerations

Methodology used in both epidemiological and experimental studies has an important implications for estimates of prevalence and delineation of typical characteristics in Parkinson's disease. This is made particularly relevant in this group of patients given the lack of a definitive clinical test for either PD, PDD or DLB until autopsy, and with disputed criteria even at autopsy stage (Braak, 2003; Jellinger, 2003). For this reason, given that few studies have had the resources to apply a prospective design, following patients until autopsy, estimates of prevalence of dementia, as well as other neuropsychiatric symptoms in PD, may be affected by a number of factors; study design, whether prospective or retrospective

following autopsy, inclusion and exclusion criteria, in particular whether attempts are made to exclude possible DLB patients, the instrument or criteria used for assessment and the source of the sample. Assessment of dementia in PD has raised a number of difficulties as it does not fall into the typical pattern associated with Alzheimer's Disease, on which the DSM criteria are broadly based, showing a combination of executive and visuospatial dysfunction rather than signs of agnosia, apraxia and aphasia and prominent memory loss as is found in Alzheimer's (Dubois et al, 2001; Emre 2003, Turner et al, 2002).

Prevalence of dementia in PD has been estimated at about 40%, according to a review of 27 studies carried out prior to 1988 (Cummings et al, 1988), and PD is thought to represent a 4 to 6-fold increase in the risk of dementia according to age. One population study found a prevalence of 27.2%, using DSM criteria for dementia, though this study found that early occurrence of autonomic failure, symmetrical disease presentation and limited response to DRT were associated with dementia (Aarsland et al, 1996), and these features are together suggestive of DLB or PDD. A more recent UK cohort study, excluding patients with symptoms suggestive of DLB and a wider index of cognitive ability (the Mini-Mental State Examination, the Tower of London task to assess isolated frontal lobe impairment, and a pattern recognition task) found a prevalence of 36% of 'cognitive impairment' (Foltynie et al, 2004).

To summarise, around one-third of PD patients have shown patterns of cognitive impairment, in cohort studies carried out since DLB became a recognised differential diagnosis, although this impairment may not fit the classical profile of a 'cortical' dementia as is defined by DSM-IV criteria.

1.3.3 DLB and PDD – similarities in motor and cognitive profile

As mentioned earlier DLB and PDD may involve similar clinical symptoms of dementia, extrapyramidal motor signs, hallucinations and fluctuations in cognition (McKeith et al, 1996; Ballard et al, 2002). Histopathological similarities also exist, with Lewy bodies found in subcortical, neocortical and cortical areas (Jellinger, 2003). Louis et al (1997) found a greater incidence of resting tremor in PD patients as compared to DLB patients, but few of their PD patients showed clinical levels of dementia. Noe et al (2004) compared PDD and DLB patients with an equivalent degree of cognitive decline, and found no differences in motor profile. Burn et al (2003) found that both PDD and DLB patients were more likely to show a PIGD pattern of motor symptoms than non-demented PD patients, suggesting greater involvement of non-dopaminergic pathology.

Few studies have investigated neuropsychological profile in DLB and PDD patients. Downes et al (1992) found that DLB patients showed more exaggerated executive decline than advanced PD patients matched for global cognitive function. However, both their groups were high functioning individuals with high-average premorbid levels of IQ. Noe et al (2004) found no differences in PDD and DLB neuropsychological profile, and both groups showed relative preservation of mnemonic function compared to a group of Alzheimer's Disease (AD) patients, but greater deficits in visual perceptual and constructional abilities. Although few studies have directly compared PDD and DLB patients matched for overall degree of cognitive impairment, the existing evidence suggests that in terms of motor and neuropsychological profile there is little or no difference.

1.3.4 Cognitive and neuropsychiatric features of PD - parallel and overlapping deficits

The character of cognitive changes in PD is of significant importance in considering neuropsychiatric features. In his review of the historical development of the concept of bradyphrenia, Rogers (1986) notes the extent to which concepts of motor impairment and cogntive and affective change can overlap. Bradyphrenia with its prominent symptoms of slowing of thought, diminished spontaneous interest and initiative and increased fatigueability resembles in many ways the features of psychomotor retardation in major depression. Drawing parallels between the cognitive and neuropsychiatric features may be valuable in suggesting cogntive mechanisms underlying these symptoms, and as Rogers suggests may be the most fruitful way defining and investigating the neuropsychiatric features of PD. For example, as discussed, generalised cogntive slowing bears similarities to features of both depression and apathy, both frequent symptoms in PD. Impairments or fluctuations in attention may be closely related to the fluctuations in arousal so typical of PD patients with excessive daytime sleepiness. Deficits in facial recognition are paralleled by delusional misidentification syndromes which are relatively frequent in DLB and widespread deficits in visual perception and visuospatial function may be reflected in the frequency of visual illusions and hallucinations. Thus each cluster of symptoms may be examined using cognitive, psychiatric or psychological approaches.

Cognitive deficits	Neuropsychiatric features
'Bradyphrenia' or cognitive slowing	Depression and apathy
Fluctuations in attention and arousal	Excessive daytime sleepiness
Deficits in facial recognition	Delusional misidentification syndrome
'Frontal' or executive deficits	Disinhibition, aggression and hypersexuality
Visuoperceptual deficits	Visual illusions and hallucinations
Recall memory deficits	Confabulation and delusions

Table 1.1 'Parallel' cognitive and neuropsychiatric symptoms in PD

The following discussion of the range of neuropsychiatric symptoms in Parkinson's Disease, can be considered using a psychiatric framework which divides symptoms into affective, psychomotor and psychotic symptoms, or into 'positive' and 'negative' symptoms as has been used in schizophrenia. Associations with cognitive change will be noted, and expanded upon in the following chapters.

1.4 Neuropsychiatric effects - range from sleep to mood to 'psychotic' type.

The following section describes neuropsychiatric symptoms that have been documented in PD patients, encompassing affective, psychomotor and psychotic type phenomena, and also sleep-related phenomena. Table 1.2 lists the range of neuropsychiatric symptoms described in PD literature.

Affective
Anxiety
Depression
Psychomotor
Apathy
Agitation
Hypersexuality
Psychotic
Hallucinations
Delusions
Misidentification syndromes
Sleep-related
Nocturnal motor problems
Sleep fragmentation
Altered dream phenomena
REM behaviour disorder
Excessive daytime sleepiness
Changes in circadian rhythm

Table 1.2 Range of neuropsychiatric symptoms described in PD

1.4.1 Range of neuropsychiatric symptoms - conceptual approaches to grouping

Table 1.2 includes a wide variety of experiences which may stem from distinct, related or overlapping pathophysiological mechanisms. In the existing literature a psychiatric approach to these symptoms has typically been used (Moskowitz et al, 1978; Cummings, 1992; Doraiswamy et al, 1995), as is reflected in the classification of symptoms in Table 1.2. In some studies of the neuropsychiatric symptoms of PD, 'psychotic' symptoms as a group have been examined and clinical correlates of them sought in an attempt to uncover the underlying pathological mechanisms (Nauseida et al, 1982; Naimark et al, 1996). This approach has been criticised on a number of grounds. Firstly, 'psychotic' symptoms include a wide range of

phenomena, which are not homogeneous either in terms of their pattern of occurrence (i.e. they do not all occur simultaneously in the same individual), or in the mechanisms underlying them (Frith, 1992; Bentall, 1994). Bentall (1994) argues for a single-symptom approach where hallucinations, delusions and other psychotic phenomena are considered individually, as studying broader 'syndromes' may confuse distinct underlying mechanisms, and reduces the specificity of predictor variables and of testable models derived. Frith (1992) argues that the distinct phenomena should be examined separately, or as a cluster of symptoms that have shown robust empirical associations. In this way the underlying mechanisms of each phenomenon can be delineated, and then an integrated model of co-occurring phenomena derived within a larger framework.

The concept of 'schizophrenia' as a clinical syndrome or a single diagnostic entity has been criticised, and more recent approaches have looked at correlates of individual symptoms, and have sought to classify them using empirical associations (Andreasen & Olsen , 1982) into "positive" and "negative" symptoms which have since been replicated. Frith (1992) and others have developed models which have generated testable hypotheses about, for example, the specific cognitive and perceptual biases underlying hallucinations, within a wider framework of positive symptoms. The framework is built by noting similarities in underlying cognitive bias across positive symptoms, and used to generate testable hypotheses for each of the positive phenomena. To summarise, there are strong arguments for examining single symptoms such as hallucinations and their concomitants, before drawing findings into a wider model or framework which considers underlying mechanisms, rather than vice versa.

1.4.2 Range of neuropsychiatric symptoms - empirical approaches to grouping

An empirical approach to grouping symptoms on the basis of co-occurrence has been used in both the schizophrenia literature and the Alzheimer's Disease and dementia literatures (Andreasen, 1982; Lerner et al, 1994; Ballard et al, 1995; Harwood et al, 1998; Lysetskos et al, 2001). Many of these studies have used a factor analytic approach, which examines correlations between symptoms to derive a number of factors or clusters of empirically related symptoms (Field, 2001). This approach may be beneficial in examining 'psychotic' and neuropsychiatric symptoms in PD.

Earlier studies of neuropsychiatric symptoms in PD posited a progression through a series of stages in levodopa-induced psychosis, starting with sleep disturbance and parasomnias, and leading to hallucinations and delirium (Nauseida et al, 1982). Stated empirically, this model predicts that there is a hierarchy of symptoms following a Guttman scale. However, statistical analysis of this kind was not applied, and so no empirical support for this model was provided. This has been a common weakness of many studies of neuropsychiatric symptoms in PD, and factor analytic approaches have rarely been used. One notable exception is a recent study by Aarsland et al (1999b) who assessed survivors 4 years into a longitudinal population-study using the Neuropsychiatric Inventory (NPI) (Cummings et al, 1994). The experience of 139 PD patients fell into 2 factors; the first consisting of delusions, hallucinations and irritability, and the second anxiety and apathy. Depression was the most frequent symptom but failed to discriminate between the two factors, followed by apathy then hallucinations, agitation and delusions.

One drawback with this approach is that it uses empirical associations and weightings which may vary from sample to sample, thus suggesting that there may be homogeneity where in

fact associations are weak or artefactual because high frequency items tend to co-occur. However, the stability of factor structure across studies for PD has yet to be determined, and its value in suggesting the shared underlying mechanisms should not be overlooked

The following sections will describe the prevalence and phenomenology of the various neuropsychiatric symptoms in PD, and will briefly consider their clinical and cognitive concomitants.

1.4.3 Affective and psychomotor' symptoms in Parkinson's Disease

1.4.3.1 Anxiety

Anxiety disorders are common in PD and may precede diagnosis of PD, and even the emergence of motor symptoms (Prunztek, 2003). In fact anxiety is associated with an increased risk of developing PD with a recent study finding a relative risk of 2.4 (Shiba et al, 2000). Cummings finds a prevalence of between 8.8% and 19% in his review of neuropsychiatric symptoms in PD (Cummings, 1992). A recent clinic study of 90 consecutive PD patients found that panic disorders were significantly more frequent than in elderly controls, with a prevalence of 30% (Nuti et al, 2004). Some studies have suggested that on-off fluctuations may be associated with non-motor changes such as anxiety or hyperarousal (Erdal, 2001).

1.4.3.2 Depression

Depression is highly prevalent in PD, and Cummings (1992) describes prevalences of between 2% and 50 % in his review. Depression may also be a risk factor for the future development of PD (Shiba et al, 2000), although assessment is complicated by the fact that

depression may emerge as a pre-motor symptom of PD (Prunztek, 2003). The reported prevalence in community studies is lower, and Beekman et al (2000) find an overall rate of 1.8% in a review of community studies. As many depression inventories involve somatic items, depression may be overdiagnosed in PD, but a neurobiological basis of reduced dopaminergic innervation to the reward centres of the brain has been posited (Cummings, 1992)

1.4.3.3 Mania/hypomania/euphoria

Despite the preponderance of depressive symptoms in PD, manic and hypomanic episodes have been observed as a side-effect of DRT (see Cummings, 1992 for a review) and also following pallidotomy (Okun et al, 2003) and deep brain stimulation (Kulisevsky et al, 2001; 2002; Romito et al, 2002; Herzog et al, 2003). Euphoria, grandiosity, flight of ideas as well as psychomotor excitation including agitation, akathisia and hypersexuality have been described as part of manic episodes, and psychotic symptoms may occur during periods of mania. In the literature mania has always been associated with DRT or following brain surgery, and there is little consideration of euphoric episodes as being endemic to the disease process. In recent years a growing literature has described a dependence on or abuse of DRT, typically in men with young-onset PD. Koob & LeMoal's 1997 model of 'hedonic homeostatic dysregulation' (HHD) where repeated use of a substance due to its pleasurable effects is followed by neuronal adaptation which produces a negative affective state on withdrawal, has been applied to PD by Giovannoni et al (2000). Changes in the brain centres associated with reward, which are mediated by the dopaminergic system may follow increasing administration of levodopa, and other DRTs, leading to a cycle of sensitization and counter adaptation in the nucleus accumbens, the brain's reward centre (Giovannoni et al, 2000; Lawrence et al, 2003). In phenomenological terms HHD comprises violent dyskinesias, stereotypies involving

complex but purposeless motor behaviours or 'punding', euphoria, hypomania, or mania, hypersexuality, altered appetite, compulsive gambling or shopping, increased irritability and aggression, psychosis, and a cycle of craving and withdrawal which is associated with a rapid cycling of mood (Giovannoni et al, 2000; Lawrence et al, 2003). Though only recognised recently, prevalence still may be relatively low with 4% of PD referrals to a specialist tertiary centre displaying signs of dependence. Hypersexuality considered as a single-symptom has been observed in patients with dementias (Haddad & Benbow, 1993; Nagaratnam & Gayagay, 2002), but is usually considered as a medication side-effect in the Parkinson's literature (Cummings, 1992; Lemey et al, 2001). Hypersexuality may manifest itself as increased libido, increased frequency of penile erection in men, and also an "expansion in the repertoire of sexual behaviours" (Shaw et al, 2003) with adoption of previously unexpressed behaviours, orientation and fetishes (Riley, 2002). Shaw et al (2003) describe a marked decline in executive function, as well as mild global impairment in six patients with hypersexuality, and also note that this syndrome often occurred in conjunction with other impulsive behaviours such as compulsive gambling and misuse of DRT. Therefore hypersexuality may derive from a combination of hypomanic or disinhibited behaviour secondary to DRT abuse, and an effect of impaired judgment and increased impulsive resulting from the frontal deficits so characteristic of PD patients. Notably hypersexuality is reported to dwindle when DRT is withdrawn or reduced (Riley, 2002; Kanovsky et al, 2002).

1.4.4 Sleep-related phenomena

Chapter 3 describes the range of sleep-related phenomena in PD in detail, thereforeTable 1.2 will suffice to describe the range for the present discussion

1.4.5 Neuropsychiatric or 'psychotic' phenomena

The following section will concentrate in depth on the phenomenology of hallucinations in PD, and will introduce the importance of methodological issues in assessment of both presence and prevalence.

1.4.5.1 Classification of 'psychotic' symptoms

As described earlier Andreasen & Olsen (1982) used empirical associations between symptoms in schizophrenia to derive "positive" and "negative" factors. Negative symptoms of apathy, depression and flat affect are observed in many PD patients, and indeed comprise the classical view of the PD 'personality', although they may stem to some degree from motor impairment rather than an impairment in willed action (Frith, 1992). The presence of positive symptoms challenges this typology, and the idea of a reversal of the pathological processes of PD via DRT therefore seems appealing. However, this thesis will argue that effects arising from the disease process itself rather than medication underlie the positive as well as negative symptoms of PD. Frith (1992) argues for an additional "disorganised" group including aggression, agitation, irritability, hypersexuality, disinhibition and compulsive behaviours. These behaviours may also be observed in PD, and some have already been described. Table 1.3 takes a similar approach to grouping neuropsychiatric symptoms in PD.

Positive symptoms	Negative symptoms	Disorganised symptoms
Hallcuinations	Flat affect	Aggression
Delusions	Social withdrawal	Irritability
Thought disorder	Anhedonia/ apathy	Agitation
Misidentification syndromes	Depression	Hypersexuality
	Avolition	Disinhibition
		Compulsive behaviours

Table 1.3 Positive, negative and disorganised symptoms in PD, after Andreasen & Olson (1978) and Frith (1992).

1.4.5.2 Prevalence of psychotic phenomena

Reported prevalence rates for hallucinations, delusions and other psychiatric phenomena may be influenced by several factors; inclusion and exclusion criteria, in particular whether patients with moderate to severe dementia are included, the instrument or criteria used for assessment and the source of the sample.

1.4.5.2.1 The problem of overlapping diagnostic entities

Awareness of the existence of DLB has in recent years enabled population studies to exclude those 'PD patients' who may well be in the early stages of DLB, and therefore improve the specificity of such estimates It is highly likely that earlier studies of psychiatric phenomena including levodopa trials overestimated the incidence of hallucinations, when DLB was not recognised as a separate clinical entity. Goetz et al (1998) suggest that even low doses of levodopa can rapidly precipitate hallucinations in those with DLB and that this effect may therefore be an indicator of DLB itself. Therefore many of those patients in earlier studies with psychosis developing in rapid response to levodopa may in fact have been patients with DLB. Although specificity is improved, excluding those with early hallucinations and possible DLB

from prevalence rates neglects a sizable and problematic group of patients who are difficult to diagnose precisely until response to levodopa has been examined.

1.4.5.2.2 Methods of assessing neuropsychiatric symptoms

The use of standardised instruments which are sensitive to the symptom in question, and at the same time stringent enough to exclude false positives are essential for providing accurate estimates of prevalence. Ballard (1995) finds a relatively high prevalence of psychotic symptoms in a group of patients with dementia compared to other studies, by using a detailed inventory. Schedules which use single-item questions about 'psychosis' or 'delusions' fail to differentiate between what may be heterogeneous phenomena. They also fail to take into account the frequency or severity of such symptoms, and indeed the level of distress they cause. Schedules for assessing hallucinations in schizophrenia may place too much emphasis on aspects of auditory hallucinations or voices, such as identity or omnipotence which are less relevant to a population with neurodegenerative disease such as PD or dementia where visual hallucinations predominate. Fenelon et al's (2000) comprehensive study of hallucinations in PD describes a range of experiences which may be labeled as visual or other hallucinations. Such different experiences may have different predictive factors or indicate different prognoses. Use of standardised instruments will allow assessment of similar phenomena across different populations, allowing accurate comparisons to be made. Therefore estimates of prevalence and incidence should be sensitive to the symptoms in questions, and also specific about the phenomenon they are assessing, and should also take into account aspects such as frequency or severity which can have an important role in distinguishing neuropsychiatric symptoms from other 'unsual experiences' which fall within the range of infrequent but normal experience such as deja vu. Other factors which may influence

prevalence rates are criteria for hallucinations, means of assessment, whether patient, caregiver or both are questioned, and whether the population is community-dwelling or resides in nursing homes or other institutions.

1.4.5.3 Prevalence of hallucinations in PD

In a population study of 775 Parkinson's outpatients, Tanner et al (1982) report a prevalence of hallucinations of 33%, though this study included patients both with and without dementia. Cummings reviews studies of response to levodopa and other medications up to 1992, finding a range from 5 percent to 60 percent. Typically drug studies report a 10-30% prevalence of hallucinations. Recent studies of unmedicated PD patients are however unavailable, partly because diagnosis of PD can be dependent upon response to levodopa. For example, Celesia & Barr (1970) describing a trial for levodopa report a one-third incidence of 'psychic phenomena' including psychosis in 17.7% of the overall sample of 45 patients. Two cases of 'psychosis' occurred in a clear sensorium, and six were associated with confusional state. More recently, Aarsland et al (1999a) report an 11.5% prevalence for hallucinations and 13.6% for psychosis in a population study of 235 PD patients. In this study, care was taken to exclude possible cases with early DLB, reflected in the relatively low prevalence rates. This study used the UPDRS thought disorder section for assessment, whereas a further study on 139 patients who had survived four years since the initial assessment used the NPI administered to the caregiver to examine a range of neuropsychiatric symptoms (Aarsland et al, 1999b). The later study found a prevalence of 17.7 % for hallucinations, which reflects a relatively longer disease duration in the survivors, and may also be due to caregivers reporting symptoms in patients who have no insight themselves. The importance of means of assessment was reflected in Haeske-Dewick's study (1995) which found that a postal

questionnaire underreported hallucinations, and that several patients who had not reported hallucinations on the questionnaire did admit to them when followed-up by interview. Sensitivity of criteria for hallucinations and even the use of the term 'hallucination' rather than 'illusion' or 'seeing things' may determine the response given, as may setting and perceived power of the interviewer, i.e. clinician versus independent researcher.

Prevalence rates for hallucinations in Dementia with Lewy Bodies (DLB) diagnosed according to the McKeith et al (1996) consensus criteria are reported to be higher. Aarsland et al (2001) showed a linear association with presence of visual and auditory hallucinations and delusions, where PD patients showed the lowest prevalence, PDD a higher prevalence, and DLB the highest prevalence, with 72% of the DLB patients experiencing visual hallucinations.

1.4.5.4 Phenomenology of hallucinations in PD

Hallucinations, similarly to psychotic symptoms as a group, have often been treated as a homogenous group of phenomena (Fernandez et al, 1992; Sanchez-Ramos et al, 1996; Graham et al,1997). Although hallucinations in PD are most often experienced in the visual modality (VH), auditory (AH), tactile (TH) and olfactory (OH) hallucinations have also been reported. Aarsland et al (2001) find a prevalence of 8% VH compared to 7% AH in non-demented PD patients, and a prevalence of 50% VH and 21% AH in PDD patients.

Table 1.4 presents studies that have reported prevalences of hallucinations in different modalities in PD samples, using various interview and questionnaire methodologies.

Study	N	Visual (N)	Auditory (N)	Olfactory (N)	Tactile (N)
Goetz et al (1998)	H = 60	60	11	4	6
Inzelberg et al (1998)	H = 45 NH = 76	45	10	NR	NR
Fenelon et al (2000)	H = 86 NH = 130	48	21	NR	NR
Haeske-Dewick (1995)	H = 16 NH = 36	9	3	2	6
Holroyd et al (2001)	H = 28 NH = 74	26	1	0	0
Moskowitz et al (1978)	H = 23 NH = 57	19	3	NR	1

Table 1.4 Hallucinations in PD according to modality. NR = not reported

It is clear from the above table that visual hallucinations predominate in PD, although auditory hallucinations are also frequent. Hallucinations in different modalities often co-occur in the same individual, although it is rare that they coincide i.e. a hallucinated figure is heard to speak (Haeke-Dewick, 1995). Fenelon et al (2002) described tactile hallucinations in 8 PD patients, defined as "the perception of being touched or of something under the skin", and Goetz et al (1998) found that 'early' hallucinators, who were later more likely to be rediagnosed with DLB or another dementing condition, were more likely than late hallucinators to experience tactile hallucinations, suggesting they are indicative of more serious pathology. Inzelberg et al (1998) studied 10 PD patients with auditory hallucinations, finding differences with the paranoid-type auditory hallucinations described in schizophrenia. Five of the ten patients found their auditory hallucinations to be incomprehensible, and they were non-imperative and non-paranoid in nine patients, and no patients showed evidence of thought disorder such as thought insertion or broadcast, alien control or heard voices commenting on

their behaviour (Inzelberg et al, 1998). Musical hallucinations in PD have also been described (Clark, 1998)

Fenelon et al (2000) made a comprehensive study of hallucinations in PD, distinguishing between 'minor' and complex hallucinations. Minor hallucinations of three types were described. 'Passage hallucinations' occurred when an individual perceived something to have moved, for example a mouse, in their peripheral field of vision. 'Illusions of presence' consisted of a feeling that someone else was present, for example feeling as though a dead spouse was in the bedroom. Critically no visual, auditory or tactlile percepts were involved, rather a 'sense' that someone else was present. 'Object illusions' occurred when an object was perceived as something else, for example a vase of flowers was seen as a dog. Complex visual hallucinations were considered to have occurred when a detailed visual image was perceived in the central field of vision, and was unrelated to any external stimulus. This classification within hallucinations again emphasises the point that hallucinations are not a homogenous group of phenomena. Whether these minor and major hallucinations co-occur empirically in a factor or cluster has yet to be determined.

1.4.5.5 Delusions and 'Thought Disorder'

In an early study of the effects of levodopa medication, Celesia & Barr (1970) described psychosis and confusion in six patients, out of 45, which was severe enough to warrant restraint. Cummings (1992) claims that formal thought disorder such as tangentiality, loosening of associations, neologisms or incoherence or first-rank Schneiderian symptoms such as thought broadcast or insertion, external control etc, are not common in drug-induced psychosis (which he posits as the cause of neuropsychiatric symptoms in PD), and that delusions occur in a clear sensorium. However, Meco et al (1990) found that hallucinating

patients had higher scores on the MMPI schizophrenia scale, suggesting that hallucinating patients either posses premorbid personality styles likely to predispose them to hallucinations in the presence of PD and dopaminergic medication, or experience other phenomena similar to schizophrenic-type psychosis during periods of hallucinations. Aarsland et al (2001) find a prevalence for delusions of 7% in non-demented PD patients, and 29% in PDD patients, although the most common delusion is that of a "phantom boarder" which may arise from repeated experience of hallucinations of figures. Systematised delusions are prominent in DLB, and supportive of differential diagnosis (Aarsland et al, 2001; Del Ser et al, 2002).

1.4.5.6 Misidentification syndromes

Delusional misidentification syndromes (DMS), most commonly Capgras syndrome have been infrequently reported in Parkinson's Disease, although Aarsland et al (2001) report that they are more common in DLB. Roane et al (1998), Miwa & Mizuno (2001) and Edelstyn et al (1998) describe three cases of Capgras syndrome in PD with patients believing a family member to be an imposter or a replacement, and one with duplication of a spouse although no 'replacement' was deemed to have occurred. Two of these patients also displayed a reduplicative paramnesia, involving duplication of the patient's own home, and one of these also had problems with failing to recognise other family members. Roane et al also report a third case concerning duplication of the place with the patient claiming that he was simultaneously in two locations in two different towns. All five patients had experienced visual hallucinations prior to or simultaneously with the onset of DMS and all had at least mild levels of dementia. Edelstyn et al's patient fulfilled diagnostic criteria for DLB, though pathological conformation of this could not be obtained.

In his study of psychotic symptoms in dementia Ballard (1995) found that patients with vascular dementia and DLB were more likely to experience DMS than those with Alzheimer's. DMS were related to the presence of visual agnosia, and the prominent visuospatial deficits in both DLB and PD may play a contributory role.

1.4.6 The effects of hallucinations and neuropsychiatric symptoms in PD on patients and caregivers

Goetz & Stebbins (1993) found that presence of hallucinations was the biggest predictor of institutionalisation in PD, and had a greater effect than either disability or cognitive decline. Aarsland et al (2000) found that age and disability were the two most strongest predictors of nursing home placement in PD patients, but that hallucinations also conferred a relative risk of 2.5. This association between hallucinations and institutionalisation is likely mediated by the effects of neuropsychiatric symptoms on caregivers, and Aarsland et al (1999) found that a higher score on the Neuropsychiatric Inventory (NPI) predicted higher depression and lower well-being in caregivers. Hallucinations and related symptoms are difficult to deal with for caregivers, and may lead to distressing and unpredictable behaviour in patients, which can also be stigmatising for the family. Goetz et al (1995) followed-up the sample from their earlier studies, and found that hallucinations were stable over time, and that once institutionalised, all patients had died within the two year follow-up period.

1.4.7 Summary and hypotheses

This chapter has described the archetype and range of hallucinatory experiences in PD, has discussed issues of quantification and assessment, and ways of classifying hallucinations

within the range of neuropsychiatric symptoms. The impact on both patient are caregiver has been described, demonstrating how valuable it would be to the clinician to be able firstly to identify those more at risk of developing hallucinations, and secondly to understand the mechanisms underlying hallucinations in PD.

Hypotheses for the present study concerning the literature reviewed in Chapter1 are as follows:

1. Sleep-related symptoms and unusual perceptual experiences in PD are not uni-dimensional constructs. Both groups of symptoms will show more than one factor with an eigenvalue of greater than one when analysed using a principal components analysis.
2. The different sleep and unusual perceptual experiences factors will show a different pattern of relationships with clinical variables such as age, disease severity and cognition. Critically, sleep distinct factors will show a different pattern of relationships with the hallucinations factor.
3. Motor severity as measured by individual items on the UPDRS is not a uni-dimensional construct. Different motor factors will show different patterns of association with global cognition, hallucinations scores and other clinical variables.

Chapter 2 describes studies assessing the "risk factors" of hallucinations in PD by seeking concomitant variables, and chapters 2, 3 and 4 describe theories of mechanisms underlying hallucinations in PD.

CHAPTER 2

RISK FACTORS FOR HALLUCINATIONS IN PARKINSON'S DISEASE

In chapter one, the phenomenological aspects of hallucinations and other neuropsychiatric symptoms in Parkinson's Disease were reviewed and issues of how hallucinations should be quantified and examined within the spectrum of neuropsychiatric symptoms were addressed. In addition, the impact of hallucinations on both patient, in terms of quality of life, mental health, prognosis and other outcomes, and on the caregiver was discussed. Given that hallucinations imply a poorer prognosis for PD patients, partly due to a greater risk of institutionalisation, and poorer mental health and strain for caregivers, it would be valuable to the clinician to be able to identify those patients who are more vulnerable to hallucinations. This would allow the clinician to take steps in considering the best pharmacological management, and also in educating both patients and caregivers on how to prepare for or manage such symptoms.

Identifying those vulnerable to hallucinations has been the aim of a number of studies which sought the concomitants of hallucinations in PD, that is, those demographic, clinical and psychological factors associated with hallucinations. With assessment of risk as the primary aim of earlier studies, their design merely sought to identify concomitants, rather than testing *a priori* hypotheses about the mechanisms underlying hallucinations. Although valuable to the clinician, these studies were weak methodologically in that only recently were longitudinal studies conducted with the goal of assessing risk factors for hallucinations prospectively.

As discussed in the introduction, early models were medical and psychiatric in nature, with cognitive decline, increased disease severity and medication factors assumed to underlie hallucinations in PD. However, more sophististicated models have since emerged, drawing on models of hallucinations in other disorders such as narcolepsy, schizophrenia and the

dementias. In recent years, studies of hallucinations in PD have sought to test specific hypotheses about the underlying pathophysiological mechanisms. These studies will not only aid the clinician in identifying other risk factors, but may also suggest alternative treatments and interventions, and will add to knowledge by testing a model of hallucinations in PD, and also by testing generalised models of hallucinations across a range of disorders.

This chapter will review the existing literature on concomitants of hallucinations in PD, in reference to the following issues. *Firstly*, the methodology of the existing studies will be discussed in terms of their assessment of hallucinations, the representativeness of the sample, and their methods of analysis. The ways in which the present study will address these problems will be presented. *Secondly*, earlier medical, pharmacological and psychiatric theories and models of hallucinations in PD will be described and the evidence for demographic, clinical and psychological factors as concomitants of hallucinations, as hypothesized by earlier models will be reviewed. *Thirdly*, implications for theory of the studies reviewed will be discussed, and areas which have not been fully investigated highlighted. Hypotheses drawn from earlier models for the present study will be presented. *Fourth*, models drawn from hallucinations in Charles Bonnet Syndrome (CBS), narcolepsy, schizophrenia and dementia will be described. *Finally*, a brief review of third generation studies investigating the perceptual, neuropsychological and sleep-related concomitants of hallucinations will be made. These studies will be commented upon in greater depth in Chapters 3 and 4.

2.1 Methodology of concomitant studies – what are the weaknesses?

2.1.1 Inclusion and Exclusion criteria – are the samples representative?

As presented in Chapter one, earlier studies may have included some patients who would have been classified as having dementia with Lewy bodies (DLB) at autopsy. This is simply due to the fact that DLB was not recognized as a separate clinical entity until the mid 1990s. Studies carried out in the late 1990s have mostly attempted to exclude those whose symptoms suggest underlying or early DLB. However, this has been problematic, as any patients with some degree of dementia, and with Parkinsonism and hallucinations fulfil the existing clinical criteria for DLB. Therefore several studies have excluded those patients who have shown little response to L-dopa, who show fluctuating cognition or who develop dementia soon after motor symptoms emerge. For example, the study by Aarsland et al (1999) distinguished between cases of probable DLB (who were excluded) and possible DLB, and those with apparently pure idiopathic PD.

PDD (Parkinson's Disease with dementia) is also now accepted as a clinical term, although whether it is pathologically or clinically distinct from DLB, other than by a later onset of dementia is controversial. Some studies, including earlier studies excluded PDD patients from their samples, partly because of difficulty in testing these patients, and partly for reasons of diagnostic specificity. However, as there is a robust association between cognitive decline and hallucinations in PD, this neglects a large group of patients whose hallucinations should be investigated, and who represent a significant problem for the clinician in terms of their management. Excluding these patients may increase the risk of a Type II error, by missing associations between hallucinations and other phenomena which are more frequent in patients with cognitive decline. Furthermore, some studies have suggested that subtypes of PD hallucinators exist, some with little cognitive decline, but with greater disease severity and motor fluctuations, and some with moderate dementia,

but few motor symptoms. These two groups may have distinct concomitants for their hallucinations, suggesting different underlying mechanisms, and if so these should identified for the more demented group. Alternatively, the same concomitants may operate on a continuum of severity, in which case excluding more demented patients will increase the risk of a Type II error.

To summarise, inclusion of dementing patients may increase the risk of including patients with DLB, but a model of hallucinations in PD is likely to share many similarities with a generalised model for the α-synucleinopathies. Although DLB patients have cortical pathology, their neuropsychological profile is remarkably similar to PD but with an increased magnitude in deficits, and may be indistinguishable from PDD (Noe et al, 2004). In addition, excluding dementing patients neglects a large proportion of hallucinators who represent a sizeable problem for the clinician, and may increase the risk of missing significant correlates of hallucinations.

2.1.2 Assessment of hallucinations – how are hallucinations quantified?

This issue was touched upon in the previous chapter. Most concomitant studies have used a group comparisons design, classifying patients into hallucinators and non-hallucinators. However, Fenelon et al (2000) highlighted the fact that a group of patients experiencing 'minor' hallucinations also exists. Most studies use a dichotomous variable for hallucinations; they are either present or absent. Few have attempted to quantify the severity of hallucinations, thus limiting analysis in terms of looking for a linear relationship between concomitants and hallucinations. Given that both disease severity and cognitive decline exist on a continuum, their contribution to hallucinations is also likely to be continuous. In the Alzheimer's disease literature, by contrast, scales have been developed to assess both the severity of hallucinations, and other neuropsychiatric symptoms. As

described in Chapter one, a factor analytic approach has been fruitful in finding neuropsychiatric symptoms which cluster together, thus providing a continuous measure in the form of a factor score. As Fenelon's (2000) study has shown that hallucinations are a heterogeneous group of phenomena, this approach is ideally suited to the study and quantification of Parkinsonian hallucinations. Again, this approach has statistical advantages in terms of reducing the likelihood of a Type II error, as subtle linear associations between hallucinations and their concomitants may not be detected by the group comparisons approach.

2.1.3 Design – how useful and valid are the findings?

In selecting a group of hallucinating and non-hallucinating patients, rather than a consecutive series of patients, some studies have given a false impression of the prevalence of hallucinations. Although fewer PD patients hallucinate than do not, a more representative sample will be achieved by recruiting consecutive patients.

Many studies use group comparisons to detect differences between hallucinators and non-hallucinators on clinical variables, thus identifying the concomitants of hallucinations. The between groups comparison design has a fundamental weakness in that is does not address the relative value or weight of each of the concomitants, and compare their power in predicting hallucinations. Using a single group, with a hallucinations score for each subject, would allow linear regression models to be developed which could assess the amount of variance explained by each concomitant. This design would permit more thorough testing of models in that those variables which did not add to the variance explained could be discarded as artefactual or non-predictive concomitants. Those variables which exerted a significant effect on the dependent variable hallucinations, would be more valuable to the clinician in identifying vulnerable patients, and would also suggest

that those variables represented some kind of mechanism that contributed to the genesis of hallucinations.

Most studies of hallucinations in PD have consisted of a single-phase, and are thus cross-sectional in design, and can not make prospective predictions. Only recently have data been published on longitudinal studies of hallucinations (Goetz et al, 2001a; 2004; Onofrij et al, 2002). Although cross-sectional studies can test hypotheses about the mechanisms underlying hallucinations, they are less useful to the clinician in identifying which patients are likely to develop hallucinations in the future. In addition, longitudinal studies can also assess outcomes for those patients who hallucinate at baseline, in terms of rapidity of disease progression, cognitive decline, and also rates of mortality.

2.1.4 Analysis – do the methods of analysis address the full question?

The issues pertinent to the analysis of data in these studies have already been touched upon. A continuous variable representing the severity of hallucinations would allow more powerful regression models to be use, thus giving weight to each independent variable. The failure to covary confounding variables is one flaw that applies to nearly all the existing concomitant studies. Disease severity is associated with both cognitive decline and hallucinations (Barnes and David, 2001; Barnes et al 2003; Onofrij et al 2002, 2003), and therefore they should be covaried when assessing the relationship between hallucinations and cognitive decline. Age is another factor which may explain this association (Friedman and Sienkewicz, 1991; Naimark et al 1996). Group comparison studies could address this by either using ANCOVA when comparing clinical variables between groups, or by using a binary logistic regression model which assessed whether concomitants added significantly to the model after factors such as age, disease severity and cognitive score had been built in. A linear regression model, using a continuous score for hallucinations as the dependent

variable would also solve this problem. Undoubtedly, if disease severity and cognitive decline account for a large proportion of the variance in a hallucinations score, then the medical model would indeed be supported. However, if other neuropsychological or sleep-related factors added further to the model, or were more powerful independent variables, this would suggest that the model should be expanded to include other contributory factors.

2.1.5 The model – do these studies address theory or test models?

Most studies until the mid-1990s have investigated demographic, clinical and psychological variables and their association with hallucinations, in an attempt to identify concomitants. As identification of 'risk factors' was the primary objective, models of hallucinations in PD were essentially post-hoc, and a priori hypotheses derived from models were not directly tested. The third generation of studies, drawing from models in other areas has exploited both existing theory and paradigms, and applied them to the PD population to directly tests hypotheses about underlying mechanisms. For example, Arnulf et al (2000) drew parallels with the narcoleptic phenotype of hypnopompic and hypnogogic hallucinations, and excessive daytime sleepiness, and used polysomnographic techniques to investigate the role of daytime sleep and REM activity in hallucinations. Furthermore, Barnes et al (2003) drew on models of psychosis populations, where a loss of 'reality monitoring' ability is associated with hallucinations, and adapted paradigms from the schizophrenia literature to investigate reality monitoring in hallucinating and non-hallucinating PD patients. This approach has advanced theory about hallucinations in PD considerably in the last few years, and has identified not only further avenues for investigation, but the possibility of treatments or interventions other than the existing management recommendations to reduce or change dopaminergic medication, or introduce antipsychotics.

2.1.6 How can these methodological flaws be addressed? Implications for the present study

The present study will address the methodological issues discussed above in the following ways:

a) The present sample will exclude those patients whose symptoms indicate probable DLB. It will however include PDD patients who score 16 or above on the Mini-Mental State Examination, indicating mild to moderate dementia. It is unlikely that patients with a cognitive score less than this would be able to complete the cognitive battery proposed, leading to a possible floor effect, or would be able to give full answers to the semi-structured interview, which includes some relatively complex questions about the phenomenology of hallucinations.

b) A series of questions asking about different types of hallucinations and illusions, defined as 'unusual perceptual experiences', and their frequency over the last 3 months will be used to generate a score for each patient, rather than using a single item question.

c) The present study has been designed to allow a regression model predicting the severity of hallucinations to be used, as well as a between group comparison. The group comparisons will include 3 PD groups; non-hallucinators, those with minor unusual perceptual expericnces (UPE, i.e. Fenelon et al, 2000) but not complex hallucinations, and those with complex hallucinations, and also a control group of healthy older adults for most of the measures.

d) Analysis will include a linear regression model to predict hallucinations severity and group comparisons, using ANCOVA to covary possible confounding variables such as age, premorbid IQ, current global cognitive score, disease severity and depression.

e) The present study will test a series of a priori hypotheses based on the existing literature and models and paradigms derived from other populations, i.e. the dementias,

schizophrenia and narcolepsy. The regression model will test whether the earlier medical model can be significantly improved upon by adding other variables.

2.2 Early models of hallucinations in PD – first and second generation studies

2.2.1 The pharmacological model

The earliest studies of hallucinations in PD were descriptive in nature, and observed that hallucinations emerged in a proportion of patients after commencing L-dopa therapy (Celesia & Barr 1970; Jenkins & Groh, 1970; Goodwin, 1971). A simple model of hallucinations as a side-effect of L-dopa was proposed, with increased doses of L-dopa expected to increase the risk of hallucinations. This model complemented pharmacological models of schizophrenia very well, with the excess levels of dopamine being implicated in the genesis of psychotic experience. The effectiveness of dopamine antagonists as antipsychotics in schizophrenic patients supported this hypothesis, although this relationship could not be directly tested in PD patients, as it would have a highly detrimental effect on motor function. However, many studies failed to observe a dose-response relationship between L-dopa hallucinations in the PD population, and the theory became more sophisticated to encompass new knowledge about changes in receptor sensitivity and function over time. In an influential paper published in 1978, Moskowitz et al proposed a 'kindling' hypothesis, where dopamine receptors become 'hypersensitive' over time, as endogenous supplies of dopamine decline, and that dopaminergic medication overstimulates these receptors (see also Klawans et al, 1977). Such hypersensitivity in the nigrostriatal pathway might lead to the expression of motor fluctuations and dyskinesias, and if the same process occurred in mesocortical or mesolimbic pathways, abberant moods, perception and cognitions might be the result, such as anxiety and depression, vivid dreams or hallucinations (Moskowitz et al, 1978).

The pharmacological model has come up against a number of problems in its original form. Firstly, few studies have found a clear dose-response relationship between dopaminergic therapy and hallucinations, even when L-dopa equivalent dosages have been calculated across the range of dopaminergic medications. Secondly, the two experimental studies which have investigated hallucinations and psychosis in PD in relation to dopaminergic function (Mellers et al, 1995; Goetz et al, 1998) have not found an association between L-dopa infusion and hallucinations, nor growth hormone response to apomorphine (an index of central dopaminergic receptor sensitivity) and psychosis. Thirdly, it suffers from a lack of specificity about which of the five striato-thalamo-cortical dopaminergic pathways is implicated in hallucinations. Although it is difficult to measure dopamine receptor sensitivity unless using brain scanning or autopsy techniques, the emphasis has shifted away from a purely dopaminergic model, as has also been the case with the schizophrenia literature with the advent of novel antipsychotics. Recent findings have challenged the emphasis on dopamine and hallucinations in PD, finding increased levels of a serotonergic metabolite salsolinol in the urine of hallucinating PD patients, prompting speculation that serotonergic turnover may increase in response to L-dopa treatment, which is supported by the efficacy of Mianserian (a 5HT antagonist) in treating hallucinations in PD (Moser at al, 1996; Ikeguchi & Kuroda, 1995). Recent autopsy studies of DLB patients with psychotic symptoms have highlighted the possible role of the cholinergic system, with findings of greater ChAT loss in the lateral frontal and inferior temporal cortices, and greater overall ChAT loss and α7nAChR in DLB patients with hallucinations (Perry et al, 2003) and upregulation of muscarinic M1 receptors in DLB patients with delusions (Gomez-Tortosa et al, 1999). The only autopsy study of PD hallucinators found an increased number of Lewy

bodies in the temporal lobes and amygdala (Harding et al 2002), again implicating more widespread pathology, outside the dopaminergic system.

This thesis will not review neurobiological models of hallucinations in PD and the α-synucleinopathies, as the tools for assessing neurotransmitter function and histopathology were not available to the present study. However, it is clear that the original model of dopaminergic overstimulation is inadequate to explain more recent findings.

2.2.2 The medical model – the role of age, disease severity and cognitive decline

Cognitive decline and increased disease severity have shown the most robust associations with hallucinations in PD according to the concomitant studies (Sanchez-Ramos et al, 1996; Graham et al, 1997; Fenelon et al, 2000). These studies conceptualise hallucinations as being more likely in those individuals who are more advanced in the disease or who show some degree of cognitive decline. In addition, older patients have been found to be more likely to develop hallucinations by some studies (Friedman and Sienkewicz, 1991; Naimark et al 1996).

2.2.2.1 Cognition as a concomitant of hallucinations in PD

Cognitive decline in these studies has been most often measured using a global index, such as the Mini-Mental State Examination, or the Blessed Dementia Rating Scale .These are non-specific measures of cognitive function, and do not specify which areas of cognition (attention, executive function, memory, visuospatial perception or construction) are most affected. The presence of dementia, usually defined according to a cut-off score on the index used, has also been reported to be more frequent in hallucinators (Miyoshi et al 1996). However, most studies compare raw scores on a cognitive index between groups, rather than comparing frequency of demented and non-demented individuals. If risk of hallucinations increases in a linear fashion as cognitive impairment increases, using

raw scores is probably a better comparison, as in the absence of brain scan confirmation of a dementing process, the distinction between demented and non-demented individuals is somewhat artificial. More recent studies have used brain scanning, imaging and electroencephalography (EEG) techniques (Okada et al, 1999; Klein et al, 1997; Kraft et al, 1999) in attempt to find a physiological correlate of reduced cognitive functioning, and a single autopsy study has looked at distribution of Lewy bodies in hallucinators and non-hallucinators (Harding et al, 2002). Table 2.1 shows studies which have investigated association between global cognitive function and hallucinations in PD. For a more detailed summary see Appendix A.1

Hallucinators: more likely to show dementia or confusional states	Klein et al, 1997; Sanchez-Ramos et al, 1996; Fenelon et al, 2000; Auditory hallucinators: more likely to show confusional states Inzelberg et al, 1998
Hallucinators: Lower scores on the MMSE or other global measures	Meco et al, 1990; Fernandez et al, 1992; Haeske-Dewick et al, 1995; Davies et al 1998; Aarsland et al, 1999; Fenelon et al, 2000; Goetz et al, 2001b; Holroyd et al, 2001; Onofrij et al, 2003
Hallucinators: Lower scores on verbal fluency test	Haeske-Dewick et al, 1995; Graham et al, 1997
Hallucinators: Reduced blood flow in left lower temporal and left upper temporo-occipital areas	Okada et al, 1999
No CAT scan or EEG differences	Klein et al, 1997
No increase in cerebral white matter lesions	Kraft et al, 1999

Table 2.1 Studies of global cognition and its pathophysiological correlates in hallucinating PD patients

Both greater frequency of dementia or confusional states, and reduced score on the MMSE or other global measures have been consistently found in association with hallucinations according to the studies detailed above. Two studies have examined cognitive function in early hallucinators (within 5 years of PD onset) and late hallucinators (more than 5 years of PD onset), finding that early hallucinations are not associated with cognitive decline (Graham et al, 1997; Fenelon et al, 2000). Late hallucinators however showed lower

scores on global measures of cognition (Graham et al, 1997; Fenelon et al, 2000). These findings suggest that there may exist subtypes of hallucinators, late hallucinations occurring as a result of cognitive decline, and early hallucinations due to some other factor such as medication. Another study which compared cognitive status in 'early' and 'late' hallucinators used a different definition; early hallucinators (within 3 months of commencing DRT) were more likely to have developed a dementing condition 5 years later than those whose hallucinations emerged later (Goetz et al, 1998b). This suggest that a subgroup of PD patients may be especially vulnerable to the pharmacological effects of DRT, but that they have a sub clinical dementing condition which may explain this vulnerability. Unfortunately the studies by Graham et al (1997) and Fenelon et al (2000) did not follow their sample over time, and so the cognitive prognosis of their 'early' hallucinators was not examined.

2.2.2.1.2. Problems with the model

As *non-specific* measures of cognitive function have been used for the above studies, the medical model says little about how loss of cognitive ability leads to abnormal percepts, or to acceptance of misperceptions as real. Hallucinations are of course more frequent in dementing populations whether they have Alzheimer's Disease, Multi-Infarct Dementia or an α-synucleinopathy dementia. Hallucinations in PD are generally agreed to occur in one third of patients, with a greater frequency in PDD and DLB, yet they are less frequent in AD patients with a similar degree of cognitive impairment (Jeste et al, 1992; Hirono et al, 1999). The cognitive deficits observed in these diseases are quite distinct, and an equivalent score on the Mini Mental State Examination (MMSE) in AD and PD patients may actually represent quite a different cognitive profile (Noe et al, 2004). Therefore the model cannot identify what it is about the cognitive impairment in PD and the α-synucleinopathies that renders patients more vulnerable to hallucinations. Few studies

have attempted to analyze the different components of the MMSE or the Blessed Dementia Rating Scale (BDRS) in relation to hallucinations in PD, and so whether the 'dementia' associated is of a cortical or subcortical nature is unknown. Therefore, although cognitive decline in PD hallucinators is a robust finding, the model suffers from lack of specificity about the nature of the cognitive decline, fails to answer why PDD and DLB patients have a higher frequency of hallucinations than AD patients with a similar degree of dementia, and has advanced understanding of hallucinations in PD very little, other than in identifying risk..

2.2.2.2 Disease severity as a concomitant of hallucinations in PD

The model of disease severity as a cause of hallucinations asserts that pathological changes associated with the disease contribute to hallucinations, either by loss of function in nigrostriatal and other dopaminergic pathways, by the development of hypersensitivity of dopamine receptors that are reflected in motor fluctuations (similarly to the pharmacological model), or by the presence of certain motor symptoms such as axial signs which suggest extrastriatal or non-dopaminergic pathology, possibly in the cholinergic system. In this way there is a degree of overlap with the pharmacological model, but changes endemic to the disease process itself, rather than simply the side-effects of medication are postulated to be causal. Of course the disease process and pharmacological processes may work in tandem to produce hallucinations, although stronger and more robust effects have been found for disease severity and duration than for DRT dose. Table 2.2. shows those studies which have investigated disease severity in PD in relationship to hallucinations. For a more detailed summary see appendix A.2.

H : more severe PD than NH	Haeske-Dewick 1995; Sanchez-Ramos et al 1996; Miyoshi et al 1996; Arnulf et al 2000; Kraft et al 1999; Fenelon et al 2000, Barnes and David 2001; Goetz et al 2001b; Holroyd et al 2001; Onofrij et al 2002; Barnes et al 2003
No differences between N and NH in terms of disease severity	Tanner et al 1983; Fernandez et al 1992; Graham et al 1997; Knlein et al 1997; Inzelberg et al 1998; Fuente-Fernandez et al 1999; Pappert et al 1999.

Table 2.2 Studies of disease severity in hallucinating PD patients

It is clear that disease severity as a concept, whether indexed by disease duration, motor performance, level of disability or stage, is in many studies robustly associated with hallucinations. Studies which have investigated this relationship further have revealed an interaction between disease duration and severity. Those patients with hallucinations have been demonstrated to have a more rapid decline in motor function over time, whether indicated by greater disease severity despite having a similar duration of disease (Kraft et al, 1999). This has implications for the prognosis of hallucinators, and suggests that they have a more rapid deterioration of nigrostriatal dopaminergic levels, which is supported by the greater prevalence of motor fluctuations in hallucinators according to some studies (Fenelon et al, 2000). Other studies have shown that hallucinators display more axial signs, which are suggestive of extrastriatal pathology, possibly in the cholinergic system (Graham et al, 1997; Fenelon et al, 2000). Again, disease duration shows an interaction with motor severity as early hallucinators (within 5 years of PD onset) have a more rapid onset of motor fluctuations (Graham et al, 1997), and late hallucinations (more than 5 years after PD onset) display more axial signs, and more loss of balance when turning, indicative of extrastriatal pathology (Fenelon et al, 2000; Graham et al, 1997). The co-occurrence of axial signs and cognitive decline in late hallucinators is suggestive of Postural-Instability-Gait Dominant (PIGD) PD, where patients displaying axial signs are

more likely to develop cognitive decline and have a poorer prognosis (Jankovic et al, 1990; Levy et al, 2002). Those studies which have looked at type of motor symptoms, rather than treating disease severity as a homogenous concept, have advanced the model by suggesting that some patients are more vulnerable to the 'hypersensitivity' effect of DRT, with early hallucinations and rapid onset of motor fluctuations, and that others may display late hallucinations and motor characteristics that are indicative of extrastriatal pathology, and a greater vulnerability to cognitive decline.

2.2.3 Age as a concomitant of hallucinations in PD

Age has also been associated with hallucinations in PD (Friedman and Sienkewicz, 1991; Naimark et al 1996; Kraft et al 1999, Fenelon et al 2000; Fuente - Fernandez et al, 1999), with hallucinating patients being older than non-hallucinators. Age may increase vulnerability to hallucinations in two ways. Firstly age is likely to be correlated with cognitive decline. Therefore age may represent a confounding factor which should be covaried when comparing cognitive status between hallucinators and non-hallucinators. Secondly, age affects vision, with a greater frequency of cataracts, macular disease and glaucoma (Lepore, 1997). Several studies have investigated the presence of visual disease in hallucinators, with some finding an association (Haeske-Dewick, 1995; Holroyd et al, 2001). Patients with visual disease or partial blindness are more likely to experience both illusions and complex visual hallucinations (Holroyd et al, 1992), and poor visual acuity has been associated with Charles Bonnet Syndrome (Teunisse et al, 1994; 1995), where complex visual hallucinations occur in a non-demented elderly population. Peripheral visual deficits may impair an individuals ability to perceive the world around them correctly, and when coupled with a level of cognitive decline, incomplete visual input may be misinterpreted by top-down visual processes. This idea adds a level of complexity

to the medical model, however, in the existing literature on hallucinations in PD this theory has not exploited the well-developed models of human vision that are available. The model makes few predictions about the point at which peripheral perceptual processes interact with top-down higher level visual processes, or with other cognitive processes such as reality monitoring.

2.2.4 Psychiatric disorders as concomitants of hallucinations

Patients with a history of psychiatric disorders or current affective disorders may also be more vulnerable to hallucinations, and several studies have reported a higher prevealnce of depression in hallucinating patients (Haeske-Dewick, 1995; Sanchez-Ramos et al, 1996; Fenelon et al, 2000). This association has been explained as an individual vulnerability of patients with previous or current psychiatric problems to psychotic phenomena.

Meco et al (1990) investigated the personality of hallucinating and non-hallucinating PD patients, using the Minnesota Multiphasic Personality Inventory (MMPI), finding that hallucinators scored more highly on the Schizophrenia scale. This suggests that they possess personality traits that predispose them to psychotic phenomena. One problem with this study is that it was not prospective, and thus the personality 'traits' may simply have reflected *current* psychotic-type thinking experienced by hallucinators, rather than a premorbid personality type. Furthermore, few PD patients have a history of psychosis, partly because neuroleptic-induced Parkinsonism is usually excluded, and so a psychiatric model of this kind says little about other PD patients.

Depression is prevalent in PD and has been associated with hallucinations in some studies, prompting speculation that the pathophysiology underlying depression in PD may also be related to hallucinations. A key problem with this explanation is that depression may of course be secondary to hallucinations, and is also more likely to occur in those individuals with more advanced disease and cognitive decline (Tandberg et al, 1997).

Elegant cognitive-behavioural models have been developed for depression, anxiety-disorders and for psychosis (Beck, 1989), yet the medical model says nothing about whether certain cognitive biases may contribute to hallucinations in PD, but simply looks at the presence of psychiatric disorder as an indicator of idiosyncratic vulnerability to hallucinations. For a more detailed summary see Appendix A.3

2.2.5 Weaknesses of the pharmacological and medical models

The medical model which dominated the literature on hallucinations in PD until the mid-1990s has sought primarily to identify those PD patients at greater risk of developing hallucinations. The pharmacological model regards hallucinations as a side-effect of medication, and seeks no other explanation for why some individuals are more vulnerable to those side-effects. More recently autopsy studies have identified changes in receptor density and function, or Lewy bodies in certain areas of the brain which correlate with hallucinations in the α-synucleinopathies (Gomez-Tortosa et al, 1999; Perry et al, 2003). However, unless the functions of these brain areas can be mapped onto the affected areas, within a cognitive or neuropsychological model of hallucinations, which would allow assessment of relevant neuropsychological function via psychometric means, the clinician is no closer to identifying at risk patients.

The medical model has identified a number of risk factors for hallucinations, although these have rarely been investigated prospectively. However, it suffers from a lack of specificity, using a global measure of cognitive decline which does not identify specific neuropsychological deficits associated with hallucinations, and it fails to exploit not only recent advances in neurobiological and neuropsychological knowledge, it also fails to address more recent cognitive-behavioural models of psychosis which emphasise biases

in normal cognitive processes, instead adopting a psychiatric approach of individual pathology or abnormality.

These models fail on a fundamental level to address epistemological issues of research. Bentall (1997) argues that an overly neurobiological approach regards hallucinations merely as an epiphenomena of biological processes, ignoring their "intentionality" as a behaviour and an active cognitive process. He argues that all such processes must be driven by intention, in the case of hallucinations to perceive and understand the world around, and that in treating such processes as an interesting side-effect of medication or neurodegeneration, they become essentially "epistemologically empty". Frith (1992) makes a similar case for explanations which address the interaction between mind and brain and provide frameworks which apply to both, and also provide feasible models which are accepted in current literature. Claims that hallucinations are caused by "hypersensitivity of dopaminergic neurons in the mesolimbic pathway" mixes levels of explanation and leaves a gap, effectively ignoring how dopaminergic systems interact with the mind and the concept of what is real and not, or with perception itself. Searching for concomitants or associations in a non-directed way increases the likelihood of false positives and of spurious correlations which are interpreted as causal. The application of a neuropsychological methodology to the study of hallucinations can provide models of normal functioning, and of localisation of deficits. However the finding of a specific deficit in hallucinators or non-hallucinators cannot be assumed to be the underlying mechanism unless it is framed within a descriptive functional model of how different cognitive processes may contribute to the phenomenon.

2.2.6 Hypotheses for the present study – clinical concomitants of hallucinations

4. The PD group as a whole will differ from controls on measures of global cognition, independently of premorbid IQ, age and depression and anxiety.
5. Hallucinators will show greater impairments in global cognition and increased levels of disease severity compared to non-hallucinators independently of premorbid IQ, age and depression and anxiety.

2.3 Alternative models of hallucinations in PD

2.3.1 Hallucinations associated with visual deficits and Charles Bonnet Syndrome

Visual hallucinations have a higher incidence in an elderly population (Tien et al 1991), partly because of the greater frequency of visual disease (Lepore et al, 1997; Berrios & Brook, 1984), and greater levels of cognitive decline. Deafness has also been associated with auditory hallucinations and paranoid delusions in the elderly, emphasising the role of sensory loss in producing abnormal percepts (Corbin & Eastwood, 1986). Charles Bonnet Syndrome, the occurrence of complex visual hallucinations in 'psychologically normal' people, has been associated with a number of risk factors including older age, poor visual acuity, ophthalmic disease and living alone (Holroyd et al, 1992; Teunisse et al, 1994; Teunisse et al, 1995). The contribution of cognitive impairment is unlclear; Schultz & Melzack (1993) and Teunisse et al (1994) found no differences in cognitive score between hallucinators and age-matched controls, whereas Holroyd et al (1992) found lower cognitive score to be a risk factor for visual hallucinations in patients with macular degeneration. However, when the hallucinators from the Holroyd et al study were followed over three years, they did not show a significant decline in cognitive score (Holroyd et al, 1996), arguing against the idea that subclinical dementia was present.

Theories developed to explain CBS and the prevalence of illusions and hallucinations in peripheral ocular disease, have focused on the idea of 'disinhibition' of top-down visual processes, caused by reduced afferent visual input (Rosenbaum et al, 1987; Schultz & Melzack, 1991). The visual cortex is driven by an "effort after meaning", in other words the processing of afferent visual input to construct a meaningful interpretation of the world. If incomplete or disorganised visual input is transmitted to the visual cortex then Gestalt formation and other top-down visual processes may construct a percept that is not in accordance with the real world. In a strict sense this misinterpretation of visual input is an

'illusion'. Ffytche & Howard (1999) argue that separating hallucinations (percepts without afferent visual signals) and illusions (false percepts derived from afferent visual signals) may diminish the "underlying neurobiological message". In other words a common neural substrate, whether provoked by actual afferent input, or abnormal activity in the visual cortex provoked by disinhibition of the visual system in the absence of input, may explain both phenomena.

Ffytche & Howard (1999) investigated the phenomenology of visual illusions and hallucinations in patients with ocular disease, describing a range of 'positive' pathologies of vision, ranging from elementary VH to complex VH, and in a later study of CBS patients (Santhouse et al, 2000) used a factor analysis to classify VH according to content. An earlier fMRI investigation by the same group, of four CBS patients, had found that specific types of hallucinations, i.e. colourful, hallucinations of faces, hallucinations of objects were found to correlate with activity in those parts of the visual cortex specialized for colour, face processing, and object recognition respectively (Ffytche et al, 1998). Santhouse et al (2000) proposed that their three factors of hallucination content corresponded to abnormal activity in three areas of the brain; visual ventral stream activity in the case of hallucinations of figures and landscapes, superior temporal sulcus activity in the case of hallucinated faces, and visual dorsal stream in the case of more elementary visual hallucinations. This series of studies has applied models of normal visual processing, and methods for assessing localised brain activity to generate testable hypotheses about the pathophysiological correlates of specific types of illusions and hallucination.

The application of a model of incomplete or disorganised visual input leading to erroneous percepts to a PD population can be considered appropriate for two reasons. Firstly, PD patients display a number of visual deficits that may lead to incomplete visual afferent signals, including double vision, reduced visual acuity and reduced contrast sensitivity

(Muller et al, 2002; Biousse et al, 2004; see Harris, 1998 for review). Secondly higher-level visual processing may be affected in PD, with deficits in figure-ground discrimination, visual componential processing, facial discrimination and object recognition (Villardita et al, 1982; Levin et al, 1990; Cousins et al, 2000; Hovestadt et al, 1987; Laatu et al, 2004). Investigation of visual deficits as a concomitant of hallucinations and illusions in Parkinson's disease may extend the model by assessing whether deficits in visual and perceptual processing contribute to hallucinations.

2.3.2 Hallucinations associated with the dementias

The presence of hallucinations and delusions in the dementias is often independent of any effects of medication, and is therefore thought to reflect the pathological effects of the disease itself. Ballard et al (1995) found a 35.5% prevalence of visual hallucinations in a group of dementing patients with diagnoses of Alzheimer's Disease, DLB and vascular dementia, which is slightly higher than the presence in PD, when care is taken to exclude DLB patients (Aarsland et al, 1999). However, DLB patients accounted for a large proportion of VH, and displayed significantly more psychotic symptoms overall than the other groups, and therefore the α-synucleinopathies as a group may be more vulnerable to VH than other dementing populations. It is also likely that hallucinations occur at a higher level of cognitive function in PD, than in AD. An 'inverted U' model has been proposed for the occurrence of psychotic phenomena in AD (Ballard et al, 1991), with hallucinations most likely to occur when MMSE score falls between 11 and 20 points (Jeste et al, 1992), i.e. in the range of moderate dementia. Given the prevalence of 20-30% of hallucinations in PD in those studies which excluded demented patients, it seems that PD hallucinations emerge at a milder stage of cognitive impairment, suggesting a role for other mechanisms apart from cognitive decline.

The study of hallucinations in Alzheimer's Disease and other dementias has followed a similar path to that of the Parkinson's Disease literature, identifying concomitants of hallucinations and searching for pathophysiological correlates, mainly using a clinicomedical approach (Lopez et al, 1991; Gormley & Rizwan, 1998; Paulsen et al, 2000). The literature is instructive however, as more sophisticated design and statistical techniques have been used, and models have been developed as to the role of visual impairment and circadian rhythm disruption.

Firstly, several studies have examined the factor structure of psychotic phenomena in Alzheimer's disease, and have found visual hallucinations to be associated with other specific symptoms, although these have not been consistent across samples (Lerner et al, 1994; Ballard et al, 1995; Harwood et al, 1998). This approach has so far not been utilised in PD patients despite the fact that hallucinations in PD have been shown to be a heterogeneous group of phenomena (Fenelon et al, 2000). Secondly, several studies have investigated the role of visual impairment and visuoperceptual deficits in hallucinations in Alzheimer's Disease and other dementias. Visual hallucinators have been consistently found to have poorer visual acuity (Holroyd & Shelden-Keller, 1995, Chapman et al, 1999; Murgatryd & Prettyman, 2001), and in addition visual agnosia (Holroyd & Sheldon-Keller, 1995) and poorer performance on the object recognition subtest of the CAMCOG, and the clock-drawing test (Murgatroyd & Prettyman, 2001).Therefore patients with visual hallucinations and dementias demonstrate both peripheral visual deficits, and high-order visual processing deficits. The model of impaired object recognition in visual hallucinators has good face validity in explaining Fenelon et al's (2000) phenomenon of object illusions, where everyday objects are misinterpreted as something else. Murgatroyd & Prettyman (2001) also found that there was a trend for lower ambient illumination in the residences of hallucinators, suggesting that poorer illumination increases the chances of misperceiving

surroundings, or serves to increase the chance of hallucinations arising out of lack of visual stimulation, akin to theories of sensory deprivation. PD patients also tend to report that their hallucinations occur in conditions of low-lighting or darkness (Goetz et al, 1998). Thirdly, hallucinators in the dementias are more likely to demonstrate sleep disorders (Bassiony et al, 2000), and periods of psychotic behaviour and experience may fluctuate in a circadian manner, i.e. 'sundowning' (Bliwise et al, 1993; Volicer et al, 2001). Abnormal circadian rhythm in AD has been well-documented, with disintegration of the daily signal into a polyphasic rhythm, with fragmented sleep at night and increased frequency of napping during the day (Van Someren et al, 1996).

To summarise, the literature on hallucinations in the dementias has firstly utilised a methodology of seeking 'clusters' of co-occurring phenomena, which may be applied to the PD population. Secondly models of peripheral and higher-level visual and perceptual deficits in hallucinators extend the literature on CBS hallucinators, by positing a role for impaired object recognition, which may be applied to a PD population. Thirdly, the association between hallucinations, sleep disorders and disruptions in circadian rhythm should also be investigated in PD, as sleep disorders are prevalent, and PD patients also share a profile of fragmented nocturnal sleep, and increased daytime sleepiness (Trenkwalder, 1998; Pal et al, 1999).

2.3.3 Hallucinations associated with narcolepsy

Hallucinations, usually visual, vivid and complex frequently occur on the borders of sleep and wake in narcoleptic patients, with 25-30% reporting this phenomena. Hallucinations which occur at sleep onset have been termed 'hypnagogic' hallucinations, and those which occur at awakening are 'hypnapompic' hallucinations. Such phenomena are also reported in the general population, with 37% of a representative community sample reporting

hypnagogic experiences, and 12.5% hypnapompic experiences (Ohayon et al, 1996). However, in narcolepsy hypnapompic hallucinations predominate. Other symptoms in the narcolepsy 'tetrad' are excessive daytime sleepiness, cataplexy and sleep paralysis (Yoss & Daly, 1957; Zeman et al, 2001). Excessive daytime sleepiness is a frequent problem in PD, and many patients report that their hallucinations often occur at the onset of sleep or upon awakening either during the night or day (Arnulf et al, 2000; Manni et al, 2002). Hallucinations in narcolepsy have been associated with sleep onset REM episodes (SOREMS), that is, the occurrence of REM sleep (i.e. dream mentation) within 20 minutes of sleep onset. Abnormally rapid onset of REM sleep is one of the polysomnographic hallmarks of narcolepsy (Zeman et al, 2001), and it has been found to coincide with reported hallucinations, suggesting that hallucinations in fact represent REM activity on the borders of consciousness (Hishiwaka et al, 1978). A model describing the affect of REM activity on visual processing has been developed further by Manford & Andermann (1998) to encompass a range of diseases in which complex visual hallucinations occur. The authors suggest that the reticular activating system (RAS) which is responsible for control of REM sleep, slow wave sleep and wake, may function abnormally in diseases such as narcolepsy, Parkinson's Disease and peduncular disease. The RAS projects to the thalamus, and therefore its excitatory activity may interfere with the transmission of afferent sensory input from the retina to the visual cortex, specifically via the dorsal lateral geniculate nucleus. In this way the "fidelity" of retino-geniculo-cortical sensory transmission may be compromised, leading to erroneous cortical representations of the outside world (Manford & Andermann, 1998).

The application of a model of abnormal dream mentation and rapid onset sleep in narcolepsy is highly suitable for a PD population as parasomnias including vivid dreams and nightmares are prevalent, as is excessive daytime sleepiness (Zeman et al, 2001).

Manford & Andermann (1998) have already applied their theoretical model to a PD population, and the co-occurrence of daytime sleepiness, vivid dreams and other sleep-related phenomena, as well as nocturnal sleep pattern warrants investigation.

2.3.4 Hallucinations associated with schizophrenia

The disorder with the most developed neurobiological, neuropsychological and psychological models of hallucinations is the schizophrenia. Such advances have been driven by a motivation to advance knowledge of normal and abnormal brain function and also to develop alternative treatments to antipsychotics. Therefore, clinicomedical and psychiatric approaches have been largely overtaken by elegant models of neuropsychological function in psychosis (i.e. Bentall et al, 1991; Frith, 1992; Fleminger et al, 1997). In this regard the existing literature and theory on hallucinations in PD has lagged behind in terms of sophistication, and in implementing existing experimental paradigms. Although schizophrenic hallucinations are predominantly auditory, generalised models of deficits in reality monitoring, and qualitatively different profiles in performance for patients with positive versus negative symptoms may be applied to a PD group, or other populations regardless of the modality of psychotic phenomena.

Earlier studies of schizophrenic found that patients with hallucinations had a bias towards making false alarms during signal detection paradigms (Bentall & Slade, 1985; Rankin & O'Carroll, 1995). This finding was interpreted as a failure in 'reality monitoring' i.e. the ability to distinguish 'real' from 'unreal' events, but this concept has been subsumed under the umbrella of 'source monitoring' (Johnson et al, 1993), which is the ability to distinguish between events that occur externally and internally. Frith (1992) has argued that many 'positive' psychotic phenomena, i.e. hallucinations, delusions, delusional misidentification are associated with a source monitoring deficit (see also Bentall, 1990), where an

individual has a general bias towards labelling internally generated events as being external. Frith's (1992) model of psychotic phenomena in schizophrenia posits different neuropsychological correlates of patients in predominantly positive and predominantly negative symptoms. Positive symptoms are hypothesised to be associated with a response bias towards false alarms, and also with the production or erroneous or irrelevant material during testing. Negative symptoms are hypothesised to be associated with a lack of response or poorer accuracy. These prediction have found partial support in recent experimental studies by Brebion et al (1997; 1998; 1999; 2000) focusing mainly on memory, where positive schizophrenic symptoms were correlated with a bias towards false alarms on recognition tests and a greater production of intrusions or 'confabulated' material on recall tests. Depressive symptoms were negatively correlated with discrimination accuracy on recognition tests, supporting Frith's posited 'lack of response', although no other negative symptoms were associated with this pattern (Brebion et al, 1998).

The association between hallucinations, response bias and production of intrusions or confabulatory material on the one hand, and depressive symptoms and lack of accurate response on the other warrants investigation in PD. The model may be extended to incorporate paradigms other than recognition and recall, to tests of executive function such as verbal fluency for example, where words that did not correspond with the cue would represent intrusions, and poor production of correct words would correspond with a lack of response. The same response criteria might also be applied to visual perceptual tasks where false alarms might be made visual detection tests, incorrect identifications of stimuli would constitute errors, and failure of identification or passes would constitute a lack of response. In this way Frith's (1992) neuropsychological model of psychosis could incorporate the posited role of visual perceptual deficits in hallucinations in PD.

2.3.6 Brief review of "third generation" studies

The previous section described models of the mechanisms underlying hallucinations in populations other than Parkinson's Disease. A third generation of studies investigating hallucinations in PD patients has begun to utilise these models, making a priori predictions based on the models, and testing them using paradigms adapted from the original populations.

The posited role of specific peripheral and higher level visual deficits in the genesis of hallucinations has been investigated using electrophysiological techniques by Diederich et al (1998) and Buttner et al (1996), finding deficits in colour discrimination, contrast sensitivity and chromatic contour perception in hallucinators; by Onofrj et al (2002) investigating visual evoked potentials, and by Barnes et al (2003), finding deficits on tests of object perception and recognition in hallucinators.

The model of excessive daytime sleepiness, and REM activity in contributing to hallucinations, based on the model of narcolepsy has been investigated by Arnulf et al (2000), with a greater incidence of sudden onset REM episodes (SOREMs) in hallucinators in a lab setting, and by Manni et al (2002), with a co-occurrence of sleep episodes and REM activity with hallucinations in patients own homes, using ambulatory polysomnography.

Finally the elegant neuropsychological models of psychotic experience derived from the schizophrenia literature have been adapted by Barnes et al (2003) to investigate reality monitoring in hallucinating PD patients, and finding a greater tendency for hallucinators to identify mentally generated images as having been externally presented.

CHAPTER 3

SLEEP CHARACTERISTICS IN PD - RELATIONSHIP TO DISEASE-RELATED VARIABLES, AND TO HALLUCINATIONS

3.0 Sleep problems in Parkinson's Disease – implications for patient and caregiver quality of life, prognosis and susceptibility to hallcuinations

Chapter 2 briefly described studies showing disruption in the normal sleep-wake cycle as a concomitant of hallucinations. Findings include changes in the structure of nocturnal sleep, with reduced REM activity (Comella et al, 1993), increased altered dream phenomena (Pappert et al, 1999) and REM behaviour disorder (Onofrij et al, 2002), and greater levels of daytime sleepiness (Fenelon et al, 2000; Arnulf et al, 2000, Tandberg et al, 1999). These concomitants can be considered as representative of three facets of sleep disorder, as conceptualized by Pal et al (1999) in their review of sleep disturbances in Parkinson's disease; insomnias, parasomnias and daytime sleepiness.

This chapter reviews sleep problems in PD which are in their own right an important source of extra burden and work for the caregiver, and of distress and functional impairment to both P and CG. There is certainly evidence that poor sleep in AD patients is related to institutionalisation (Sanford, 1975; Pollack & Perlick, 1991; Pollak et al 1990). Less is known about whether poor sleep in PD and relates to poor prognosis, although it has been found that excessive daytime sleepiness is related to cognitive decline in PD, and that disrupted circadian rhythm is a hallmark of dementia (Tandberg et al, 1999; Gjersted et al, 2002; Van Someren et al, 1996).

The following chapter will describe these disturbances in more depth, their prevalence in a PD population relative to healthy older adults, and their concomitants in PD patients. Studies

investigating sleep as a concomitant of hallucinations in PD will be reviewed in detail, validity of methods of sleep assessment used discussed, and finally hypotheses made concerning the present study.

3.1 Sleep related phenomena in a Parkinson's population

The following table describes the range of sleep-related phenomena that have been observed in the Parkinson's population, and gives their prevalence according to the existing literature. (Tables 3.1- 3.11 shown later in the chapter will give a more in depth review of prevalence in the PD population, frequency and severity compared to healthy older adults, and their clinical concomitants in PD).

3.1.1 Nocturnal disease and motor-related phenomena

Many of the phenomena described in Table 3.1 below can be represented as nocturnal manifestations of the motor symptoms that many PD patients experience during the daytime i.e. rigidity, problems turning, nocturia. Others symptoms are expressed mainly during the night i.e. periodic leg movements, myoclonus etc, but are motor problems in nature, and may arise the same pathology that produces daytime motor dysfunction. Together these motor phenomena can result in problems getting to sleep, or may interrupt sleep causing the sleep fragmentation that is so characteristic of PD patients (Van Hilten et al 1993).

Table 3.1 Nocturnal disease and motor-related phenomena

Symptom	Description	Prevalence in PD studies
Rigidity	Rigidity may cause discomfort, and problems turning	20 – 55% (Lees et al 1998; Stocchi et al, 2000; Tandberg et al, 1998)
Painful cramps	Typically occurring in the lower limbs in the early morning, these may be associated 'off' periods	
'Off' periods	Off periods may be uncomfortable or painful, with inability to move in med, get out of bed to visit the toilet, and turn in bed	42.5% (Stocchi et al, 2000)
Problems turning	Rigidity, off periods and muscle weakness can lead to problems turning in bed, and pulling up bedclothes	72 % (Oerlemans & de Weerd, 2002)
Dyskinesias	Dyskinesias are suppressed during sleep but may lead to increased sleep latency, and increased wake after sleep onset	3.75% (Stocchi et al, 2000)
Nocturia	Increased urinary frequency has been associated with PD and other α-synucleinopathies, caused autonomic disturbances	59% - 79 % (Oerlemans & de Weerd, 2002; Lees et al, 1988)
Nocturnal myoclonus	Myoclonic jerks of limbs occur at sleep onset or during light NREM sleep	10%, - 24.3% (Stocchi et al, 2000; Tandberg et al, 1998)
Periodic leg movements of sleep (PLMS)	Occurring mainly in the first half of the night, PLMS are repetitive, rhythmic unilateral movements, usually extension and flexion of the big toe and ankle	
Restless legs syndrome	A 'creeping' sensation, usually in the legs with the compulsion to move them. The sensation can sometimes be relieved by vigorous activity	6.25% to 56% (Henderson et al, 2003; Menza & Rosen, 1995;Oerlemans & de Weerd, 2002; Stocchi et al, 2000; Ondo et al, 2001)
Nocturnal akathisia	Subjective 'inner restlessnesss', sometimes accompanied by stereotyped movements	26% (Lang & Johnson, 1987)

3.2.2 *Insomnias*

Insomnias are defined as disorders of sleep initiation or maintenance, and are prevalent in PD.

The sleep of PD patients is characteristically light and fragmented, often interrupted by the

motor phenomena described above. Sleep fragmentation is reflected in subjectively rated poor sleep quality, and often patients do not wake feeling 'refreshed' as they used to. Interrupted nighttime sleep is bothersome for many patients, and may result in both drowsiness and fatigue the next day. Disrupted nighttime sleep may also be quantified in polysomnographic terms as changes in sleep architecture, with increased sleep latency, reduced sleep efficiency and changes in the duration and percentage of REM and slow wave sleep (SWS).

Table 3.2 Insomnias

Insomnias	Changes in nocturnal sleep architecture	
Initial insomnia	Difficulty initiating sleep, reflected in increased sleep latency. Tends to occur after commencing levodopa therapy	16% - 67% (Oerlemans & de Weerd, 2002; Van Hilten et al, 1993; Factor et al, 1990)
Sleep fragmentation	Increased frequency of awakenings, often caused by nocturnal motor symptoms (see above). Reflected in lower sleep efficiency and greater wakefulness after sleep onset (WASO)	74.4% - 80% (Factor et al, 1990; Oerlemans & de Weerd, 2002; Van Hilten et al, 1993)
Problems waking up	Difficulty with waking, confusion on waking	12% (Van Hilten et al, 1993)
Changes in sleep architecture	Reduced levels of REM sleep, and REM latency, and reductions in stages 3 and 4 of slow wave sleep.	

3.2.3 Parasomnias

Parasomnias are undesirable behaviours which are either exaggerated by sleep or expressed exclusively during sleep. They often arise from changes in REM sleep characteristics i.e. vivid dreams or nightmares, or from loss of the normal atonia during REM sleep, leading to 'acting out' of dreams i.e. REM behaviour disorder (RBD). RBD can especially distressing for caregivers who may be injured by their partner's aggressive movements, and distressing

parasomnias such as RBD, nocturnal hallucinosis and wandering, which are prevalent in the α-synucleinopathies and dementias can prompt institutionalization if the caregiver is unable to cope (Sanford, 1975, Pollack & Perlick, 1987, Pollack et al, 1990).

Table 3.3 Parasomnias

Parasomnias		
Altered dream phenomena	These may consist of dreaming that is more vivid, emotionally intense or frightening than previously, including nightmares and night terrors	11% - 30.7% (Henderson et al, 2003; Oerlemans & de Weerd, 2002; Lees et al, 1988; Van Hilten et al, 1993; Sharf et al, 1978)
Sleep related hallucinations	Hallucinations in PD may occur at the onset of sleep (hypnogogic hallucinations) or after waking (hypnopompic hallucinations)	16% (Lees et al, 1988)
Sleep related psychotic behaviour	Delusions, wandering and searching behaviour may occur upon waking from sleep	
REM Sleep Behaviour Disorder (RBD)	This syndrome is characterized by vigorous and sometimes injurious behaviour during REM sleep, and is often associated with vivid dreams of a violent nature. Episodes tend to occur at least 90mins after sleep onset. RBD precedes the onset of PD motor signs in a significant proportion of cases (Schenk et al, 1996).	13% - 33% (Oerlemans & de Weerd, 2002; Comella et al, 1998; Gagnon et al, 2002)
Sleeptalking	Nocturnal vocalizations may range from murmuring to shouting and screaming, which is paradoxical given the effects of PD on speech for many patients.	7 - 24% (Oerlemans & de Weerd, 2002; Van Hilten et al, 1993)
Somnambulism	Sleepwalking or nocturnal wandering occasionally occurs, again paradoxically given the disability experienced by many patients during the daytime	1% (Van Hilten et al, 1993)

3.2.4 Sleep disordered breathing

Respiratory disturbances during sleep are known as sleep apnoeas, which may be caused by obstruction of the upper airways (obstructive sleep apnoea), or by failure of the autonomic systems that control breathing (central sleep apnoea). These disturbances to normal respiration lead to a reduction in oxygen intake, sometimes to hypoxic levels, and have implications for fatigue and exhaustion the following day, and for cognitive function. Both have been described in the α-synucleinopathies, although they are more prevalent in MSA than in PD (Trenkwalder, 1998).

Table 3.4 Sleep-disordered breathing

Sleep disordered breathing		
Obstructive apnoea	Obstruction of the upper airway during sleep, which reduces oxygen intake	12% (Oerlemans & de Weerd, 2002)
Central apnoea	Respiratory difficulties caused by failure of autonomic control	

3.2.5 Daytime sleepiness

Daytime sleep episodes that occur frequently, in inappropriate situations, without warning or that are overwhelming in nature have been described in PD. "Excessive daytime sleepiness" in PD has been defined in several ways; in terms of duration of time slept during the day, frequency of naps or in terms of standardized scales such as the Epworth Sleepiness Scale, with established normal criteria. "Sleep attacks" have also been described, and in recent years the literature has focused on the risk of falling asleep at the wheel as a side-effect of certain dopamine agonists (Frucht et al, 2000). How exactly to differentiate a sleep "attack" from excessive daytime sleepiness is controversial, but some authors have drawn parallels with the

narcoleptic phenotype; rapid onset sleep, with little warning, and have applied methods of assessing the rapidity of sleep such as the Multiple Sleep-Latency Test (MSLT).

Table 3.5 Daytime sleepiness

Daytime sleepiness		
Excessive daytime sleepiness	Undesirable sleepiness during the day, which may equate to clinical levels according to the MSLT or the Epworth Sleepiness Scale.	9.9 % - 51% (Hobson et al, 2002; Hogl et al, 2003; Henderson et al, 2003; Brodsky et al, 2003; Whitney et al, 1998; Stocchi et al, 2000; Van Hilten et al, 1993; Kumar et al, 2003; Braga-Neto et al, 2004; Rye et al, 2000; Tandberg et al, 1999; Gjerstad et al, 2002; Tan et al, 2002; Carbonari et al, 2002; Rascol et al, 2001; Happe & Berger, 2001)
Sleep attacks	Rapid onset sleep, which is overwhelming in nature. Some authors draw parallels with narcoleptic sleep episodes	0% - 34.3% (Braga-Neto et al, 2004; Schlensinger & Ravin, 2003; Tan et al, 2002; Pal et al, 2002; Rascol et al, 2001; Stover et al, 2001)

3.2.6 Disruption to circadian rhythm

Few studies have investigated circadian rhythm in Parkinson's Disease. Fragmented sleep at night and increased frequency of napping during the night are both suggestive of an overall disruption to the normal biphasic circadian rhythm, although this may merely be equivalent to or an exaggeration of the effects of age. It is clear that Alzheimer's Disease patients show disrupted circadian rhythm with a polyphasic pattern of sleep and wake (Van Someren et al, 1996), but it is less clear whether PD, PDD or DLB patients show the same pattern. Motor symptoms in PD often show circadian variation, with a proportion of patients experiencing

"sleep benefit" in the mornings (Hogl et al, 2000; Tandberg et al, 1999), but whether this is expressed as global changes in rest-activity rhythm, or is reflected in purer measures of circadian rhythm such as body temperature, cortisol or melatonin levels is as yet uncertain.

Table 3.6 Circadian rhythm disturbance

Circadian rhythm disturbance		
Sleep benefit	Transitory improvement of motor symptoms following morning waking, and in some cases following naps.	42.2% - 55.1% (Merello et al, 1997; Tandberg et al, 1999)
Disturbance of circadian rest-activity rhythm	Reduction in amplitude of activity, more low to high activity transitions during each 24hr period and a weaker circadian signal across days.	

3.2.7 Summary

It appears that the sleep-wake cycle is affected in PD across a range of domains; firstly with expression of motor-related symptoms during the night, secondly as changes in nocturnal sleep architecture, somnolence during the day, and overall 24hour activity pattern which can be quantified by observational, self-report or electrophysiological means, and thirdly phenomenologically, with the experience of various parasomnias and changes in sleep-wake which may differ qualitatively form the normal experience.

Prevalence for each 'symptom' in the above tables varies considerably according to the methods of assessment used, i.e. objective versus subjective reports, and exclusion criteria used in each study i.e. excluding patients with depression or dementia. The following section will review these studies in more detail and with reference to three questions; firstly, which studies and assessment methods are likely to give more valid prevalences, secondly, whether there is evidence that these symptoms are any more prevalent in a PD population compared to

healthy older adults, and thirdly, whether studies of clinical concomitants of sleep phenomena in PD can provide clues to the pathophysiological mechanisms underlying them

3.3 Sleep phenomena in PD – comparisons with healthy older adults, and clinical concomitants

3.3.1 Nocturnal disease and motor-related phenomena

Table 3.7 Correlates and relative prevalence of nocturnal disease and motor-related phenomena

Symptom	Prevalence in PD studies according to method of assessment	Comparison with healthy older adults	Concomitants
Painful cramps	55% survey, Lees et al 1998 20%, interview, clinic study, Stocchi et al, 2000 43.5%, single quest, community study, Tandberg et al, 1998	> freq Appiah-Kubi et al, 2002 > severity Chaudhuri et al, 2000 NS Tandberg, 1998	
'Off' periods	42.5%, interview, clinic study, Stocchi et al, 2000		Lesser et al, 1979 – diurnal motor fluctuations
Problems turning	72 % single quest, comm. survey (Oerlemans & de Weerd, 2002)		
Dyskinesias	3.75%, interview, clinic study, Stocchi et al, 2000		
Nocturia	59% > 3 times nightly, comm. survey (Oerlemans & de Weerd, 2002) 79% frequency, survey, Lees et al, 1988	> severity Chaudhuri et al, 2000	

Table 3.7 Correlates and relative prevalence of nocturnal disease and motor-related phenomena (cont)

Symptom	Prevalence in PD studies according to method of assessment	Comparison with healthy older adults	Concomitants
Nocturnal myoclonus	10%, interview, clinic study, Stocchi et al, 2000 24.3%, quest, comm. Study (Tandberg et al, 1998)	> freq Tandberg, 1998	Klawans et al, 1975 – dyskinesias
Periodic leg movements of sleep (PLMS)		> PLM during wake periods, sleep periods and > PLM associated arousals (PSG), Wetter et al, 2000	
Restless legs syndrome	50% single quest (Henderon et al, 2003) 43% single quest, support group (Menza & Rosen, 1995) 13% suggestion from series of questions, comm. survey (Oerlemans & de Weerd, 2002) 6.25%, interview, clinic study, Stocchi et al, 2000 19.5% record analysis, large study, Ondo et al, 2001	> freq Hendeson et al, 2003 > freq Menza & Rosen, 1995	Menza & Rosen (1995) – depression, no of awakeninngs, motor fluctuations, NS LD dose, age Appiah-Kubi et al (2001)- daytime sleepiness Braga-Neto et al (2003) – DD>5yrs
Nocturnal akathisia	26% questioned, Lang & Johnson, 1987		Lang & Johnson, 1987- bradykinesia and stiffness

Metholodology key: Single quest = symptom assessed by a single question;
Population key: Comm. Survey = community survey; Clin survey = Consecutive series clinic survey
Comparison key: > freq = greater frequency; > sev = greater severity

Amongst the most frequent and bothersome motor-related problems experienced by PD patients during the night are problems turning over in bed, nocturia, cramps, periods of akinesia and restless legs (Factor et al, 1990; Van Hilten et al, 1993). The prevalence of these symptoms has been ascertained using survey, questionnaire and interview studies of

outpatients and patients attending local support groups. Some studies have used single item questions to evaluate prevalence, although in the case of restless legs, and akathisia more in depth questioning is necessary to distinguish between the various types of sleep-related movements, as 'restlessness' as a concept covers a variety of phenomena, and is a vague term to use in questioning. Not surprisingly a relatively lower prevalence was found by studies which used a series of questions or an interview to evaluate Restless Legs Syndrome (RLS) (13% by Oerlemans & de Weerd, 2002; 6.25% by Stocchi et al, 2000; 19.5% by Ondo et al, 2001). PLMS is evaluated by polysomnographic, and more recently actigraphic means, but no prevalence figures are available for PD patients.

Motor-related nocturnal phenomena certainly appear to be more prevalent in PD patients than healthy older adults (see Table 3.7) and may explain the high occurrence of problems with sleep maintenance in PD (Pal et al, 1999; Trenkwalder, 1998). The impact of these symptoms has been described in a survey by Van Hilten et al (1993) which asked about the causes of problems with sleep initiation and maintenance. Other than worries and pain, PD patients reported nocturia, problems with turning and pain as causes of problems with sleep maintenance significantly more often than controls. The impact of PLMS on sleep in PD patients can be seen from the results of Wetter et al's (2000) polysomnographic study, with PD patients demonstrating more PLMs whilst awake, and asleep at night, and more arousals associated with PLMs than controls. Menza & Rosen found that restless legs were associated with number of awakenings during the night, and negatively with sleep quality, and Appiah-Kubi et al (2002) found that nocturnal "restlessness" was associated with unexpectedly falling asleep in the day, suggesting that the impact of fragmented sleep may last into the following day.

Few studies have assessed clinical concomitants of motor-related nocturnal problems, though they seem to be related to indices of disease severity; motor fluctuations, dyskinesias and disease duration (see above), suggesting that such phenomena become more frequent as the disease progresses.

3.3.2 Insomnias

Table 3.8 Correlates and relative prevalence of insomnias

Symptom	Prevalence in PD studies according to method of assessment	Comparison with healthy older adults	Concomitants
Initial insomnia	16% > 30 mins comm. Survey (Oerlemans & de Weerd, 2002) 18% ND PD, single quest, clinic study, Van Hilten et al, 1993 67% single quest, Factor et al, 1990	> latency Menza & Rosen (1995) NS freq Van Hilten et al (1993)	Van Hilten et al, 1993 – male sex,'Morning-type' Braga-Neto et al, (2003) – NS age, DD
Sleep fragmentation	80% single quest, Factor et al (1990) 77% > 2 comm. Survey (Oerlemans & de Weerd, 2002) 74.4% ND PD, single quest, clinic study, Van Hilten et al, 1993	> no awakenings Menza & Rosen (1995) > freq Factor et al (1990) NS freq ND PD Van Hilten et al, 1993 > severity Chaudhuri > freq Happe et al, 2001 > PLM associated arousals (PSG), Wetter et al, 2000	Menza & Rosen (1995)– motor-fluctuations, RLS, LD dose, age Van Hilten et al (1993) – male sex, LD dose
Problems waking up	12% ND PD, single quest, clinic study, Van Hilten et al, 1993	NS freq Van Hilten et al, 1993	
Changes in sleep architecture			<REM latency in depressed PD, Kostic et al (1991) < REM duration, percentage and number periods in hallucinating PD patients, Comella et al, 1993

Sleep fragmentation is the most prevalent of the insomnias affecting PD patients, with the majority of subjects reporting frequent awakenings during the night. Many studies however have assessed insomnias using a single question about "problems sleeping" or about subjective sleep quality, which does not differentiate between problems initiating and maintaining sleep. Though increasingly common with age, sleep fragmentation appears to be even more frequent in the PD population with a greater reported number of awakenings (Menza & Rosen, 1993), and more PLM-associated arousals (Wetter et al, 2002), reflecting the impact of motor-related problems. The prevalence of problems with sleep initiation is lower, and may not exceed that in a healthy older population. Bliwise et al (2000) suggest that initial insomnia is a problem encountered by PD patients after they commence DRT, but that declines after time, and is replaced by the more characteristic pattern of fragmented sleep. Given the high prevalence of depression in PD, it is also likely many patients experience sleep disruption characteristic of depression with early morning waking, and Van Hilten et al (1993) found that "worries" were the most frequently reported cause of initial insomnia in both PD patients and controls. However, Menza & Rosen (1993) studied the relationship between sleep and depression and anxiety in PD, finding that neither was predictive of total score on the Pittsburgh Sleep Quality Inventory in a regression model, but rather that age, on-off fluctuation and L-dopa dose predicted overall sleep quality. Therefore, motor symptoms and disease-related factors appear to play a stronger role in sleep disruption in PD.

Changes in nocturnal sleep architecture as measured by polysomnography have been noted in PD patients compared to controls, though the literature is small. Reductions in REM sleep have been described (Kostic et al, 1991). Comella et al (1993) found that specific changes in the pattern of REM sleep were associated with hallucinations in PD. This study will be discussed in more detail later.

3.3.3 Parasomnias

Table 3.9 Correlates and relative prevalence of parasomnias

Symptom	Prevalence in PD studies according to method of assessment	Comparison with healthy older adults	Concomitants
Altered dream phenomena	11% single quest, Henderson et al, 2003 30% single quest, comm. Survey (Oerlemans & de Weerd, 2002) 48% survey, Lees et al, 1988 24% ND PD, single quest, clinic study, Van Hilten et al, 1993 30.7% Sharf et al, 1978	No diffs Henderson et al, 2003 > freq Van Hilten et al, 1993 > severity Chaudhuri et al, 2000	Sharf, 1978 - LD dose, NS stage, age, disability, FH psychosis Van Hilten et al, 1993 – NS LD dose, sex, stage, UPDRS, dd, age, dysk Papppert et al, 1999 – sleep fragmentation, hallucinations
Sleep related hallucinations	16% survey, Lees et al, (1988)	> severity Chaudhuri et al, 2000	
Sleep related psychotic behaviour			
REM Sleep Behaviour Disorder (RBD)	13% suggestion from quests, comm. Survey (Oerlemans & de Weerd, 2002) 15% meet ICSD criteria, 15% history sleep-related injury, 25% either, clinic study, Comella et al, 1998 33% PSG diagnostic criteria, 17.2% ICSD criteria, clinic study, Gagnon et al, 2002	< freq REM sleep muscle atonia (Gagnon et al, 2002)	Comella et al, 1993 – greater freq in hallucinating PD patients
Sleeptalking	24% frequently, comm. Survey (Oerlemans & de Weerd, 2002) 7% ND PD, single quest, clinic study, Van Hilten et al, 1993	NS freq Van Hilten et al, 1993	
Somnambulism	1% ND PD, single quest, clinic study, Van Hilten et al, 1993	NS freq Van Hilten et al, 1993	

Parasomnias are reported less frequently than either motor-related sleep problems, or insomnias, although altered dream phenomena and REM behaviour disorder still affect a significant proportion of PD patients, being reported by up to one-third of subjects. Altered dream phenomena may well be under-reported in this group because they are subjective symptoms for which some patients, especially those with cognitive decline, will have little recall, unless they develop into confused or hallucinatory symptoms that are observed by caregivers. Altered dream phenomena are dreams that are *qualitatively* different from previous or normal experience, in most cases more vivid visually, or more emotionally intense. Van Hilten et al (1993) reported that dreams were more 'unpleasant' in 17 subjects, more 'frightening' in 7, and more 'intense' in 5; Sharf et al (1978) described vivid dreams in 22.7% of subjects, night terrors with vocalisation in 6.8% and nightmares in 5.7%, following the commencement of L-dopa therapy. Two of the three above studies are supportive of a higher frequency of altered dream phenomena in PD patients, compared to healthy older adults, and the fact that Sharf et al's subjects could distinguish subjective differences in dreaming following L-dopa therapy suggests that they are qualitatively different from normal experience. Although Sharf et al (1978) report that a higher L-dopa dose is associated with altered dreams, there have been no associations found for other indices of severity. However, associations between altered dreams and hallucinations have long been described in the literature (Moskowitz et al, 1978; Factor et al, 1990), and Pappert et al (1999) provide the strongest empirical evidence for co-occurrence of the two symptoms. The evidence for such an association will be described in more depth later in this chapter, but the fact that many patients hallucinate during the night (Lees et al, 1988) suggests that dreams may overlap with perceived reality for some patients.

Normally during REM sleep muscle tone is lost, yet some PD patients show increased levels muscle tone during REM sleep; that is, absence of normal atonia (Gagnon et al, 2002). In some patients this loss of atonia results in the "acting out" of dreams. Where dreams are of an aggressive or violent nature, injuries can occur to the patient or more often to their bed partner. REM behaviour disorder was first described as a clinical entity in by Schenck et al in 1986, and consists of limb or body movement associated with dream mentation, that leads to either harmful behaviours, dreams that appear to be "acted out" or sleep behaviour that disrupts sleep continuity (ASDA, 1997). RBD has since been associated both empirically and in terms of shared pathophysiology with the α-synucleinopathies (Boeve et al, 2003), and has been observed to precede diagnosis of PD by several years or more (Schenck et al, 1996). Few studies have assessed the prevalence of RBD in a purely PD population, partly because polysomnographic evidence is needed for a full diagnosis (see Bernath & Guilleminault, 1999). PSG may lead to a more complete prevalence figure, as Gagnon et al (2002) found that using an interview based on diagnostic criteria identified a 17.2% prevalence in a group of PD patients, whereas PSG methods found a prevalence of 33%. Therefore, some patients may be unaware of their nocturnal behaviour, even when a caregiver is also interviewed (Comella et al, 1998). Although dreams recalled by patients following an episode of RBD are more vivid, unpleasant and violent than normal dreams, Comella et al (1998) suggest that only one-third of patients recall such dreams, and a further 10% of their sample reported a history sleep-related injury, highly suggestive of RBD. Vocalisation during sleep is also common in PD patients (Oerlemans & de Weerd, 2002), and may form part of the same cluster of behaviours found in RBD, with loss of REM-atonia allowing vocalisations to occur during the "acting out" of the dream. Although DRT has been implicated as having potential to reduce RBD symptoms (Fantini et al, 2003; Matheson & Saper, 2003), few studies have examined clinical

concomitants of RBD. A Single-Photon Emission Computerised Tomography (SPECT) study of striatal dopamine postsynaptic receptors and presynaptic transporters, found that those PD patients with RBD had reduced striatal dopamine transporters, compared to those without RBD (Eisensehr et al, 2000). However, associations with other indices of severity have not been examined. An association between RBD and hallucinations in PD has been described by Comella et al (1993) in a small sample of PD patients, suggesting that a shared pathological mechanism may exist.

Given the above findings, it is likely that altered dream phenomena and RBD may co-occur in some patients, particularly as they are both associated with hallucinations, although their reported associations with DRT are in opposite directions. Phenomenologically, there is some overlap between the two, with intense, aggressive and vivid dreams, and both may stem from disruption to the pedunculopontine and locus coeruleus, which are implicated in the control of REM sleep and REM-atonia (Pal et al, 1999; Bliwise et al, 2000).

PD patients with some degree of dementia may be more vulnerable to parasomnias, given their reported association with psychosis and hallucinations, although no study has found a direct relationship between cognitive status and parasomnias. Parasomnias such as wandering are prevalent in AD, suggesting association with more widespread CNS pathology, but RBD is particularly prevalent in the α-synucleinopathies (Boeve et al, 2000), and changes in the circuits involving REM sleep and REM-atonia have been implicated.

3.3.4 Sleep disordered breathing

Table 3.10 Correlates and relative prevalence of sleep disordered breathing in PD

Synmptom	Prevalence in PD studies according to method of assessment	Comparison with healthy older adults	Concomitants
Obstructive apnoea	12% suggestion from quests, comm. Survey (Oerlemans & de Weerd, 2002)		

Little information exists about the relative prevalence of sleep disordered breathing in PD populations versus healthy older adults, and apnoeas are increasingly prevalent in old age. Definitive diagnosis of apnoeas requires sleep laboratory assessment. However, motor and autonomic aspects of PD may be implicated in the development of obstructive and central apnoeas respectively (Trenkwalder, 1998; Garcia-Borreguero et al, 2003). Rigidity, dyskinesias of the diaphragm, abnormal movements in upper airway structures and failure of autonomic control of respiration may contribute to apnoea, and its prevalence in the PD population would therefore be expected to increase with disease severity. In terms of outcomes of apnoea, excessive daytime sleepiness has been described in non-PD populations with sleep-disordered breathing, and a study by Braga-Neto et al (2004) found that the only significant predictor of EDS in a PD sample was snoring (OR = 3.64, CI = 1.00-11.9), which may be suggestive of SDB.

3.3.5 Daytime sleepiness

The area of sleep disruption in PD that has received the most attention recently, partly because of its implications for road safety, and partly because well-developed paradigms for assessment are available, is excessive daytime sleepiness. In addition it is this area which has

been most systematically investigated in terms of concomitants and predictor variables, again because of the need to assess the risk of dangerous "sleep attacks" in PD patients (Olanow et al, 2000; Comella, 2003).

The studies of excessive daytime sleepiness (EDS) in PD are too numerous to present in table form, but findings of increased levels in PD patients compared to healthy older adults are robust (Hogl et al, 2003; Brodsky et al, 2003; Tandberg et al, 1999; Kumar et al, 2003). Daytime sleepiness is most consistently associated with indices of disease severity and with hallucinations, but not with disrupted nocturnal sleep (Tandberg et al, 1999; Gjersted et al, 2002; Rye et al, 2000; Fenelon et al, 2000)

Prevalence of EDS in PD has been assessed using several methods; single item questions in survey studies, daily duration and frequency of naps, scores on a well-established and validated scale, the Epworth Sleepiness Scale (Johns, 1991), and using paradigms developed for the assessment of narcolepsy i.e. the Multiple Sleep-Latency Test, which assesses rapidity of sleep onset in a lab setting using polysomnographic techniques, and the presence of sleep onset REM episodes (SOREMS) during naps, which are indicative of a narcoleptic phenotype. Prevalence varies according to the means of assessment used, and how "excessive" daytime sleep is defined; those studies which used a score of 10 or greater on the ESS which is widely-agreed to indicate abnormal levels of EDS, have found prevalences of between 19.9% (in a non-demented PD outpatient population) and 40.6% in clinic studies including those with dementia. A large epidemiological survey of EDS using the Epworth Sleepiness Scale found a prevalence of 15.5% in PD patients (Whitney et al, 1998). A single study using MSLT in a small PD sample found pathological scores in 19% of patients, or 37% using a less conservative criterion (Rye et al, 2000). In terms of non-standardised measures, Tandberg et al (1999) used total daily duration of naps to delineate two groups in a large community-study

of PD patients; those with mild daytime sleepiness (1-2 hrs per day) with a prevalence of 11.3%, and those with excessive daytime sleepiness (2 or more hours per day) with a prevalence of 15.5%. The validity of the various methods of assessment is disputed, with some authors arguing that MSLT is the only definitive means of diagnosing pathological sleepiness (Rye et al, 2000). In two studies using MSLT in PD groups recruited specifically because of EDS, one using patients with ESS scores of 10 or more (Roth et al, 2003), prevalences of 39% and 43% were found for pathological sleepiness according to MSLT criteria (Arnulf et al, 2002; Roth et al, 2003). These findings have prompted debate about whether the ESS and MSLT measure different aspects of EDS, and whether EDS in PD really does resemble a "narcoleptic phenotype". Although the ESS has been validated against MSLT in a general population (Johns, 1991), studies using PD patients suggest that specificity may be lower in this group, with a false-postitve rate of 18% for the ESS according to Arnulf et al, 2002. However, the ESS has shown utility in identifying those who have a history of falling asleep at the wheel (Brobsky et al, 2003). Another study highlighted the need for verification of sleep episodes from a caregiver, as some PD patients were shown to be unaware of episodes of polysomnography (PSG) confirmed sleep during the MSLT, and under-report sleepiness on the Epworth Sleepiness Scale, suggesting that accurate recall of naps may be impaired in this group, possibly due to cognitive decline (Merino-Andreu et al, 2003).

The concept of "sleep attacks" is controversial, with prevalences reported varying from 0% to 34.3%, according to how it is defined. Parallels have been drawn with the narcoleptic phenotype, with sleep episodes occurring rapidly and without warning, and before the patient can take action to avoid sleep. The need to differentiate between the daytime sleepiness that is characteristic of many PD patients, and these more overwhelming sleep episodes arose after reports of some patients falling asleep whilst driving. The study by Andreu-Merino et al

(2003) found that three of four patients who had caused traffic accidents by falling asleep at the wheel, were unaware of their sleep episodes during MSLT. However, the distinction between EDS and sleep "attacks" may be somewhat artificial, and sleep attacks may simply be part of the continuum of daytime sleepiness. This view is supported by a study by Sanjiv et al (2001) finding that scores on two versions of the ESS, one asking about "dozing off" and one about "falling asleep without warning" for each of the eight situations. The scores for both scales were highly correlated suggesting that they are not distinct phenomena.

The bulk of the studies detailed above found that EDS was more frequent or severe in PD patients, compared to healthy older adults, and the Tandberg et al study was particularly informative as it used a more suitable control group with chronic illness; patients with diabetes mellitus were just as likely to experience 'mild' daytime sleepiness, but PD patients were more likely to experience 'excessive' daytime sleepiness (Tandberg et al, 1999). In addition, this sample was followed-up 4 years later (Gjerstad et al, 2002), showing that as disease duration for the sample increased, so did the prevalence of MDS and EDS (to 15.5% and 28.9%) respectively. This suggests that EDS is a problem that increases in prevalence as the disease progresses; moreover, the fact that all baseline patients with EDS were still diagnosed with EDS at follow-up suggests that in many cases, EDS is not a transitory symptom that resolves spontaneously.

A fairly consistent picture emerges from those studies looking at the concomitants of excessive daytime sleepiness in PD; age, disease severity, cognitive decline and hallucinations are all associated with EDS (Hobson et al, 2002; Happe et al, 2001; Braga-Neto et al, 2004; Kumar et al, 2001; Rye et al, 2000; Tandberg et al, 1999; Gjersted et al, 2002), implying a poorer prognosis for those with EDS. The strongest evidence comes from the 4-year longitudinal community-based study, with those who were diagnosed with excessive daytime sleepiness at

follow-up showing significantly larger increases in disease severity, and incidence of dementia and hallucinations (Tandberg et al, 1999; Gjersted et al, 2002). Increased disease severity and cognitive decline may contribute to EDS via a functional route, with reduced ability to engage in meaningful activity, thus increasing susceptibility to sleep. Alternatively both disease severity and cognitive decline in PD may share a similar pathophysiological substrates. The co-occurrence of dementia and hallucinations with EDS suggests that patients with PDD or DLB are more likely to develop EDS (McKeith et al, 1996), and there may in fact be phenomenological overlap with the fluctuations in consciousness and cognition that are characteristic of DLB.

Although Chaudhuri et al (2002) found that EDS was associated with greater levels of nocturnal sleep disruption, measured using the Parkinson's Disease Sleep Scale, most studies have found no association with nocturnal sleep problems. In fact, Rye et al (2000) found that those patients with MSLT scores indicating pathological levels of sleepiness actually experienced *longer* sleep duration, *increased* sleep efficiency and *shorter* sleep latency at night, suggesting that EDS patients are more somnolent both during the day *and* night. Considering these findings as a whole, there is little evidence to support the idea that EDS in PD results from poor sleep at night.

Several studies have investigated EDS and specifically sleep attacks as a side-effect of DRT. Some studies found a dose-response relationship between L-dopa and sleep attacks, and some found that dopamine agonists, and specifically pramipexole were associated with EDS (Tan et al, 2002; Carbonari et al, 2002; Schlesinger & Ravin, 2003; Hauser et al, 2000; Arnulf et al, 2002). Results are not unequivocal; Pal et al (2001) and Sanjiv et al (2001) found an equal propensity to nap in PD patients taking L-dopa, pramipexole, and other dopamine agonists, and therefore a class effect rather than effects for specific DRTs appears to explain

the dose-effect relationship (Manni et al, 2004). One weakness of these studies (with the exception of Sanjiv et al, 2001) was that they failed to covary disease severity and duration as a confounding variable which may predict both levels of EDS and DRT dosage. It may be that DRT has a differential effect on sleep at different stages in the disease (Rye & Jankovic, 2002). Finally, one small study of three PD patients has investigated levels of the neuropeptide hypocretin, which is deficient in narcolepsy patients (Overeem et al, 2001). Hypocretin levels were however normal in the three PD patients, suggesting that although PD patients may display a narcoleptic *phenotype*, the underlying mechanisms for EDS are different (Overeem et al, 2002).

To summarise, daytime sleepiness at a level considered to be abnormal or pathological, is a problem for a considerable number of PD patients. Though DRT may play a role in contributing to sleepiness, disease severity, cognitive decline and hallucinations have been associated with EDS consistently, with the longitudinal study (Tandberg et al, 1999; Gjersted et al, 2002) providing the strongest evidence, therefore implying a poorer prognosis for patients with daytime sleepiness. No study has yet investigated whether tremor dominant (TD) or postural-instability-gait dominant (PIGD) patients are more prone to EDS. If PIGD patients show a greater propensity to nap, the contribution to EDS of fluctuations in cognition and consciousness and vice-versa warrant investigation.

3.3.6 Circadian rhythm disruption

Table 3.11 Correlates and relative prevalence of circadian rhythm disruption

Symptom	Prevalence in PD studies according to method of assessment	Comparison with healthy older adults	Concomitants
Sleep benefit	55.1%, questionnaire, large clinic study, Merello et al, 1997 42.4%, questionnaire, comm. Study, Tandberg et al, 1999		Merello et al (1997)– male, age, DD, no. awakenings. NS: sleep meds, latency, RLS Hogl et al (1998) – NS max L-dopa plasma conc, and time to max L-dopa conc, nocturnal PSG, depression, morningness-eveningness, *trend* more awakenings and arousals Tandberg, (1999) – LDD, fluctuations. NS: age, DD, LD dose, HY, UPDRS, MMSE, depression.

Sleep benefit after morning awakening appears to be prevalent in a PD population, with many PD patients saying that the morning is their best time of day in terms of motor function. Accordingly, sleep benefit is associated with motor fluctuations, suggesting that sleep has a restorative effect on striatal dopamine levels (Tandberg et al, 1999). Two studies showed an association with a greater number of awakenings and arousals at night, which may simply reflect a greater number of motor-related problems at night for these patients.

The presence of alterations in circadian rhythm in PD, as indexed by changes in body temperature, melatonin or cortisol, is as yet unclear, with only weak evidence for dysfunctions of suprachiasmatic nucleus (SCN) mediated circadian rhythm. The greater prevalence of nocturnal sleep problems in DLB, than in AD, does suggest that the α-synucleinopathies may indeed result in disrupted rest-activity rhythms, but the precise nature of any changes have yet to be delineated.

3.3.7 Relationship amongst sleep phenomena – shared pathophysiological mechanisms ?

The facets of sleep-related phenomena described above have been grouped according to existing classificatory systems and reviews of sleep disruption PD (Trenkwalder, 1998, Pal et al, 1999, Garcia-Borreguero et al, 2003). Nonetheless, from the results of clinical concomitant studies of sleep described above, it is clear that some facets show empirical associations with one another, and with the same clinical concomitants. Motor and disease-related nocturnal problems clearly contribute to sleep fragmentation and the insomnias, shown most clearly by the increase in PLM associated arousals, compared to elderly controls (Wetter at al, 2000). Underlying this association are correlations with daytime motor problems as indexed by scores of overall disease severity, disease duration and motor fluctuations. Changes in circadian rhythm, though less well documented, are intimately related to both insomnias at night and excessive daytime sleepiness, and are really a reflection of these two symptoms on a global level. Sleep benefit, with increased mobility in the morning is likely to be reflected by greater levels of activity in the morning, followed by reductions later in the day, thus influencing 24 hour rest-activity rhythms, and again motor fluctuations, disease severity, and medication-related factors are likely to contribute. Sleep-disordered breathing, whether obstructive or central in nature, is again likely to be related to disease severity (Trenkwalder, 1998) Excessive daytime sleepiness and parasomnias on the other hand, may be associated with a different cluster of concomitants, sharing an association with hallucinations, thus suggesting that they indicate a poorer prognosis. This has been confirmed for EDS by the longitudinal study (Tandberg et al, 1999; Gjersted et al, 2002) with greater increases over time in disease severity, dementia and hallucinations for those with EDS. Theories of EDS in PD focus upon

pathological disease-related changes in central dopaminergic pathways, and Rye & Jankovic (2002) suggest that extrastriatal pathways mediating arousal state via their action on thalamocortical neuron excitability, may be implicated. The presence of SOREMs in many excessively sleepy PD patients also suggests pathology in the pathways controlling REM activity, namely the reticular activating system (RAS) which is comprised of the dorsal raphe nucleus, locus coeruleus and pedunculopontine nucleus (Garcia-Rill, 1997; Pal et al, 1999; Rye & Jankovic, 2002). The RAS controls sleep, wake and arousal via pathways ascending from the brainstem. Cholinergic, serotonergic and noradrenergic pathways work in tandem to mediate changes between REM, slow wave sleep and waking states (Garcia-Rill, 1997). The pedunculopontine nucleus has a strong reciprocal connection with the substantia nigra (SN) and also inhibitory inputs from the locus coeruleus (LC), and so may be in effect disinhibited by reduced input resulting from cell death in both the SN and LC which is known to occur in PD The PPN also has strong connections with the REM-atonia circuitry and the REM-phasic generator (Garcia-Rill, 1997; Pal et al, 1999). Therefore, sleep disturbances involving changes in the expression of REM activity (excessive daytime sleepiness with SOREMs, altered dream phenomena) and with changes in the level of REM-atonia (REM behaviour disorder), may arise from disruption to the pathways of the reticular activating system.

As mentioned previously, excessive daytimes sleepiness, altered dream phenomena and REM behaviour disorder have all been associated with hallucinations in PD. Manford & Andermann (1999) propose a neurobiological model of hallucinations in PD and other disorders, whereby sensory information transmitted from the retina to the cortex, via thalamic relay nuclei, can be influenced by activity of the RAS which can effectively disinhibit thalamic transmission. Therefore the "fidelity" of sensory information transmitted via the thalamus may be compromised, and thus cortical representations may not reflect the outside world, but rather

internally generated interpretations, in other words "hallucinations". This elegant model may explain the cluster of hallucinations, EDS with SOREMs and altered dream phenomena that occurs in PD. The following section reviews those studies which have investigated disturbed sleep in Parkinson's Disease as a concomitant of hallucinations, comments on their validity, and considers which paradigms and methods of assessment may be appropriate for investigating sleep in the present study. Finally hypotheses regarding sleep in PD and its association with hallucinations are presented.

3.4 Sleep-related phenomena and hallucinations

3.4.1 Review of concomitant studies

The studies in tables 3.12 to 3.15 have been described previously, but will be commented on in more detail here.

Table 3.12 Phenomenological sleep-related associations with hallucinations in PD

Phenomenological studies					
Study	Design	N	Exclusions	Methods of sleep assessment	Findings
Moskowiz et al, 1978	Descriptive only	H = 26 NH = 62	Severe dementia, history of psychosis	Presence of vivid dreams	61.3% of hallucinators have current of previous vivid dreams
Pappert et al, 1999	Log-linear models	H = 33 NH = 93	Suggestion AD, DLB and history of stroke	Presence of 'altered dream phenomena' and 'sleep fragmentation'	Altered dreams independently associated with hallucinations and sleep fragmentation

Earlier studies of hallucinations noted that a large proportion of hallucinators had a history of altered dream phenomena (Moskowitz et al, 1987; Nauseida et al, 1982), and Nauseida et al (1982) suggested a progression from sleep fragmentation, through a series of parasomnias to the development of hallucinations. This hypothesis was not assessed using statistical methods however. More recently, Pappert et al (1999) found that altered dream phenomena were

significantly associated with hallucinations, but that sleep fragmentation was not, thus arguing against the notion of a simple continuum.

Table 3.13 Sleep-related concomitants of hallucinations in PD

Concomitant studies					
Study	Design	N	Exclusions	Methods of sleep assessment	Findings
Fernandez et al, 1992	Group comparison	50	Nil reported	Reported 'vivid dreams' and nightmares	No association
Sanchez-Ramos et al, 1996	Group comparison	H = 55 NH = 158	Nil reported	History of 'sleep disturbance'	Hallucinators have a *greater* frequency of history of sleep disturbance
Klein et al, 1997	Group comparisons	H = 29 NH = 58	Gross sensory impairment	'Sleep disturbances'	Hallucinators have a *greater* frequency of history of sleep disturbance
Fenelon et al, 2000	Group comparisons Regression model	H = 48 NH = 130	Previously diagnosed schizophrenia	Presence of 'severe sleep disturbance' (2 or more nocturnal sleep problems) Daytime somnolence	No effect for severe sleep disturbances Increased frequency of daytime somnolence in hallucinators Daytime somnolence is a significant predictor in multivariate logistic regression

Some second generation concomitant studies have used single-item self-report measures of 'sleep disturbance', which does not distinguish between insomnias and parasomnias, or a single question about vivid dreams (Sanchez-Ramos et al, 1996; Klein et al, 1997; Fernandez et al, 1992). Though Sanchez-Ramos et al (1996) and Klein et al (1997) found a greater frequency of sleep disturbance in hallucinators, their findings suffer from a lack of specificity. Fenelon et al (2000) asked about presence of initial insomnia, sleep fragmentation, early morning awakening, nocturnal agitation and vivid dreams, but they do not report individual associations with hallucinations, instead using a combined score. This "severe sleep disturbance" (2 or more symptoms) was not associated with hallucinations, but the combining of symptoms may have led to a type II error. They did however find an association between hallucinations and daytime somnolence.

Table 3.14 Third generation studies of sleep in hallucinating PD patients

'Third generation' studies					
Study	Design	N	Exclusions	Methods of sleep assessment	Findings
Comella et al, 1993	Group comparison	H = 5 NH = 5		Overnight polysomnography	Hallucinators show: Reduced total sleep time Increased wake after sleep onset Reduced SE Reduced REM sleep time Reduced REM sleep %age Reduced no. of REM periods Increased frequency of RBD-like behaviours
Arnulf et al, 2000	Group comparison	H = 10 NH = 10	Moderate to severe dementia	MSLT Overnight PSG	Hallucinators show: Reduced nocturnal sleep latency Shorter daytime sleep latency at 8am No effect for: TST, WASO, REM sleep In addition: 5/10 hallucinators show 2 or more SOREMs during MSLT
Manni et al, 2002	Naturalistic study of hallucinations	H = 20 NH = 13	Nil reported	Ambulatory PSG, sleep logs	29% of 24 hallucinatory episodes occurred in association with sleep episodes
Nomura et al, 2003	Group comparison	H = 14 NH = 8	Nil reported	Nocturnal PSG	Hallucinators show: Increased number of awakenings Increased %age of Stage 1 – REM sleep with tonic EMG No effect for: TST, SE, WASO, Stage I, II, III + IV or REM sleep

TST = total sleep time; SE = sleep efficiency (%); WASO = wake after sleep onset

A third generation of studies has attempted to look at the specific components of sleep architecture using polysomnographic techniques, with the hypothesis that hallucinators will show abnormalities of nocturnal REM sleep, that they will show a greater level of EDS as measured by MSLT, and that SOREMs may be associated with hallucinatory episodes. In addition, associations between RBD and hallucinations have been investigated.

The first study by Comella et al (1993) found REM sleep reductions (in time, percentage, and number of periods) for hallucinating patients, prompting the authors to speculate about the role of REM 'intrusion' in hallucinations, but a larger studies by Arnulf et al (2000) and Nomura et al (2003) failed to replicate these findings. Both Comella et al (1993) and Nomura et al (2003)

found a poorer overall pattern for sleep in hallucinators, with increased wake after sleep onset (WASO), decreased total sleep time (TST) and sleep efficiency, and an increased number of awakenings respectively. Arnulf et al (2000) on the other hand found no differences in nocturnal sleep apart from reduced sleep latency in hallucinators. This finding is interesting in the light of the MSLT results for this study with hallucinators displaying more pathological levels of daytimes sleepiness (five hallucinators showed 2 or more SOREMs during testing), as hallucinators show an ability to fall asleep rapidly during both day and night, suggesting that their EDS is not secondary to poor nocturnal sleep. In addition, two hallucinating patients recalled dreaming after SOREMs. This phenomenon was again shown by a naturalistic study using ambulatory PSG (Manni et al, 2002), which found that 29% of hallucinations experienced during monitoring were associated with sleep episodes. Four episodes of nocturnal hallucinations occurred shortly after awakening from REM sleep. Although findings are mixed, there does appear to be evidence for abnormalities of or a co-occurrence of REM dream activity and hallucinations.

Comella et al (1995) also found that four of their five hallucinating patients showed PSG results consistent with RBD, and Nomura et al (2003) found an reduced degree of atonia during Stage 1 – REM sleep in hallucinating patients. RBD and hallucinations may represent two outcomes of a shared pathophysiological process, as the role of RBD is difficult to explain as a mechanism for hallucinations, whereas altered dreams overlap phenomenologically with hallucinations, especially on the borders of sleep and wake.

Table 3.15 Longitudinal studies of sleep and hallucinations in PD

Longitudinal studies					
Study	Design	N	Exclusions	Methods of sleep assessment	Findings
Goetz et al, 2001a	4 year longitudinal study GEE model	Baseline: H = 29 NH = 60	AD, strokes, delirium, delusions, neuroleptic treatment	Subjective reports 'sleep fragmentation' and 'altered dream phenomena'	No effect on probability of having hallucinations after 48 months for either
Goetz et al, 2004	6 year longitudinal study GEE model	Baseline: H = 29 NH = 60	AD, strokes, delirium, delusions, neuroleptic treatment	Subjective report sleep phenomena	Presence of altered dream phenomena significantly associated with concurrent hallucinations. No predictive effect for ADP on future hallucinations
Onofrij et al, 2002	8 year longitudinal study Logistic regression	Baseline H = 5 NH = 75	Nil reported	Overnight PSG RBD questionnaires	Presence of RBD significantly related to presence of and prediction of hallucinations

TST = total sleep time; SE = sleep efficiency (%); WASO = wake after sleep onset

Two longitudinal studies have been conducted assessing the predictive power of sleep-related phenomena in explaining hallucinations (Goetz et al, 2001a; 2004; Onofrij et al, 2002). Goetz et al (2001a;2004) found that altered dream events were significantly associated with concurrent hallucinations, but that they did not predict future onset of hallucinations either at 4 years or 6 years. Sleep fragmentation did not show any association with hallucinations. Goetz et al (2004) comment that sleep disturbances were not stable over time, whereas hallucinations increased in frequency and were stable over time. This study therefore refutes the idea that altered dream events emerge prior to the onset of hallucinations, and that they can be used as a clinical index of vulnerability to future hallucinations.

The study by Onofrij et al (2002) found that polsysomnographically-assessed RBD at baseline did show predictive utility in identifying those who were hallucinators eight years later. Again, RBD may share a pathophysiological mechanism which overlaps with that of hallucinations. Although all of the above studies failed to covary disease severity as a possible confounding

variable, the fact that RBD often appears *prior* to the onset of PD suggests that severity is not mediating this association.

Summary

The association between altered dream phenomena and hallucinations that was reported anecdotally by early studies, and some studies have since reported empirical evidence of the association.. However, altered dream phenomena do not appear to have value in predicting the onset of future hallucinations, whereas RBD does.

3.4.2 Theories concerning sleep and hallucinations – a shared mechanism ?

As mentioned in Chapter 2 the sleep problems in PD overlap with sleep disruption in a number of other groups; healthy older adults show a more fragmented nocturnal sleep, other movement disorders such as PSP and MSA show a high incidence of apnoeas, RLS and PLMS, narcolepsy patients display both excessive daytime sleepiness and sleep-related hallucinations, and the dementias (including DLB and AD) show a polyphasic circadian rhythm, with parasomnias and hallucinations. Models of sleep disruption in these groups have been applied to the PD in an attempt to explain the various types of sleep-related phenomena in this group.

The application of the narcoleptic model has been limited in success; although PD patients display a narcoleptic *phenotype* of excessive daytime sleepiness with SOREMs and hallucinations, normal hypocretin levels have been found in PD patients with hallucinations, and human leukocyte antigen (HLA) typing is not indicative of narcolepsy (Overeem et al, 2002; Arnulf et al, 2000; Onofrij et al, 2003). Therefore, a neurobiological model of narcolepsy is likely to be less applicable to PD patients. In Alzheimer's Disease, a polyphasic circadian

rhythm is observed, with periods of agitation, confusion and hallucinatory behaviour occurring more often around the 'sundown' period (Bliwise et al, 1993; Volicer et al, 2001). In AD the pathophysiology thought to be causing these changes is degeneration of the supra-chiasmatic nucleus (SCN) which is considered to be the 'pacemaker' for the sleep-wake cycle. There is weaker evidence for circadian rhythm changes in PD as indexed by melatonin and other SCN-mediated factors, and the pathology of PD is unlikely to extend to the SCN, unless Lewy bodies have extended to the hypothalamus.

Studies of sleep architecture have suggested a role for abnormalities of REM sleep as a mechanism for hallucinations in PD, and the finding of EDS and SOREMs which co-occur with dream and hallucinatory episodes in PD supports Manford & Andermann's (1999) model of abnormal activity in the RAS both disrupting transmission of visual and other sensory information during perception, and abnormal changes in arousal states. The pedunculopontine nucleus (PPN), as part of the RAS, is connected to both the REM-atonia circuits, and via its connections with the substantia nigra to the REM-phasic generator circuitry. Abnormalities in both the dopaminergic striatal system and the cholinergic PPN may therefore have implications for both the timing and expression of REM activity, and the degree of atonia during REM sleep (Garcia-Rill, 1997; Pal et al, 1999; Rye et al, 2000; Rye & Jankovic, 2002).

Manford & Andermann's model of RAS abnormality bears some similarities to models of psychotic phenomena in schizophrenia and sleep deprivation; most simply expressed as the idea of 'REM breakthrough' into waking consciousness (Comella et al, 1993; Garcia-Rill, 1997).

3.4.3 Hypotheses

Hypotheses for the present study concerning sleep-related phenomena in PD and their association with hallucinations are as follows:

6. PD patients will show increased levels of sleep-related symptoms and unusual perceptual experiences than controls, independently of age, global cognition, anxiety and depression.
7. PD patients will show increased levels of sleep fragmentation, wake after sleep onset, shorter sleep duration, greater daytime sleepiness, and a more disrupted pattern of circadian rhythm compared to controls, independently of age, global cognition, anxiety and depression.
8. Hallucinators will show increased levels of sleep-related symptoms as measured by the QUE, greater daytime sleepiness, and a more disrupted pattern of circadian rhythm compared to non-hallucinators, independently of age, disease severity, global cognition, anxiety and depression.

CHAPTER 4

COGNITIVE FUNCTION IN PD AND RELATIONSHIP WITH HALLUCINATIONS

This chapter does not attempt to provide a detailed review of cognition in PD, but rather will be guided by models of mechanisms underlying cognitive deficits in PD, theories of hallucinations, and paradigms from experimental studies of other hallucinating groups.

4.1 History/Background of cognitive change in PD.

Despite James Parkisnon's stance, cognitive changes had long been described in classic PD and in cases of encephalitis lethargica. In 1922 Naville described a syndrome of fatigue and mild memory impairment, alongside reductions in voluntary attention, spontaneous interest, initiation of and persistence in effortful tasks, and hence coined the phrase 'bradyphrenia'. Therefore slowing in cognitive processes (bradyphrenia) had a direct parallel to the slowing in motor processes (bradykinesia). Over the 20th century several authors questioned whether this concept of bradyphrenia could in fact be distinguished from the results of simple motor slowing, which confounded assessment of cognitive function, or indeed from the presence of depression. In 1971 Ajuriaguerra examined the effect of L-dopa in patients with post-encephalitic Parkinsonism and paralysis agitans and suggested that L-dopa could in fact ameliorate aspects of bradyphrenia. The idea that DRT had some impact on cognitive function was backed up by findings of improved cogntive abilities when patients were in the 'on' state compared to the 'off' state (Delis et al, 1982), although there were suggestions that this was achieved by a non-specific effect of improved affect and increased arousal (Brown et al, 1984).

4.1.1 'Subcortical dementia'

Ideas of cognitive change that arose from the same area of dysfunction as motor impairment, and which responded favourably to DRT led to the emergence of the concept of 'subcortical dementia' (Albert, 1974). Albert's original study included patients with progressive supranuclear palsy (PSP), but a similar pattern of clinical features and subcortical lesions were found in PD, Huntingdon's Disease, Wilson's Disease and Multi-System Atrophy (MSA), and so the model was applied to these diseases as a group. Features of subcortical dementia included cogntive slowing, dysexecutive syndrome, memory deficits and changes in personality and affect, *and critically* in the absence of aphasia, apraxia or agnosia (Cummings, 1986). In this way subcortical dementia was clinically differentiated from 'cortical' dementias such as AD.

The mechanism behind subcortical dementia was envisaged as loss of function in the basal ganglia impacting on ascending pathways to the thalamus and cortex, leading to amongst other effects reduced innervation of the pre-frontal cortex, and a wider effect on the whole of the meso-cortico-limbic dopaminergic system. A loss of function in areas innervated by projections from the basal ganglia would have implications not only for frontal type cognitive deficits but also for *affect* mediated by the limbic system, which might explain the high prevalence of depression in PD patients. This model represented a crucial difference between PD and AD; one arising from subcortical lesions and affecting ascending pathways, and one from diffuse cortical pathology with a typical pattern of frontal and temporal atrophy.

This distinction predicts that the two groups (cortical and subcortical dementias) will show a different pattern of impairments across a range of neuropsychological tests. Several studies have demonstrated a distinct profile in AD and PD, although patients with PDD, rather than non-demented PD patients are the most suitable group for comparisons with AD. The failure of

earlier studies of this kind to match PD patients with their AD counterparts for current IQ or global functioning meant that such differences may have been unavoidable, and simply represented more severe global impairments in the AD patients. For example, Huber et al (1986) found that AD patients scored significantly more poorly compared to PD patients on several domains, and both scored more poorly than controls. However, the mean MMSE score in the PD group was 27.16 (well above the cut-off of 24), but it was 18.54 in the AD group (well below the cut-off), and thus differences in verbal fluency, apraxia and orientation may simply reflect differences in global functioning. Recent studies attempting to match global IQ however, have found that attentional deficits are indeed more exaggerated in PDD compared to AD, where mnemonic deficits dominate the cognitive profile (Noe et al, 2004)

To summarise, PD and PDD patients show a distinct pattern of neuropsychological impairment when compared to AD, which reflects the differences in underlying patterns of impairment in the brain.

4.1.1.1 Neuroanatomical and neurobiological models of subcortical dementia

Recent advances in histopathology and knowledge of brain structure and neuroanatomy have allowed development of the concept of subcortical dementia into a well-defined neuroanatomical model. Five parallel but segregated basal ganglia-thalamocortical circuits have been described (Alexander et al, 1990) which may account for some of the cognitive and affective deficits in PD.

Figure 1.1 (Chapter 1) shows a schematic diagram of the connection between basal ganglia pathways and the thalamus and cortex.

Of the five circuits, the motor and oculomotor circuits have been studied most extensively, and their functions operationalised as primarily motor-related. The other three circuits are firstly the

dorsolateral prefrontal circuit with projection to the dorsolateral prefrontal region and inputs from the posterior parietal cortex and arcuate premotor area, secondly the lateral orbitofrontal circuit with its connections to and from Brodmann's area 10 and the auditory and visual association cortices, and thirdly the limbic circuit with projections to the ventral or 'limbic' striatum with inputs from the hippocampus, amygdala, entorhinal and perirhinal cortices, temporal pole, inferior temporal gyrus, medial orbitofrontal area and anterior cingulate (Alexander et al, 1986; 1990). Given the specificity of each circuit in terms of the different areas targeted this model presents a tantalising opportunity to investigate different cognitive, affective and neuropsychiatric symptoms in PD and other 'subcortical dementias' in relation to the different pathways (Darvesh & Freedman, 1996). However, as yet functional imaging and histopathological techniques are not precise enough either to have identified the exact functions of some of the targeted regions, nor to have shown strong evidence of reduced functioning in these pathways in patients with specific neuropsychiatric symptoms.

Taylor & Saint-Cyr (1995) review the evidence for the role of the basal ganglia and ascending DA pathways in cognition, and in particular in reference to the learning and strategic processes mediated by the frontal cortex. They argue that the modality of the task is not important, but rather that it is the task conditions and the demands made upon executive abilities that determine whether a PD patient is able to complete a task or not. They integrate evidence from several sources that different areas of the striatum have differential effects on input from the cortex and thalamus; either excitatory or inhibitory (Freund et al, 1984). This "orchestration" may have the effect of modulating the signal-to-noise ratio of striatal outflow. When considered across different levels of the basal-ganglia-thalamo-cortical loops and across five parallel circuits, dopamine may function to boost a desired signal by inhibiting background noise, thus

increasing likelihood of selection of that signal (Robbins & Brown, 1990; Owen et 1993; Downes et al, 1993).

Taylor & Saint-Cyr apply this mechanism to a model of indirect learning where a patient is confronted by a novel task for which no set of rules have been explicitly defined, for which heuristics have not yet developed, and in the absence of external cueing. Such a task will require a trial and error approach which in normal individuals would result in the emergence of a heuristic, or a cognitive 'set'. Of course, such a task is typical of executive tests. Therefore, in this example, the loss of overall transmission or the finer orchestration of dopamine would slow the process of signal selection, as the correct set would take longer to emerge without the aid of "boosting", or enhancement. This would lead the PD patient to rely on more 'top-down', effortful and laborious cortical strategies for solving the task (Taylor & Saint-Cyr, 1995), reflecting the 'protective' effect of IQ on some tasks.

As yet, the precise correlation between different types of cognitive task and which of the five circuits are primarily involved has not been delineated. However, several authors argue that all deficits displayed in PD patients are due to executive dysfunction arising from basal ganglia interactions with the prefrontal cortex; 'non-executive' deficits such as those in recall or visuospatial function are in fact an artefact of the task demands, many of which do have some executive component (Taylor & Saint-Cyr, 1995; Dubois & Pillon, 1997). The concept of 'subcortical dementia' thus seems plausible and a useful model for generating predictions.

4.1.1.2 Evidence for a model of subcortical dementia - problems and limitations

Evidence cited by Dubois & Pillon (1997) for selective nigrostriatal loss contributing to cognitive deficits is three-fold; firstly from correlations between cognitive impairment and dopaminergic loss assessed by functional imaging studies and clinical motor assessment, secondly poorer

cognitive performance in *untreated* patients, and thirdly improved performance in patients in the 'on' state as compared to 'off'. However, Emre (2003) criticises the strength of the evidence for DRT in ameliorating cognitive deficits, and concludes that more recent studies have found little evidence for a beneficial effect. Recent investigations of the effect of dopaminergic medication on cognition in PD have shown that their administration, in effect increasing function in the basal ganglia, has limited effects on cognitive functions thought to be mediated by the cortex. Although reaction-time is invariably slower in off states, purely cognitive components may be unaffected by administration of DRT. There may however, be a specific effect for some cognitive aspects dependent upon information processing such as control of attention and working memory (Pillon et al, 2001). Explanations for disparate findings across studies include the possibility that DRT influences DA transmission in motoric and cognitive pathways differently. Taylor & Saint-Cyr (1995) argue that differential loss of dopamine in the putamen (part of the motor pathway) and the caudate (part of the cognitive pathway) during the natural progression of the disease (Kish et al, 1988) may lead to a differential effect of DRT on the two areas and their thalamo-cortical projections.

The 'subcortical dementia' model is further complicated by the fact that 'cortical' dementias often show subcortical lesions, for example loss of cholinergic function in the nucleus basalis of Meynert in AD (Whitehouse et al, 1981), and 'subcortical' dementias may have cortical features, such as neocortical and cortical Lewy bodies, plaques and tangles in PD (Hughes et al, 1993). A second possibility, currently gaining favour (Levy et al, 2002; Aarsland & Ehrt, 2003) is that cognitive impairment may well reflect pathology in other ascending pathways involving other neurotransmitters. The neuropsychological overlap between DLB and PD and PDD supports the idea that cholinergic pathways in particular may play a vital role in the dementing process. Taylor & Saint-Cyr argue for a more detailed examination of the

relationship between motor signs and cognitive deficits; that specific motor signs may correlate with some cognitive impairments, but not with others. However, the relationship of specific motor symptoms to cognitive impairment suggests that is in fact those motor symptoms such as axial signs which represent non-dopaminergic symptoms (i.e. are less responsive to DRT), in fact reflect underlying cholinergic dysfunction (Pillon et al, 1988; Jankovic et al, 1990; Levy et al, 2000; Burns et al, 2002). Therefore recent literature is moving away from the idea of a subcortical dementia syndrome which is mediated solely by dopamine.

4.1.2 Alternative cognitive models – the theory of processing resources

Brown & Marsden (1990) provide an excellent review of cognitive deficits in PD, and also a critique of another possible model for considering the cognitive deficits, this time a purely 'psychological' model which not tied to specific neuroanatomical substrates. Norman & Shallice's (1980) supervisory-attentional-system (SAS) with its central processor which is crucially *limited in capacity* is hypothesised to be further reduced in PD (Stam et al, 1993), thus producing deficits when task demands compete for limited processing capacity. This kind of model has been fruitfully applied to patients with frontal deficits (Shallice, 1988) and to schizophrenics (Frith, 1989), and is particularly well-suited to accounting for executive type deficits such as decision making and planning, and in novel tasks and those which require set maintenance or shifting.

Just as PD patients show difficulty with carrying out two simultaneous motor tasks (such as walking and talking), they show marked impairment on interference tasks such as the Stroop and dual tasks (Stam et al, 1993). Furthermore, inability or slowness in executing self-cued motor processes (i.e. hesitation prior to taking a step) is paralleled by deficits on tasks requiring internal cueing such as alternating verbal fluency paradigms where the subject is

continuously required to initiate searches within the lexicon, which can be largely overcome by external cueing by the experimenter (Sharp, 1991; Downes et al, 1993). However, Brown & Marsden (1990) criticize the model for lacking predictive value as such an abstract concept as limited-capacity mental processing can be fitted indiscriminately to almost any task which produces deficits in PD.

Despite its shortcomings, the information processing framework has been of value in building models of positive and negative symptoms in schizophrenia, and in considering how cognitive processes and deficits may contribute to them (Frith, 1989). One advantage of using a model which is not tied to neuroanatomical considerations is that 'psychological' processes can be considered in a more abstract and flexible form, and that mechanisms and patterns of deficits and symptoms can be modeled without needing to provide as yet unobtainable evidence of localised neurological damage. Frith (1992) has argued that these two types of model, neuroanatomical and neuropsychological have different values in terms of the level of explanation required; although there may be neurobiological evidence for hypersensitivity of dopamine receptors in the mesolimbic pathway, this observation provides no theory about the deficits in cognitive processes arising from such pathology, nor generates testable hypotheses about the performance of patients on neuropsychological tests. The previous literature on cognition and hallucinations in PD and DLB has been largely medical-anatomical, seeking explanations for which clinical and pharmacological solutions can be sought. However, they essentially miss one level of explanation which can be of great theoretical, functional and predictive value; the neuropsychological explanation. Given the current controversies surrounding the neuroanatomical substrates of PD, PDD and DLB, and indeed the neuroanatomical differences and similarities in PDD and DLB, any explanations based on neuropathology which are not bolstered by autopsy or imaging correlates are lacking. This

thesis seeks to explore, first and foremost, the cognitive and psychological explanations of hallucinations in Parkinson's Disease.

4.1.3 Summary

Although the subcortical model provides a neat explanation for some cognitive deficits in PD, the concept of subcortical versus cortical dementia may not help to clarify understanding of cognition in PD in relation to neuropsychiatric symptoms such as hallucinations, which are prevalent in AD, PD, PDD and DLB. The existence of DLB itself presents an interesting problem for the model, sharing as it often does cortical and subcortical pathology and clinical features of both cortical and subcortical dementias (McKeith et al, 1996; Jellinger et al, 2003). Although the possible role of subcortical pathology in negative symptoms of schizophrenia offered new avenues or research, the symptoms of interest in the current discussion are by definition *positive* symptoms. Rogers (1996) argument for an integrated examination of cognitive and neuropsychiatric features appears compelling, and will provide the basis for theorising on the cognitive contribution to neuropsychiatric features in PD in this review. The following review of neuropsychological deficits in PD will examine the evidence for deficits across separate cognitive domains, and highlight the possible role they may play in the genesis of hallucinations.

4.2 Review of the neuropsychological deficits of Parkinson's Disease

As mentioned previously, the character of cognitive decline does not typically fall into a model of cortical dementia such as described in the DSM-IV criteria. Changes are often subtle and insidious and may not be severe enough to impair daily functioning (Emre, 2003). Dubois &

Pillon (1997) emphasise that DSM criteria are better adapted for 'cortical' dementias such as Alzheimer's with its prominent memory loss, and less with for dementias with frontal / executive deficits and concurrent motor disorder. In addition many standardised neuropsychological assessment batteries largely neglect to examine executive function in depth. A subclinical decline in global functioning may be found in many PD patients, but reaches levels compatible with a diagnosis of dementia in only a subgroup.

4.2.1 Executive function

Perhaps the most prominent feature of PD cognitive change is a 'dysexecutive' deficit (Dubois & Pillon, 1997; Emre, 2003). Mild changes in executive function are found in nearly all PD patients, even from early on in the disease process, and have a plausible mechanism resulting from basal ganglia damage, that is, reduced function in the pathways from the striatum to the frontal lobe (Darvesh & Freedman, 1996). Deficits on tests requiring concept formation, rule-finding, strategic planning, set-shifting and maintenance or other aspects of mental flexibility are found in both non-demented and demented patients (Agid et al, 1987; Cools et al, 1984; Girottti et al, 1988; Stam et al, 1993; Green et al, 2002), and bear some similarities to those found in patients with frontal lesions (Stuss et al, 1997). However, perseveration is less common a feature than in frontal patients, rather PD patients show a tendency to shift attention to new stimuli, so a distractibility effect is found (Owen et al, 1993). This tendency is reflected in the beneficial effect which providing cues has in directing attentional resources, for example, by prompting the subject with a cue in set-shifting paradigms including verbal fluency (Downes et al, 1993; Owen et al, 1993). Stam et al (1993) describe a number of executive deficits in PD

patients which they posit results from a disturbance in the SAS which regulates attentional resources.

Dubois and Pillon argue that all cognitive deficits in PD can be explained by an underlying dysexecutive syndrome which impacts on other cognitive domains such as attention, memory, visuospatial ability and construction, which are in effect secondary deficits resulting from inability to perform a wide range of tasks due to problems with planning, initiation of an appropriate response, shifting attention and loss of ability to monitor responses adequately (Dubois & Pillon, 1997).

Deficits in other domains are well-documented, although it could be argued that many paradigms used to examine these domains require in tact executive abilities. Deficits truly reflecting impairment in other domains would require that they were independent from executive function statistically. If present, such deficits would imply either that subcortical damage exerted a wider effect on cognitive function, or that neocortical or cortical damage was present (Darvesh & Freedman, 1996).

4.2.2 Mnemonic function

Memory deficits in PD and PDD differ from the widespread and profound loss of both recall and recognition in Alzheimer's (Pillon et al, 1991; Stern et al, 1993). Although deficits in recall are observed, paradigms utilising cueing or probing conditions can substantially reduce observed deficits, by eliciting a response via external cueing or initiation (Flowers et al, 1984; Brown & Marsden, 1988). Accordingly, recognition does not show the consistent deficits found in Alzheimer's Disease (Flowers et al, 1984; Pillon et al, 1991). This pattern suggests that storage systems are in tact, but that is *retrieval* that is impaired. This suggests a possible role for an underlying dysexecutive syndrome; PD patients are less able to generate or initiate

appropriate retrieval strategies or to carry out 'self-cueing', and may also be less able to encode information in a strategic and organised fashion (Brown & Marsden, 1987; 1990; Dubois & Pillon, 1997). Recognition however, which can be considered as an essentially 'passive' process (Flowers et al, 1984) does not require such internal cueing, mental manipulation nor organisation of a response. The fact that executive deficits can be greatly ameliorated by providing cues to signal each change (Sharp, 1991; Downes et al, 1993) suggests that memory deficits in PD may parallel executive deficits, and may therefore be described using a similar framework.

4.2.3 Attentional dysfunction

Deficits in attention have been well-documented, in terms of reaction-time, vigilance and ability to carry out continuous performance tasks (Litvan et al, 1991). As described earlier, attention is particularly impaired in DLB, where patients display fluctuations in arousal, attention and accordingly other cognitive domains (McKeith et al, 1996; Klatka et al, 1997). A recent study comparing PD, PDD and DLB patients found equivalent 'micro-fluctuations' in reaction speed in PDD and DLB patients (Ballard et al, 2002). Deficits in attention may arise from either cholinergic loss or pathology in the brainstem centres responsible for controlling arousal, i.e. the reticular activating system, and are closely linked to increased daytime somnolence in DLB patients (Ferman et al, 2004). It is easy to see how changes in attention might exaggerate an already impaired executive ability, or be influenced themselves by executive problems with set maintenance or set-shifting, and difficulty initiating a planned action (Stam et al, 1993; Downes et al, 1993).

4.2.4 Visual and perceptual dysfunction

Visuoperceptual deficits appear relatively early in the disease trajectory, though they may be exaggerated by peripheral and central visual deficits. Visual deficits in PD include contrast sensitivity, colour discrimination, loss of acuity due to retinal dopamine loss and double vision (see Harris, 1998 for review). These early deficits appear to be independent of global cognitive impairment, though some authors suggest they are related to disease severity and to dopamine loss in the retina and visual pathways(Harris, 1998; Buttner et al, 2000) with some abilities declining at an early stage, and some later in the disease (Cousins et al, 2000; Muller et al, 2002). Cumming & Huber's (1992) review of earlier studies describes a wide range of visuospatial deficits involving nearly all categories of visuospatial ability namely sensory abilities, visuoperceptual ability and discrimination, visuomotor abilties, visuospatial attention, visuospatial cognition and body-spatial orientation, with only recognition abilities preserved. Pillon & Dubois (1998) argue that all visuospatial dysfunction can be described in terms of executive deficits, contrasting with Harris's (1998) description of inherent visual sensory impairments.

4.2.4 Language and instrumental function

Language functions in PD do not display the gross deficits found in Alzheimer's Disease where there is evidence of degraded storage of the lexicon itself, which may result in some degree of aphasia and in semantic deficits. Indeed the main impairment in PD in the language domain is in tests of verbal fluency, which carries an important executive component involving self-generation of search strategies, and is improved by cueing (Sharp, 1991; Pillon et al, 2001; Dubois & Pillon, 1997)

4.2.5 Summary

Amongst the cognitive deficits associated with Parkinson's Disease, executive function plays a dominant role, by contributing to other deficits such as impaired recall, and any other cognitive processes which involve internal cueing (Brown & Marsden, 1988; 1990). Some authors have even argued that executive function is responsible for most deficits observed in PD, as most cognitive tasks involve and executive component, especially those where retrieval or organization of information must be carried out (Dubois & Pillon, 1997). The presence of executive dysfunction is well-supported by the neuroanatomical models of PD by the projection of ascending dopaminergic pathways from the basal ganglia to the prefrontal cortex. It has been demonstrated that executive deficits and dysfunction contribute to the apathy that is frequently observed in PD (Brown et al, 2002). However, the contribution of executive dysfunction to hallucinations in PD has not yet been fully investigated, although some studies have found poorer performance on verbal fluency in hallucinators, but it is not clear whether this simply reflects overall cognitive impairment in this group (Haeske-Dewick, 1995).Visual perceptual deficits are also prominent in PD, and often emerge early in the disease. The case for visual deficits as a contributor to hallucinations seems compelling, given the presence of visual disease, agnosia and other visual perceptual deficits in hallucinating AD and DLB patients (Holroyd & Sheldon-Keller, 1995; Murgatroyd & Prettyman, 2001; Mori et al, 2000). Both peripheral visual deficits caused by ophthalmic disease or loss of retinal dopamine (Harris, 1998), or higher-level deficits in visual cognition may contribute to hallucinations. The projection of dopaminergic pathways to the visual association cortex is supportive of the presence of deficits in higher-level visual cognitive processes such as object recognition, as has been demonstrated by Laatu et al (2004). Models of illusions and hallucinations suggest that top-down processes may be involved in errors of perception, and the contribution of

higher-level visual deficits to visual hallucinations warrants investigation. Attentional deficits, which may arise partly from pathology in brain stem or the cholinergic system, are also a possible candidate for contribution to hallucinations. Limited attentional resources may lead to a distractibility effect, where internally-generated thoughts or associations are not suppressed, and intrude into ongoing cognitive processes. Alternatively visual attention deficits may lead to top-down visual processes overriding bottom-up perceptual processes, if stimuli are not attended to fully (Collerton et al, unpublished).

The following section reviews those studies which have investigated the cognitive and perceptual concomitants of hallucinations in PD.

4.3 Second generation studies – cognition, perception and hallucinations in PD

4.3.1 Visual deficits as concomitants of hallucinations in PD

Visual disease was associated with hallucinations in some of the studies reviewed in Chapter 2. Table 4.1 shows those studies which examined peripheral visual function in greater detail, including measures of visual acuity, but which were not based on any specific models of how deficits in peripheral vision or visual cognition might contribute to hallucinations. These studies aimed largely to determine whether change in peripheral vision was a concomitant of hallucinations in PD.

Table 4.1 *Studies investigating visual and perceptual concomitants of hallucinations in Parkinson's Disease*

Study	Design	N	Inclusion/exclusion	Methodology	Findings
Haeske-Dewick, 1995	Group comparison	H = 16 NH = 20	Psychiatric history, sensory pathology, thalamotomy, stroke, MID, AD or DLB	Bilateral visual acuity	Non-significant trend for poorer visual acuity in hallucinators
Miyoshi et al, 1996	Group comparison of patients with hallucinosis and delirium	Not stated	Nil reported	Presence of metamorphopsia and inverted vision	Metamorphopsia and inverted vision more frequent in the hallucinosis group
Graham et al, 1997	Group comparisons: Hallucinators versus non-hallucinators Early and late hallucinators versus non-hallucinators	 H = 32 NH = 97 EH = 19 LH = 13	Nil reported	CANTAB: Pattern recognition Spatial recognition	No differences observed
Holroyd et al, 2001	Prospective Group comparison (MANOVA)	H = 26 NH = 72	Atypical features suggesting PSP, DLB etc Absence of response to L-dopa DSM criteria delirium	Visual acuity	Hallucinators have significantly poorer visual acuity

The studies detailed above suggest that poorer visual acuity is associated with hallucinations in PD (Holroyd et al, 2001; Haeske-Dewick, 1995), that some hallucinating patients experience unusual visual effects such as metamorphopsia and inverted vision, suggesting pathology of the visual system (Miyoshi et al, 1996), but that higher level visual cognitive functions and pattern recognition are unaffected (Graham et al, 1997).

4.3.2 Specific cognitive deficits as concomitants of hallucinations in PD

Greater decline in global cognitive function in hallucinating PD patients compared to non-hallucinators has been established as a robust finding in the existing literature, however less is know about specific cognitive function in hallucinating PD patients. Given the vast amount of literature that exists on cognitive deficits and profile in PD, and the well-developed models of cognitive processing in PD, it is surprising that there is a relative paucity of data on the cognitive profile of hallucinating patients. Some earlier studies have used a range of neuropsychological tests to compare performance of hallucinators and non-hallucinators, but in most cases this was done in a non-directed way, without a model of the contribution of specific cognitive deficits to hallucinations. Table 4.2 shows the results of some of the earlier investigations of cognition in hallucinating PD patients.

Table 4.2 Performance on specific cognitive tests as a concomitant of hallucinations in PD

Study	Design	N	Exclusions	Cognitive assessment	Findings
Meco et al, 1990	Group comparison	H = 9 NH = 10	MMSE < 18	Luria-Nebraska Neuropsychological Battery (LNNB)	No differences found on any subtests of the function scales or the localisation scales
Haeske-Dewick, 1995	Group comparison	H = 16 NH = 20	Psychiatric history, sensory pathology, thalamotomy, stroke, MID, AD or DLB	NART Verbal fluency (FAS)	No difference in pre-morbid intelligence (NART) Hallucinators score more poorly on verbal fluency test
Graham et al, 1997	Group comparisons: Hallucinators versus non-hallucinators Early and late hallucinators versus non-hallucinators	 H = 32 NH = 97 EH = 19 LH = 13	Nil reported	CANTAB: Spatial WM Digit ordering Set shifting Verbal fluency (FAS) NART	No differences found on any of the CANTAB subtests, verbal fluency or premorbid intelligence with hallucinators and non-hallucinators. Late hallucinators show poorer verbal fluency scores that late non-hallucinators
Barnes & David, 2001	Group comparison	H = 21 NH = 23	DLB and AD diagnosis	Word recognition Face recognition	Hallucinators perform more poorly on face recognition

The studies reviewed in Table 4.2 reveal firstly that there appear to be no differences between hallucinators and non-hallucinators on pre-morbid intelligence (Haeske-Dewick, 1995; Graham et al, 1997), that executive function as indexed by the verbal fluency test is compromised, particularly in 'late' hallucinators (Haeske-Dewick, 1995; Graham et al, 1997), and that recognition memory for faces appears to be impaired in hallucinators (Barnes & David, 2001). Despite the fact that Meco et al (1990) used a wide-ranging cognitive battery no effect was found for hallucinating patients on any of the subtests of either scale. However, there appears to be evidence for specific cognitive deficits in hallucinating patients in executive function and face recognition, although how these may contribute in a functional sense to hallucinations has not been commented upon by the authors.

4.3.1 Problems with the second generation studies – what has been neglected ?

One flaw of the studies in Table 4.2 is that global cognition scores have not been covaried, and neither has disease severity. Therefore the independence of specific cognitive deficits from global cognitive decline and from motor-related factors which may impair completion of tasks has not been assessed. Secondly, any speculation about the role of specific deficits in contributing to hallucinations in PD is essentially post-hoc as there were not *a priori* hypotheses regarding which areas of cognition would be impaired.

The studies and models of hallucinations in other populations described in section 2.3 have been instructive in highlighting which areas should be investigated in relation to cognition, perception and hallucinations in PD. Firstly, the role of peripheral visual deficits, and higher-level visual cognition warrants investigation, as there is evidence for impairment in both areas in AD and DLB patients with hallucinations (Holroyd & Sheldon-Keller, 1995, Chapman et al, 1999; Murgatroyd & Prettyman, 2001; Mori et al, 2000). Secondly, following neuropsychological models of cognitive deficits and biases in psychosis, phenomena such as reality monitoring deficits, a bias towards

false positives, and the production of erroneous material in the form of intrusions or confabulation should be investigated as they are associated with 'positive' psychotic symptoms such as hallucinations (Frith, 1992; Bentall, 1990; 1994; Brebion et al, 1997; 1998; 1999). In recent years a series of studies has begun to investigate the role of both perceptual and cognitive deficits and biases in hallucinating PD patients, and these will be reviewed in the following section.

4.4 Third generation studies – hypothesised role of impaired perceptual and cognitive function

This section reviews the small number of studies which have investigated perceptual and cognitive biases and deficits in PD patients with hallucinations.

4.4.1 Visual perception and its role in visual hallucinations in PD patients

Table 4.3 describes studies of visual perception and function in hallucinating and non-hallucinating PD patients, which have utilised a more in-depth approach to examine visual perception.

Table 4.3 Studies investigating visual and perceptual concomitants of hallucinations in Parkinson's Disease

Study	Design	N	Exclusion	Visual assessment	Findings
Buttner et al, 1996	Group comparison controls vs PD Regression to predict hallucinations	H = 10 NH = 63	Colour blind individuals	Visual acuity Colour discrimination Chromatic contour perception	NS visual acuity NS colour discrimination Hallucinators more impaired on chromatic contour perception
Diderich et al, 1998	Group comparison	H = 14 NH = 21	Snellen acuity <0.6	Ophthalmic history Visual acuity Contrast sensitivity Colour discrimination	NS ophthalmic history NS visual acuity Hallucinators are more impaired on tests of colour discrimination and contrast sensitivity.
Onofrij et al, 2002	Longitudinal study Logistic regression	Baseline: H = 5 NH = 75		Visual evoked potential Contrast sensitivity, Electroretinography, Visual P300 ERP	No predictive effect of hallucinations for visual 'abnormalities' or abnormalities of cognitive ERPs
Barnes et al, 2003	Group comparison	H = 17 NH = 20	Diagnosis of AD and DLB Eye disease, migraine, concurrent medical disease	Visual Object and Space Perception Battery	Hallucinators perform more poorly on: Incomplete letters Silhouettes Object decision Progressive silhouettes NS for: Dot counting Position discrimination Number location Cube analysis

Findings have been consistent for impaired colour discrimination in hallucinators (Buttner et al, 1996; Diederich et al, 1998), although the authors differ on pinpointing the source of this deficit, Diederich et al (1998) arguing for the involvement of retinal dopamine, and Buttner et al (1996) highlighting a possible role for pathology in the pathways of the visual cortex, and specifically the V4 area. Impaired chromatic contour perception and contrast sensitivity have also been found in hallucinators (Buttner et al, 1996; Diederich et al, 1998). Diederich et al (1998) interpret their findings in the framework of visual disinhibition as has been proposed for CBS. They argue that loss of colour discrimination and contrast sensitivity has a "depatterning" effect on visual input, and so 'release' of internally generated percepts, normally suppressed by sufficient visual input. The application of visual psychophysics to hallucinating PD patients has therefore provided supportive evidence for models of visual disinhibition.

Barnes et al (2003) used an alternative approach, investigating the role of visual cognition in hallucinating PD patients. Hallucinators performed significantly more poorly on four subtests of the VOSP battery which have been demonstrated to tap object perception, but showed no differences on four subtests which tap spatial perception (Warrington & James, 1991; Rapport et al, 1998). The VOSP requires subjects to identify objects in conditions of reduced information, either by requiring processes of visual closure, or by providing only silhouettes of objects viewed from unconventional perspectives. Such deficits are highly interesting in light of the fact that many PD hallucinators experience hallucinations in conditions of low-lighting or at night (Meco et al, 1990; Goetz et al, 1998), and many of these experiences can be more accurately described as 'object illusions' (Fenelon et al, 2000), where real objects are misinterpreted as something else. Deficits on object perception, and relative preservation of spatial perception suggests that pathology in the ventral visual stream which groups information for object recognition may underlie hallucinations. This idea fits in with Santhouse

et al's (2000) typologies of hallucinations, with hallucinations of figures, as are common in PD, hypothesised to arise from abnormal activity in the ventral stream.

4.4.2 Cognitive processes and their role in hallucinations in PD

To date, only one group has made specific predictions about the neuropsychological performance of PD hallucinators based on hypotheses derived from existing models of hallucinations. Barnes et al (2003) used a reality monitoring paradigm adapted from the schizophrenia literature, and made the prediction that hallucinators would show a greater tendancy to misattribute the source of a stimulus presented as a word, which they were asked to visualize, to having been presented as a picture. This notion of a reality monitoring deficit in hallucinations is based on Bentall's (1991) model of hallucinations in schizophrenia. Barnes et al (2003) indeed found that PD patients with hallucinations were more likely to identify objects which they had visualised as having been presented pictorially rather than as words. In addition they showed a tendancy towards a greater number of false alarms on a recognition test which replicates findings on hallucinating schizophrenic patients (Bentall & Slade, 1985; Brebion et al, 1999; 2002). Other neuropsychological tests showed that hallucinators were more impaired on face recognition, again implicating visual perceptual processes, but did not perform more poorly on verbal fluency (Barnes et al, 2003). Hallucinators and non—hallucinators showed no differences on measures of premorbid IQ (NART) or on global cognitive function (MMSE), and this suggests that previous findings of poorer performance on verbal fluency may have been artefactual, because of greater overall cognitive decline in hallucinators (Haeske-Dewick, 1995; Graham et al, 1997). Given that there were no differences in global cognition, the presence of a greater number of false alarms during recognition, and of an impairment in source monitoring are all the more striking. To summarise, the study by Barnes et al (2003) has demonstrated that PD hallucinators show specific deficits

in object perception, and are prone to cognitive biases resulting in a reality monitoring deficit. This study exemplifies the more integrated and sophisticated approach taken by 'third generation' studies.

4.4.3 Summary

Experimental studies of visual perceptual and cognitive function in PD patients with hallucinations have demonstrated that deficits in peripheral vision, and higher level visual processes, and biases towards making false alarms and inaccurate attribution of source are associated with hallucinations.

Problems with object perception in hallucinators may be associated with pathology in the visual ventral stream, or the visual association cortex, which is one of the targets of the lateral orbitofrontal circuit arising from the basal ganglia. Deficits in executive function may be implicated in problems with reality monitoring or source monitoring (Frith, 1992; Johnson, 1991; Benson & Stuss, 1993), and the neurobiological and theoretical basis for executive deficits has been well established for PD patients (Taylor & saint-Cyr, 1995; Darvesh & Freedman, 1996). Therefore, once neuropsychological deficits in hallucinators have been fully delineated, they may be mapped onto the neurobiological models of cognition in PD, thus generating further hypotheses about the location of pathology, which may be tested to some extent using post-mortem or brain imaging techniques.

4.5 Existing neuropsychological theories and paradigms for examining hallucinations – how can they be adapted for the present study ?

4.5.1 Source monitoring, intrusions and false alarms

4.5.1.1 Theories of source monitoring, intrusions and false alarms

Bentall et al (1991) describe errors in source-monitoring in hallucinating schizophrenic patients, where a misattribution is made of internally generated items to the experimenter. Critically, hallucinators are more likely to show a bias of attributing the internal to the external, rather than vice-versa. Johnson (1993) argues that correct attributions of source are dependent upon attributes of the 'memory' or 'percept' such as vividness, location in time, place and context etc. It follows that errors in source monitoring may result from a lax criterion in accepting internally generated events, which may have more emotional and personal associations but are typically less rich in detail, as being "real" enough to have been externally produced (Johnson, 1993). If memory, attentional or perceptual function is impaired in such a way that the integrity or strength of normal encoding and perception of external events is reduced, three implications follow. Firstly, external events as perceived or encoded may not have the richly detailed attributes normally attached to them, and so internally generated events may seem just as vivid (Johnson, 1993). Secondly, if retrieval or perception come to rely on top-down processes in the absence of strong 'traces' or good quality sensory data then cognitive biases favouring the salience of internal events may arise (Fleminger, 1994). Thirdly, feelings of 'familiarity' based on previous experience, or expectancies and existing schemata may dictate 'memories' retrieved, representations generated or responses given (Dalla Barba et al, 2000). Such changes in the criterion for judging whether an event is external or internal, i.e. whether a real signal has been detected or not, may explain the tendancy of hallucinating patients to give

false alarms on signal-detection or recognition tests (Bentall & Slade, 1985; Brebion et al, 1999; 2002).

A reality or source monitoring framework explains the process of evaluation of an event as being internal or external. What it does not explain however is why intrusions of task-irrelevant material occur in patients with positive symptoms such as hallucinations (Frith, 1992; Brebion et al, 1997;1998;1999). In the paradigm used by Barnes et al (2003) the subjects were manipulated by the demands of the experiment into visualizing words presented. However, Brebion et al (1997;1998;1999) have demonstrated the intrusion of task-irrelevant material into responses during cognitive tests, which are essentially incidental to the task, rather than manipulated. Cognitive 'intrusions' bear similarities to the 'confabulations' demonstrated by patients with dementia and Korsakoff's syndrome. In these populations, confabulations usually take the form of grossly inaccurate or fabricated accounts of past events, but parallels have been drawn with 'provoked' intrusions on cognitive tests, and confabulating amnesic patients have been demonstrated to show greater levels of task-irrelevant intrusions than non-confabulators (Johnson et al, 1991). Intrusions which occur during cognitive tasks may reflect bias at a *different* stage of the cognitive process than that which results in a hallucination, i.e. the intrusion of irrelevant associations or representations into an ongoing cognitive process, rather than an error of judgement about the source of an event.

4.5.1.2 Paradigms examining source monitoring, intrusions and false alarms

As described previously, studies using a reality monitoring framework have typically used signal-detection or recognition paradigms, or have asked subjects to make attributions about the source of an item presented. Studies investigating intrusions have tended to use recall paradigms, where extra inaccurate material is defined as an intrusion (Brebion, 1997; 1998;

1999), or tasks such as verbal fluency where the parameters for an appropriate response are given and responses that fall outside those confines are considered intrusions (Sharp, 1991). The Alzheimer's disease literature has investigated the phenomenon of confabulation, by using neuropsychological tasks designed to provoke intrusions. Kern et al (1993) conducted a comprehensive series of experiments in AD patients and healthy older adults. Amongst their battery were the Logical Memory test from the Wechsler Memory Scale, and the Memory for Designs test (Taylor, 1961). AD patients made a greater number of 'novel intrusions' during recall on logical memory, describing details that were not part of the original stories (Kern et al, 1993). There was also a non-significant trend for AD patients to make more 'novel embellishments' in their reproductions of the designs presented in the Memory for Designs test. Logical Memory provides indices of recall, learning and recognition, and so gives an evaluation of a range of mnemonic functions, and may also provide information about the nature of intrusions made on recall tests in hallucinating patients. The Memory for Designs test taps visual recall, but also by implication visual perception, which would provide an interesting assessment for visual hallucinators. However, it would be unsuitable for hallucinating PD patients given difficulties with writing and drawing.

Sharp (1991; Downes et al, 1993) used an alternating fluency paradigm to assess set-shifting abilities in PD patients. Errors were also recorded and could be broken down into intrusions (cue-irrelevant responses) and perseverations (failure to shift set). Intrusions may represent a faulty search for an appropriate response, or an inability to suppress inappropriate responses, and this paradigm would provide an index of frontally-mediated intrusions in hallucinating PD patients.

4.5.2 Visual perception and misperception

4.5.2.1 Theories of visual perception and misperception

Fleminger (1994) describes perception as a "blurring of sensation and cognition", whereby active process of fitting perceptual hypotheses to afferent data is carried out, in an attempt to create an accurate mental representation of the world around. As with all cognitive processes where a hypotheses must be matched to the available data, errors or biases at several points may result in an erroneous mental representation. Fleminger posits three stages to "conscious acceptance of the validity of a perceptual attribute". Firstly a "look and select" stage where a perceptual hypothesis is made about the stimulus, given the current context., secondly a "see and perceive no mismatch" stage, where sensory data and perceptual hypothesis are compared, and thirdly a "judge and accept validity" stage where validity is tested or judged in terms of the current context. Biases or deficits during any of these stages may result in a misperception. Fleminger's model emphasises the role of top-down processes, and of a reality monitoring stage as the final step in accepting the validity of a percept.

The dominance of top-down visual processes in normal vision, even in the presence of incongruous or contradictory data, has been demonstrated by the sizeable literature on visual illusions. Therefore, even when sensory data indicate that what is being perceived is not as it should be, expectancies based on perceptual schemata about the real world may override bottom-up processes and ignore incongruities. Perceptual errors of a different nature may also occur as demonstrated during neuropsychological testing in agnosic patients, especially when sensory information is limited in some way; figure-ground information may be confused, Gestalt or visual closure processes may fail, ability to focus on individual components of a stimulus may fail, salient aspects of an object such as its defining features may be ignored,

visual neglect of part of a stimulus may occur and objects may be miscategorised as real or unreal, or as belonging to a particular semantic category (Warrington & James, 1991).

4.5.2.2 Paradigms examining visual perception and misperception

The Visual Object and Space Perception Battery (Warrington & James, 1991) has been designed to detect deficits in both object and spatial perception. The object perception subtests were designed to isolate the point at which errors were made in object perception in agnosic patients. Deficits on the tests may arise from processes of visual closure if an incomplete stimulus is presented, with recognising objects when only an outline or silhouette is presented and seen from an unconventional viewpoint, with inability to select 'real' objects from an array of plausible distractors or 'pseudo-obejcts' and from difficulties with identifying objects when the main axis is foreshortened and the objects defining features hidden. As hallucinations in PD often take the form of object illusions, this test may prove valuable in isolating the point at which errors of perception or visual recognition are made.

Pillon et al (1990) used a visual test adapted from Poppelreuter's overlapping figures test , where subjects are required to isolate objects visually from an array of overlapping objects and identify them. Pillon et al used this test primarily to investigate speed of cognitive processing, but noted that PD patients had a greater tendancy to misidentify objects than healthy age-matched controls. This test has also been used by Cousins et al (2000) in PD patients as an index of visual componential processing, and so examines a different kind of visual process to the VOSP, requiring subjects to "zoom in" on local features within an array, rather than to focus on the global shape of an object. Both local and global processing of visual features of objects may be impaired in PD hallucinators, as examination of the kinds of misperception made may prove fruitful in identifying perceptual biases.

4.5.3 Hypotheses

9. PD patients will show specific neuropsychological deficits compared to controls on visual perception, executive function, recall, attention and construction, independently of age, premorbid IQ, depression and anxiety and *global* cognition.
10. Hallucinators will show specific neuropsychological deficits compared to non-hallucinators on visual perception, executive function, attention and construction, independently of age, disease severity, premorbid IQ, depression and anxiety and *global* cognition.
11. Hallucinators will show increased levels of perseverative errors and task-irrelevant intrusions across a range of neuropsychological tests compared to non-hallucinators. For percentage and composite measures of errors, hallucinators will show greater levels than non-hallucinators independently of age, disease severity, depression and anxiety, premorbid IQ and global cognition.
12. In regression models to predict a current hallucinations score, sleep-related and neuropsychological will add to the predictive value of the model significantly, *beyond* the effect of disease severity and global cognition.

CHAPTER 5

GENERAL METHODS

5.1 Choice of measures

In this investigation of hallucinations in Parkinson's Disease, a range of variables were examined including clinical, psychological, disease-related, subjective and objective sleep-related and both global and specific neuropsychological. The following section describes the measures chosen for the current study, their properties and the methodological rationale for choosing them; the theoretical reasons for choosing the following measures and paradigms was discussed throughout chapters 1 to 4. Background measures including age, sex and years of full-time education were collected for all individuals.

5.1.1 Disease severity

5.1.1.1 Duration of disease, medication and age of onset

For the current study, duration of disease was defined as time from diagnosis of PD to the time the subject was first tested. Medication duration was the time since dopaminergic replacement therapy or anticholinergic therapy was commenced. All current medications were recorded including those for PD (with dose and frequency), any psychotropic medication for sleep, anxiety and depression, and all other prescribed medication. Age of onset was defined as current age minus disease duration.

5.1.1.2 Unified Parkinson's Disease Rating Scale (UPDRS)

5.1.1.2.1 Description

The UPDRS has been described in some detail in chapter 1. It is currently the most widely used measure of clinical severity for PD, and has also been the most favoured assessment

in existing studies of hallucinations in PD. The full scale and the sections used for the current study are shown in appendix B.

5.1.1.2.2 Variables derived for the present study

Sections II, III and IV of the UPDRS were used to examine specific motor symptoms and to generate a total score for severity (see appendix C for the scoring protocol). Briefly, the motor examination scale was used as an objective clinical measure of disease severity. As described in Chapter 1, the motor examination scale has been correlated with in vivo measures of dopaminergic function using PET, and also with post-mortem measures of the extent of damage to nigrostriatal pathways. Table 5.1 shows the items used for the current study. On those items requiring a response from both left and right sides and upper and lower body (see appendix B) the total score used the worst side upper body score only, as summed over each side (see appendix B). In addition two items concerning falling and freezing from the Activities of Daily Living scale (Section II of the UPDRS) were used, which were scored using patient and carer subjective reports, and also experimenter observation for the freezing item. The Complications of Therapy scale, sections IV.A and IV.B of the UPDRS, was also completed, again using both subjective reports and experimenter observation of dyskinesias and akinesic states. For analysis of motor severity two total scores were used; a clinical motor score which was the total score on the motor examination scale for the worst side plus scores for the two ADL scale items (see below, and appendix B), and a complications of therapy scale total score.

UPDRS item	Scored				
II: ADL items					
Falling	0 – 4				
Freezing	0 – 4				
III: Motor examination					
Speech	0 – 4				
Facial expression	0 – 4				
Tremor at rest		R	0 - 4	L	0 - 4
Action tremor		R	0 - 4	L	0 - 4
Rigidity		R	0 - 4	L	0 - 4
Finger taps		R	0 - 4	L	0 - 4
Hand movements		R	0 - 4	L	0 - 4
Rapid alternating hand movements		R	0 - 4	L	0 - 4
Leg agility		R	0 - 4	L	0 - 4
Arising from chair	0 – 4				
Posture	0 – 4				
Gait	0 – 4				
Postural stability	0 – 4				
Body bradykinesia	0 – 4				
IV: Complications of therapy (in past week)					
Dyskinesia:					
Duration: Proportion of day present	0 – 4				
Disability caused	0 – 4				
Painful dyskinesias	0 – 4				
Early morning dystonia	0 – 1				
Clinical fluctuations:					
Predictable 'off' periods	0 – 1				
Unpredictable 'off' periods	0 – 1				
Sudden onset 'off' periods	0 – 1				
Duration: Proportion of day present	0 – 4				

Table 5.1 Unified Parkinson's Disease Rating Scale items used (see appendix B for scoring)

Variable	Least severe score	Most severe score
Total for motor scale UPDRS	0	56
Total fluctuations score UPDRS	0	16

Table 5.2 Disease severity variables II

Following findings that different motor signs show different patterns of association with cognitive impairment and disease progression (Jankovic et al, 1990; Levy et al, 2000; Burn et al, 2003) a factor analysis of the UPDRS items was carried out using the current sample. Scores across the motor examination scale, the two items from the ADL scale, and the

complications of therapy scale were examined using principal components analysis with varimax rotation (detailed in chapter 6) to derive factor scores for six motor factors, together accounting for 62.9% of the variance.

5.1.2 Neuropsychiatric symptoms

5.1.2.1The Questionnaire on Unusual Experiences

5.1.2.1.1 Purpose of the QUE

The UPDRS contains a 4 item scale of Mentation, Mood and Behaviour (Section I) which has been used in previous studies to assess presence of sleep disruption, hallucinations and cognitive decline. However, this scale covers a wide range of neuropsychiatric symptoms, which for the purposes of the current study were examined as separate phenomena. Furthermore, using single-item scores to assess phenomena such as hallucinations does not allow examination of the full range of experiences, and is an inadequate assessment of severity. For this reason a pilot study was carried out to validate a Questionnaire on Unusual Experiences designed to assess a range of both sleep-related and hallucinatory phenomena, and to assess their severity in terms of frequency. Chapter 6 details the pilot study and the structure and reliability of the first version of the QUE.

5.1.2.1.2 Description

The version of the QUE used for the main study included three additional items on the sleep scale, and the three scales and their items are listed in Table 5.3 below. Cronbach's alpha is also given for each scale for the main study. Both versions of the QUE are provided in appendix C.

Sleep symptom scale	Unusual experiences scale	Hallucinations scale
Physical fatigue	Spots/ zigzags	Complex visual hallucination
Drowsy in day	Flashing lights	Auditory hallucination
Naps during day	Patterns moving	Tactile hallucination
Waking many times	Peripheral movement	Olfactory hallucination
Hypnogogic imagery	Misrecognition object	
Vivid dreams	Illusion of presence	
Nightmares	Déjà vu	
Nightmares	Derealisation	
Night terror/ panic	Misrecognition person	
Confusion/disorientation	Flashbacks shock	
Sleeptalking	Interaction with vivid memories	
Motor activity during sleep		
Injury during sleep		
Sleepwalking		
Cronbach's α		
0.79	0.79	0.73

Table 5.3 Questionnaire on Unusual Experiences individual items and scale reliability

For the main study, severity for each item was assessed on the basis of the frequency of experiencing each symptom during the previous three months on the following scale:

0	1	2	3	4	5
Not at all	1-2 times	1-2 times Per month	1-2 times per week	Most days	Daily

Table 5.4 Frequency scoring for QUE items

For the main study the scale was administered within a semi-structured interview asking about sleep patterns, the experience of hallucinations, their content and perceptual features and coping strategies used by PD patients. For controls the scales took the form of a self-report questionnaire. When willing, carers were also asked to complete a self-report version of the scales asking about the patient's experience of the symptoms. Where there was disagreement between patient and caregiver about the frequency of a symptom, the highest value was used for the analysis. All versions of both interviews and self-report questionnaires are shown in appendix C.

5.1.2.1.3 Development of the QUE

The QUE was devised following initial exploratory interviews with PD patients experiencing hallucinations. The pilot study assessed the validity and reliability of the scales as a self-report questionnaire for 115 PD patients and their caregivers, finding good internal reliability within the scales, and a factor structure for the sleep scale that was to some degree replicated by the main study. Following the pilot study and further in-depth qualitative interviews on a group of 14 patients from the pilot sample, three additional items were added to the sleep scale, as it was felt that these symptoms were important in assessing the full range of experience. Following analysis of pilot study data, it was apparent that for the pilot sample median scores on the hallucinations items in particular were low, thus limiting the reliability of analysis. Therefore the frequency scale was expanded from a 5-point to 6-point scale and frequency was assessed over the previous three months rather than one month. It was clear from the additional interviews that some items were misinterpreted, giving false positives, and so it was felt that the scales were better administered by the experimenter, allowing for clarification of items and confirmation that the symptoms being described corresponded with the appropriate item. In these ways the original scale was adapted to make it more suitable for the current sample in terms of administration, coverage of the full range of experience and generation of reliable scores with a greater numerical range.

5.1.2.1.4 Variables derived for the present study

The results of the pilot study showed that factors derived using a principal components analysis to examine associations amongst the items was valuable in detecting different patterns of associations with clinical variables (see Chapter 6). A principal components analysis using varimax rotation of the sleep scale, and of the pooled items from the

unusual experiences scale and the hallucinations scale was performed. Sections 6.2.2.1 and 6.2.2.2 show full factor solutions including loadings of individual items. Table 5.5 below shows the factors which were used for analysis, variance accounted for and internal reliability.

Sleep factors	Cronbach's α	%age variance	Hallucinations factors	Cronbach's α	%age variance
Sleep activity	0.649	22.96	Visual hallucinations	0.841	42.75
Daytime sleepiness	0.918	19.68			
Altered dream events	0.541	14.63	(see section 6.2.2.1 for other factors)		
Total % age variance		57.45			-

Table 5.5 Neuropsychiatric variables I (see tables 6.2.2.1 and 6.2.2.2 for full item loadings)

Although the factor analysis for the pooled unusual experiences and hallucination items yielded four factors, the critical variables which was used in subsequent analyses was the visual hallucinations factor, which was the strongest factor and had high internal reliability.

5.1.3 Objective measures of sleep and circadian rhythm - 24 hour rest-activity rhythm using actigraphy.

5.1.3.1 Description

Wrist-worn monitors to collect data on rest-activity rhythm can be used to derive a range of possible measures; (i) a direct index of motor activity which is an indirect index of motor severity and disability, (ii) sleep quality or fragmentation, and daytime sleepiness, and (iii) a more direct index of activity-based circadian rhythm. Appendix D shows further details of how each variable is calculated using the Sleep Analysis 98 software. The activity monitors used for the present study were Cambridge Neurotechnology uniaxial accelerometers, which sum movement over 30 second epochs. They were placed on the non-dominant wrist, which has been found to give the most reliable estimates of daytime activity which is not confounded by repetitive movements such as writing or other domestic chores

(Patterson et al, 1993). Using the 30 second epoch setting, the monitors were able to store activity counts for over 5 days, in most cases allowing collection of 5 nights worth of data.

5.1.3.2 Suitability for the current sample

Activity count data from patients with movement disorders is likely to contain artefacts based on the motor symptoms experienced by individual patients. As the type and severity of motor symptoms varies across the population, no specific method of correction can be applied to the group as a whole. The use of such methods in PD patients is likely to present two problems. Firstly, an artificial absence of movement during periods of akinesia that may be interpreted as 'sleep'. Secondly, an artificial presence of movement due to dyskinesias which exaggerate levels of waking activity, and due to REM Behaviour Disorder or Periodic Leg Movements during sleep which make be interpreted as 'wake'. These biases will affect different types of data generated by the Sleep Analysis software in different ways.

5.1.3.2.1 Night-time activity

Tremor and dyskinesias disappear when the patient enters sleep, and re-emerge upon waking. Therefore periods of true sleep will appear with very little activity. In addition, many patients have difficulty in turning during the night, and therefore they are less likely to turn *during* sleep than healthy individuals. The net effect of these factors should be that true sleep is marked by very little activity, and movement during waking hours is exaggerated if gross tremor or dyskinesias are present. However, two other factors may blur these 'enhanced' or exaggerated differences. Firstly, the presence of RBD during periods of REM sleep may be interpreted by the algorithm as wake. As the accelerometers were placed on the wrist, PLMs are unlikely to affect data. During the period of monitoring, levels of RBD

reported by spousal caregivers in their diaries were low (see Chapter 8), and although small movements may have gone undetected by spouses, these may also have been of such low amplitude or of such brief duration that they were also not defined as wake periods by the algorithm. However, if a chronic low-level of movement was maintained, detection of 'wake' periods may have occurred. Secondly, nocturnal 'offs' or periods of akinesia may have been interpreted as sleep if very little activity occurred, although upper limb movements are more likely during these episodes than trunk movements. Studies validating accelerometry against PSG have found that sleep latency as measured by actigraphy tends to overestimate sleep during periods of low activity prior to actual sleep onset. In a PD population the same is likely to be true for periods of wake after sleep onset where little activity occurs.

5.1.3.2.2 Daytime sleep

More problematic than nocturnal sleep, is the interpretation of daytime sleepiness, as periods with very little or no activity may represent akinesia and general disability rather than sleep. However, upper limb placement is likely to be more sensitive than trunk placement in these cases. This problem may be counteracted by changing the 'sensitivity' of the sleep detection algorithm in the Sleep Analysis program, which can be changed for each individual's analysis. When activity falls below the threshold for a period of more than 5 consecutive 30 second epochs that period is counted as sleep. By calculating appropriate threshold or sensitivity for each individual according to overall levels of daily activity, when compared to group data from the controls, the analysis for each individual may be tailored. Therefore those PD patients (usually with dyskinesias) who showed greater activity levels than the control group mean would be assigned a proportionally

higher threshold, and those with lower activity levels (usually those with bradykinesia, akinesia and greater disability) a lower threshold.

5.1.3.2.3 Circadian rest-activity rhythm

The Non-Parametric Circadian Rhythm Analysis (NPCRA) used in the Sleep Analysis 98 program was first developed by Van Someren et al (1996) specifically for use with populations who show disrupted patterns of rest-activity rhythms that deviate from the normal sine wave model. Three variables derived reflect raw activity levels; amplitude, activity during least active 5 hours and activity during the most active 10 hours. However, relative amplitude is a proportional measures taking into account individual differences in overall amplitude of activity over 24 hours, and interdaily stability and intradaily variability of activity which are essentially within-subject indices, use the overall variance in an individual's activity pattern to derive values. These three variables are therefore independent of overall activity levels. Appendix D gives more details about how the six measures are derived.

For all actigraphic variables, equivalent subjective sleep diary variables were compared, by correlation, and for absolute values to determine whether each method over or underestimated values compared to the others. In addition, for group comparisons amongst PD patients motor severity was covaried using all six of the motor factors derived from the UPDRS (see section 5.1.2.1.4), so that the differential effects of these factors could be taken into account.

Because motor severity scores were unavailable for controls, it was felt that group comparisons between hallucinators and non-hallucinators should not include controls. Due to the factors mentioned above, controls might show similar values to hallucinators on

some measures because of artefacts, and their presence may add unwanted variance to the comparison.

5.1.3.3 Procedure

Subjects were given their actiwatches at the end of Visit 1 and asked to wear them continuously apart from when in the bath or shower until they were collected at the beginning of Visit 2. Subjects were asked to mark their data by pressing a button once when they had settled down at night and were ready to sleep, and once more as soon as they had woken up. This allowed greater ease of interpretation when analysing the activity data, and setting sleep onset and wake parameters. The activity monitors were used in conjunction with sleep diaries which are described in Section 5.1.4.2 below. The diaries were used firstly as a guide for setting appropriate parameters, although if a diary quite clearly contradicted the activity count then the more objective activity data was interpreted both by the experimenter's judgement and by the sleep-wake algorithm. Diaries were also used to derive separate variables for sleep over 5-7 nights.

5.1.3.4 Variables derived for the current study

Table 5.6 briefly lists the variables provided by the software. A more detailed description of the measures, and of the algorithms and formulae used by the software is given in appendix D.

Variable	Description
Nocturnal sleep variables	
Assumed sleep (mins)	Duration of sleep between parameters set
Actual sleep time (mins)	Duration of 'sleep' detected by algorithm
Actual sleep (%)	Percentage of 'sleep' detected over night
Actual wake time (mins)	Duration of 'wake' detected by algorithm
Actual wake (%)	Percentage of 'wake' detected over night
Sleep efficiency	The percentage of time spent asleep whilst in bed
Sleep latency (mins)	Duration from assumed sleep parameter to detected 'sleep'
No of sleep bouts	Number of detected 'sleep' periods
No of wake bouts	Number of detected' wake' periods
Mean sleep bout time (mins)	Mean duration of sleep bouts
Mean wake bout time (mins)	Mean duration of wake bouts
Immobile mins	Number of minutes immobile during night
Immobile time (%)	Percentage of minutes immobile over night
Moving mins	Number of minutes moving during night
Moving time (%)	Percentage of minutes immobile over night
No. immobile phases	Number of immobile periods
Mean length immobility (mins)	Mean duration of immobile periods
1 Minute immobility	Number of periods of 1 immobility lasting only 1 minute
1 Min immobility (%)	Percentage of 1 min epochs of 1 min immobility
Total activity score	Total activity count between parameters
Mean activity score	Mean activity score per epoch
Mean score in active periods	Mean activity score in periods where movement is detected
Fragmentation index	The addition of Moving Time % and the 1 Min immobility %
Daytime sleep variables	
Mean no. naps per day	Mean number of naps taken per day
Mean time napped per day (mins)	Mean time spent napping per day
Mean time all naps (mins)	Mean duration per nap
NPCRA variables	
Interdaily stability (IS)	Strength of daily signal across several days
Intradaily variability (IV)	Variability and change in activity level from hour to hour
Least active 5 hours (L5)	Activity count for least active 5 hours
Most active 5 hours (M10)	Activity count for most active 10 hours
Amplitude (Amp)	Difference between lowest and highest activity score over 24hrs
Relative amplitude (RA)	Difference between M10 and L5

Table 5.6 Sleep variables I – Actigraphy variables (see appendix D for more details on scoring)

For the current study interpretable or 'clean' data were obtained for at least two nights for 66 subjects; the mean number of nights was 5.26. Measures for daytime and nocturnal sleep were averaged across nights to give a mean value. For circadian rhythm, values derived are calculated across a number of 24 hour periods.

5.1.4.1 Self-reported sleep habits – semi-structured interview

A semi-structured interview asking about typical sleep pattern during the last month derived the following variables, presented in table 5.7. For the PD group, both the patients and caregiver provided information. For the control group the same variables were collected through a self-report questionnaire. The full interview schedule/ questionnaire is presented in appendix C.

	Scored	Direction
Sleep latency [1]	Mins	
Total time asleep	Hours	
Total time awake in night	Hours	
Number of wakenings		
Number of times out of bed		
Nocturnal sleep latency [1]		
Self-report sleep quality	1 – 5	1 = Very poor 5 = Very good
Number of unplanned naps		
Total daily nap time	Hours	
Able to resist sleep in day ?	0 - 4	0 = Not at all 4 = Not sleepy
Functional impact of sleepiness	0 - 3	0 = No impact 3 = Much impact

Table 5.7 Sleep variables II – Semi-structured interview (see appendix C for interview schedule). Responses were scored 1 to 4; 1 = < 10 minutes, 2 = 10 – 30 minutes, 3 = 30 – 60 minutes, 4 = > 60 minutes.

5.1.4.2 Sleep diaries

5.1.4.2.1 Description

Diaries were kept by participants during the period of actigraphic monitoring to provide a subjective account of sleep quality, and to provide a guide for actigraphic analysis. Examples of the diaries are shown in Appendix C. They required the subject (or if writing was difficult his or her carer) to enter time of sleep onset and waking and to provide a number of subjective measures of sleep duration, maintenance and quality for each night. In addition, participants were asked about their experience of sleep symptoms such as nightmares or night-time hallucinations for each night. There was also a section for daytime sleep, with number and duration of naps recorded, and to prevent confounding a section for times that the actiwatch was removed for bathing. Where possible, caregivers were asked to fill in a similar diary providing the same variables for both their own and for the patient's sleep, as the patient may have been unaware of (i) their own napping, (ii) RBD symptoms during the night, or (iii) nightmares or nocturnal hallucinations. Both diaries also asked about time and content of any hallucinations or other UPE which occurred during the period of monitoring.

5.1.4.2.2 Suitability for the current sample

The use of paper and pen diaries to supplement actigraphy is a well-established means of increasing the accuracy of interpretation of 'sleep' and 'wake' from activity records. Despite the benefits of having supplementary diary data however, a recent study of the reliability of diary methods in chronic-pain patients found that many diary entries were made retrospectively, thus reducing the reliability of self-report (Bolger, 2003). If retrospective entries are made in the current sample, recall of actual events is likely to be compromised. However, the fact that subjects knew they were also being monitored by objective wrist-

monitors may have increased motivation to comply. The diaries used were formatted in large print and designed to be as easy to use as possible for a group who have problems with vision and/or writing and may have cognitive impairment. A sleep diary asking patients to indicate whether they were asleep or awake during each half-hour period during the night was piloted, but was unsuitable as it was visually confusing for several patients. However, the current sample was expected to show some problems with compliance, because of the above reasons, and it was hoped that where possible the caregiver would be able to provide appropriate information.

5.1.4.2.3 Variables derived for the current study

Diaries provided the variables presented in table 5.8 for each day during the monitoring period. For analysis, mean values calculated across number of days monitored were used. In addition, the symptoms presented in table 5.9 were used as dichotomous variables; either present or absent on at least one night for the each subject during the period of monitoring.

Variable	Scored	Direction
How long awake during night	Mins	
How long asleep during night	Mins	
No. of awakenings		
No. times out of bed		
Sleep quality	1 – 5	1 = Very poor 5 = Very good
Refreshed	1 – 4	1 = Shattered 4 = Refreshed
Time spent napping per day	Mins	
No. of daytime naps per day	Mins	
Mean nap time per nap	Mins	

Table 5.8 Sleep variables III – Sleep diary (see appendix C for example of diary)

Variable
Nocturnal hallucinations
Upsetting dreams
Night terrors/ panic
Confusion/ disorientation
Sleep talking
Motor activity
RBD injury
Sleepwalking
Nocturnal hallucinations

Table 5.9 Sleep IV – Sleep diary

5.1.4.3 The Epworth Sleepiness Scale

5.1.4.3.1 Description

This subjective measure of daytime sleepiness (Johns, 1991) has been widely used in assessment of narcolepsy and neurological illnesses including PD (Johns, 1991; Roth et al, 2003) The scale (see appendix C) asks subjects to rate the likelihood of falling asleep in eight different situations such as sitting at home relaxing, or during a public occasion, and uses a total score to assess overall levels of EDS. Likelihood of falling asleep is measured on a scale of 0-3, giving a total possible score of 24, with higher scores indicating more daytime sleepiness.

5.1.4.3.3 Suitability for the current sample

Cut-off criteria have been established for pathological sleepiness in narcolepsy, with scores of >10 considered pathological, but the use of the scale in elderly patients presents two problems in using these criteria. Firstly, older adults show an increased tendency to nap in the day increasing normative scores on this scale (Goldstein & Lahey, 2001), and secondly patients who are unaware of their own sleepiness due to cognitive impairment may not give a reliable report. Therefore established cut-offs were not used and age and mental status were covaried when examining daytime sleepiness. In addition, Kumru et al (2004) demonstrated that PD patients were unreliable when making judgements of their own sleepiness, tending to underestimate it when compared caregiver estimates. For this reason, where possible the caregiver was also asked whether they agreed with the patient's response, and the highest value was used for analysis.

5.1.4.3.4 Variables derived for the present sample

See table 5.10 below:

Variable	Lowest score possible	Highest score possible
Epworth Sleepiness Scale total score	0	24

Table 5.10 Sleep variables V – Epworth Sleepiness Scale (see appendix C for items)

5.1.5 Neuropsychological measures – rationale for choice of tests

In choosing the neuropsychological tests for the current study several considerations were taken into account. Firstly the theoretical grounds on which the tests were chosen have been described in Chapter 4, and include prior use in similar studies, validity in a dementing population, and adaptations of existing paradigms for investigating cognition in psychotic patients. Secondly, practical considerations of test administration were paramount in this sample. PD patients' test performance may be affected by fatiguing of motor or verbal response, as well as general fatigue, lack of sustained attention and drowsiness. In addition older adults, and particularly PD patients may be affected by visual deficits and so tests needed to be visually clear, or be adapted into large print formats. Where possible written responses were avoided due to effects of speed and legibility. Disease severity was also covaried where appropriate to partial out the direct effect of motor severity on test performance. Thirdly, as is key to all psychometric and neuropsychological testing, care was taken to minimise the likely impact of educational achievement. Premorbid intelligence was assessed and where appropriate covaried, and tests of crystallised intelligence were minimised. All subjects used English as their first language. Fourthly, tests were chosen where possible on the basis of availability of published data and norms in older, Parkinsonian and dementing patients, and their sensitivity to subtle cognitive change and specific deficits. Attempts were made to collect control data from older adults for the majority of tests. The only novel test, of divided and

undivided attention, was designed specifically for the current study taking into account the above practical considerations.

5.1.6 Global measures

5.1.6.1 Mini-Mental State Examination (MMSE)

5.1.6.1.1 Description

Folstein (1975) developed the mini-mental state examination as screening tool for assessing cognitive status; those falling below a cut-off point established for normal older adults are identified as having some degree of cognitive impairment, whether a temporary state or a stable deficit. The MMSE is a brief, easy to administer test requiring simple responses. Thirty points are available in total, and the test consists of 11 components (see table 5.14 below for components and weighting). Scores of 24-30 indicate normal functioning for older adults. Those scoring 23 or below are deemed to have some degree of cognitive impairment, or 'borderline dementia'.

5.1.6.1.2 Suitability for the current study

Misclassification using the recommended cut-off can occur due to individual differences in educational level or cultural background and ethnic origin. Sensitivity of the MMSE falls when it is used to test younger people, even if they have a demonstrated neurological or cognitive impairment, especially if they are well-educated. In addition, the original study by Folstein et al (1975) included patients with psychotic and affective disorders, and the mean for some depressed patients did fall below 23, showing that motivation and attention may play a confounding role in performance. This is particularly relevant for the current sample as depression is prevalent in PD.

As far as suitability for the current sample, the MMSE is an easy test to complete, is short and requires little motor input other than speech. Visual impairment such as double vision may make the intersecting pentagons item (see below) difficult, although data suggests that PDD and DLB patients are likely to be impaired on many tests of visuo-construction that are related to visuoperceptual deficits, and therefore deficits on this item may not be artefactual (Cormack et al, 2004).

The MMSE was designed as a screening tool to identify those patients who require a more thorough neuropsychological assessment, and is therefore not adequate on its own to assess cognitive function. Its widespread use as a valid index of global cognitive function has therefore been criticised by some (see La Rue, 1992), as it was not designed as a scale measure of cognitive ability, unlike standard IQ measures, and therefore the validity of its use as a correlate is debatable. Despite this it has been used in many of the previous investigations into hallucinations in PD detailed in chapter 2 a as an index to gauge *degree* of cognitive impairment rather than presence or absence. For this reason it will be used in the current study in the first step of a regression along with disease severity to predict hallucinations score, but following steps will assess specific cognitive deficits and whether they explain a greater amount of variance.

5.1.6.1.3 Exclusion of low scoring individuals

For the current study those individuals found to score below 16 on the MMSE were excluded as they were not likely to be able to be able to complete more complex or demanding neuropsychological tests, and the MMSE alone is unable to give a very accurate profile of cognitive status.

5.1.6.1.4 Variables derived for the current study

Variable	Poorest score possible	Best score possible
MMSE total score	0	30
MMSE orientation score	0	10
MMSE repetition	0	3
MMSE serial task	0	5
MMSE recall	0	3
MMSE object naming	0	2
MMSE Phrase repetition	0	1
MMSE Three stage task	0	3
MMSE 'Close your eyes'	0	1
MMSE sentence	0	1
MMSE pentagons	0	1

Table 5.11 Mini-Mental State Examination variable – total score and subtests

5.1.6.2 National Adult Reading Test - Premorbid IQ

5.1.6.2.1 Description of the test

The NART (Nelson, 1983) consists of 50 English words with irregular pronunciations, which the subject is required to read aloud . Problems in using this test with older subjects or PD patients include fatiguing, particularly as a prolonged verbal response is required. For this reason the 50 words were split into 25 consecutive pairs, and one word from each pair chosen at random. The resulting 25 words were therefore still sequentially graded in terms of frequency of everyday usage and difficulty.

5.1.6.2.2 Suitability for the current study

Accuracy of pronunciation has been shown to correlate highly with other measures of intelligence, but unlike word-meaning or semantic processing is preserved in many neurological and dementing conditions (Bright et al, 2002; McGurn et al, 2004). The NART is therefore thought to give a good index of premorbid function prior to the onset of ageing or cognitive deterioration. Hanley & Kay (2003) warn that some recent studies have shown that moderate to severe dementia, in particular Alzheimer's Disease where reading deficits are prominent, decrements on the NART may correlate with the severity of dementia, and

increase as the disease progresses. However, Bright et al (2002) found that IQ scores at age 11 correlated with NART performance in late life, and PD patients are shown to have preserved reading and language abilities. As those with moderate to severe dementia were excluded from the current study the NART has been used as a covariate in group comparisons for other neuropsychological tests to minimise the confounding effect of overall intelligence and educational achievement.

5.1.6.2.3 Variables derived for the current study

Variable	Poorest score possible	Best score possible
Half NART total score	0	25
Full NART equivalent score	0	50

Table 5.12 National Adult Reading Test variables

5.1.6.3 Mill Hill Vocabulary Scale - Current Verbal IQ

5.1.6.3.1 Description of the test

The Mill Hill Vocabulary Scale requires the participant to match the word presented with a choice of five alternatives, one of which corresponds in meaning. The original test uses 44 items, which was felt to be too long and off-putting for the current sample and so the Mill Hill Short Form was used, with 22 of the original 44 items graded in difficulty. The Scale is divided into two parts, a Junior and Senior scale. The first 5 items comprise the Junior Scale, and the final 17 the Senior scale.

5.1.6.3.2 Suitability for the current study

The Mill Hill Vocabulary Scale is essentially a test of crystallised intelligence which reflects *current* verbal IQ. It therefore complements the NART in achieving a fuller picture of current IQ and decline since onset of cognitive deterioration. This scale has also shown strong correlations with educational attainment, and older adults typically score more highly than their younger counterparts.

5.1.6.3.3 Variables derived for the current study

Variable	Poorest score possible	Best score possible
Mill Hill Form A Score	0	5
Junior Scale	0	17
Senior Scale	0	22

Table 5.13 Mill Hill Vocabulary Scale variables

5.1.7 Mnemonic function

5.1.7.1 Logical Memory Test

5.1.7.1.1 Description

The Logical Memory test is part of a wider battery of mnemonic function, the Weschler Memory Scales – III . For the logical memory test, the participant is asked to listen to two short stories about everyday events and characters, and to repeat them using words as close as possible to the original. Measures of immediate recall, learning (on repetition of the 2nd story), delayed recall (25-35 mins later) and of recognition are derived. The recognition test takes the form of a forced choice decision (yes/no) task, where participants are presented with details that may or may not have been part of the stories presented. The present study also used a further measure of delayed recall 4 to 7 days after the initial test.

5.1.7.1.2 Suitability for the present sample

Logical memory has high levels of face validity for elderly subjects, who are able to understand what is required of them even when some degree of cognitive impairment is present (La Rue, 1992). Recall is sensitive to age (Butters et al, 1988) and educational levels, and norms are available for the WMS-III to the age of 89 providing a standard against which degree of memory impairment can be gauged in terms of percentile score in the normal population. However, in populations with low levels of education floor effects

have been observed (Klonoff & Kennedy, 1966). For recall trials both verbatim recall and gist are scored, and due to differential effects of age on the two measures (Abikoff et al, 1987) gist recall is less prone to floor effects. Retention between immediate recall trials and delayed recall is generally good for elderly populations (Abikoff et al, 1987), but is a sensitive index of the type of memory impairment found in AD, though retention is likely to be better in patients with PD and other 'subcortical' dementias (Bradley & Kapur, 2003). In terms of demands made on the participant a spoken response is required, but although the test itself is carried out over the space of 40 minutes, actual verbal response required by the participant is not too demanding. However, factors such as depression and apathy, as well as possible word-finding problems may artificially lower verbatim recall for PD patients. Qualitative analysis of errors produced during logical memory has revealed characteristic patterns for both amnesic and dementing patients, with a greater level of intrusions from one story to the other, and a greater ratio of extra-story and 'novel' intrusions in dementing patients compared to healthy older adults (Kopelman, 1987; Butters et al, 1987; Kern et al, 1992). The case for analysis of errors of commission in dementing and psychotic patients was made in Section 4.1.

5.1.7.1.3 Variables derived for the present study

The structure of the logical memory test was altered for the current study by including a further delayed recall trial 4-7 days after the first visit. For recall trials the two stories were scored for recall of verbatim detail and of gist. Scores for verbatim recall were out of a total of 25 points for each story, and gist was scored out of a possible 7 points for story 1, and out of a possible 8 points for story 2. The slope of the learning curve was calculated by comparing recall on trial 1and trial 2 of story 2 (both immediate recall following presentation). The recognition test presented 15 details relating to each story, and

therefore the total possible score was 30. Scoring for the delayed recall during the second visit was identical to that of the other recall trials. Variables and possible score ranges are presented in Table 5.14 below.

Variable	Poorest score possible	Best score possible
Logical memory Total Recall 1+2	0	50
Logical memory Total Recall 1+2+2	0	75
Logical memory Total Recall II	0	50
Logical memory Visit 2 story recall	0	50
Logical memory Learning slope		
Logical memory Total Theme 1+2+2	0	23
Logical memory Total Theme II	0	15
Logical memory Visit 2 theme recall	0	15
Logical memory Total Recog	0	30

Table 5.14 Logical Memory Test (WMS-III) variables

Following Butters et al (1987) and Kern et al (1993), errors of commission made during recall were categorised as follows (see Table 5.15):

Recall inaccuracy (RI) - a response that is categorically correct with respect to subject content, but is inaccurate in detail (e.g. "Anna Thomas" instead of "Anna Thompson" or "She was from South Bristol" instead of "South London".)

Novel intrusion (NI) - a response which describes a story element not included in the original passage (e.g. "the woman was shot and killed")

Cross-trial errors (CTE) - a response made for one story that would be correct only for the other story (e.g. "Joe Grant was from South London")

In practice, distinguishing between recall inaccuracies and novel intrusions was difficult in some cases, and so 5 raters were asked to categorise each error made by participants. All raters had experience in administering memory tests to older adults, patients with dementia or with amnesic symptoms. The majority decision was use to categorise each error. Each

type of error was summed over the five recall trials during Visit 1 to give a total error score. (Second visit recall was excluded from analysis as controls did not complete this part of the test). In addition, those errors which were in fact perseverations or repetitions of previous errors and which had become part of the participants established 'memory' of the story were discounted to give a 'new' errors score for each type of error. Kern et al (1992) found reduced total output on the logical memory (LM) test, i.e. less responses overall whether correct or incorrect in their AD group, and therefore calculated percentage scores for errors in terms of total output. Percentage scores also allow more complex statistics to be used in analysis, as raw error scores tend to be low, and for some groups the median may be zero or one. For the present study this generated six new scores (see table 5.18 below). Lastly, a percentage score for all types of errors was calculated.

For the recognition task, answers were analysed and scored using a signal detection approach giving the following variables (see Table 5.15):

Hits – correctly identifying details that were part of the story

Correct negatives – correctly identifying details that were not part of the story

Misses – rejecting details that were part of the story

False alarms – accepting details that were not part of the story

In addition a ratio of false alarms to correct negatives was calculated to measure the overall bias towards accepting false details.

	Error variables
Raw scores	LM Recall inaccuracies new
	LM Novel intrusion new
	LM Cross-trial errors new
	LM Recall inaccuracies total
	LM Novel intrusion total to trial
	LM Cross-trial errors total to trial
Percentage scores	LM Percentage new recall inaccuracies
	LM Percentage new novel intrusions
	LM Percentage new cross-trial errors
	LM Percentage total recall inaccuracies
	LM Percentage total novel intrusions
	LM Percentage total cross-trial errors
	LM Percentage all-types of errors LM
Recognition bias	Hits LM recognition
	Correct negatives LM recognition
	False alarms LM recognition
	Misses LM recognition
	False alarms: correct negative ratio LM

Table 5.15 Error variables derived from Logical Memory Test (WMS-III)

5.1.8 Executive Function

5.1.8.1 Verbal Fluency Test - Letter, Category and Alternating Conditions

5.1.8.1.1 Description of the test

Verbal fluency (Thurstone, 1938) is a widely used test of executive function, particularly with elderly and dementing subjects, which is relatively brief and easy to administer and has a good degree of face validity (La Rue, 1992). Typically subjects are given a letter or a category and asked to produce as many words as they can either beginning with the letter or belonging to the category within one minute. The number of words produced gives an index of executive function. The paradigm has been adapted by several studies to assess set-shifting ability, another component of executive function and attentional control, by asking subjects to alternate between two letters, two categories and a letter and category (Newcombe, 1969; Cools et al, 1984; Downes et al, 1992). The current study uses a

version of the test adapted from Downes et al (1993) where 5 trials are used with different probes; a single letter, a single category, alternating letters, alternating categories and alternating letter and category. The paradigm was adapted from that used by Downes et al (1993), which used the 5 conditions detailed above, but with two trials each, one uncued and one cued by presentation of the appropriate probe. The present study used 5 uncued trials only. Probes used were 4 letter and 4 category taken at random from the 16 used by Downes et al, and the order of conditions was always as above, but the order of probes was counterbalanced to ensure that different probes were used in the single versus alternating conditions, and that different combinations of probes were used in the alternating conditions.

5.1.8.1.2 Suitability for the current sample

Some studies have found that there is mild decline in test performance related to age, though rarely marked (Benton et al, 1981). Several studies however have found deficits in a Parkinsonian population, although the effect appears to be stronger for semantic than phonemic fluency (Henry & Crawford, 2004), and particularly when alternating cues are used, and especially for alternating letter and category probes, that is, extra-dimensional set-shifting (Cools et al, 1984; Downes et al, 1993). Severity of disease may of course produce confounding effects as speed of speech will affect overall scores. Level of education and particularly verbal intelligence and vocabulary also correlate with verbal fluency scores (Hanley, 1990). Therefore both disease severity and a verbal measure of IQ should be covaried when examining verbal fluency scores in this population.

Verbal fluency can to some degree be seen as a test of inhibitory function, that is, selection of an appropriate response via inhibition of competing but inappropriate responses (Burgess, 2003). Types of errors produced during the verbal fluency task may fall into a

number of categories, and some studies have found that PD patients are more likely to make errors of perseveration when switching between alternating probes. Repetition of previously named words, and intrusion of words which are appropriate to neither probe are other types of errors which occur more frequently in patients with AD and other dementias . Analysis of errors may be especially revealing in examining performance in patients with psychosis.

5.1.8.1.3 Variables derived for the current study

Scores for correct words produced for each trial were used for analysis, and a total score across all five trials was calculated (see table 5.16 below).

Variable	Poorest score possible	Best score possible
Verbal fluency letter total	0	-
Verbal fluency category total	0	-
Verbal fluency alternating letter total	0	-
Verbal fluency alternating category total	0	-
Verbal fluency alternating let/cat total	0	-
Verbal fluency grand total	0	-

Table 5.16 Verbal fluency test variables

In addition error scores for each type of error were generated, and for total errors, and percentage of each type and for overall errors in terms of total output were calculated.

Following Downes et al (1993) in the present study errors were categorised as follows:

Repetitions (R) of items within the same 60 second trial

Perseverations (P) (for alternating trials only) where participants continued responding to the previous probe rather than switching to the current one, i.e. failure to shift set.

Intrusions (I) of words inappropriate to either probe.

Extending Downes et al's design, intrusions were categorised further:

Cross-trial intrusions (CTI) where a word appropriate to a previously used probe was used wrongly in a current trial.

Novel intrusions (NI) where a word was inappropriate for the current trial and for any previous probes.

Table 5.17 below lists the variables derived from verbal fluency for the current study.

	Error variables
Raw scores	VF repetition total
	VF perseveration total
	VF intrusion total
	VF cross-trial intrusions
	VF novel intrusions
Percentage scores	VF repetition percentage
	VF perseveration percentage
	VF intrusions percentage
	VF novel intrusion percentage
	VF cross-trial intrusion percentage

Table 5.17 Error variables derived from verbal fluency test

5.1.8.2 Reitan Trail Making Test

5.1.8.2.1 Description

The trailmaking test is part of the Halstad-Reitan Battery and involves two parts (Reitan, 1953). Trail A requires the participant to join, in order, a series of numbers from one to 25 which are placed randomly on a page. Trail B involves a similar sequencing task but subjects are required to alternate between consecutive numbers and consecutive letters. The test is timed, and if an error is made the watch is stopped whilst the experimenter prompts the subject to return to the last correct response. In most studies it is the total time taken for each part which is used as the key variable for analysis, and norms are based on total time taken to completion (Reitan, 1953, Davies, 1968; Lezak, 1995).

5.1.8.2.2 Suitability for use in the current study

This test taps a number of cognitive abilities, requiring visual search, motor tracking and single and alternating sequencing. In addition, for the current sample the visual search component will present difficulties due to both visuospatial deficits (Knopman & Selnes, 2003) and slowness of occulomotor saccades. In addition bradykinesia and tremor will also reduce speed on the motor tracking component. The trailmaking test has been chosen for the current study to assess both visual search and also executive function, specifically set-shifting ability and the ability to inhibit previous set. Using Trail A as a baseline measure which assesses visual search and motor tracking, the set-shifting component of Trail B can be isolated and extra time taken for B can be said to reflect set-shifting (Lezak, 1995). In the current sample, the slowness of visual search and motor tracking are likely to exaggerate any set-shifting deficits as working memory must hold the previous, current or next target for a relatively longer period. In this way the Trail B may be *more* sensitive in detecting executive deficits in PD patients compared to other populations as there is an added burden of other difficult components which may act akin to a concurrent cognitive task.

5.1.8.2.3 Variables derived for the current study

Total time taken (when completed) for each test will be used for analysis. However, a floor effect may be likely as Lezak (1995) recommends that part A of the test should be terminated after 2 minutes if not completed, and part B after 5 minutes. Therefore time taken for each correct response on Trail A and Trail B will be calculated, and as a measure of the performance decrement associated with having to shift-set time per correct response for Trail A will be deducted from time per correct response for Trail B. In addition, the proportion of the test completed in terms of number of correct responses for both A and B

out of a total of 25 will be recorded, and also number of errors which is independent of correct responses. Errors may reflect either a *visual* misperception of the target (i.e. mistaking '8' for 'B'), a lapse in the correct sequence, a failure to shift set or a combination of all three. However, it would be difficult to say which of these errors has occurred without asking the subject, and therefore cueing them as to the correct response. The benefits of cueing in executive tasks were discussed in Chapter 4. See table 5.18 below for a list of the variables produced for the Trailmaking task for the current study.

	Variable	Poorest score possible	Best score possible
Timed scores	Trail A time (in secs)	-	-
	Trail B time (in secs)	-	-
	Trail A time per correct response	-	-
	Trail B time per correct response	-	-
	Trail B – Trail A time per correct response	-	-
Raw scores	Trail A complete / 25	0	25
	Trail B complete / 25	0	25

Table 5.18 Trail Making Test variables

5.1.9 Visual Perceptual Tests

5.1.9.1 Visual Object and Space Perception Battery

5.1.9.1.2 Description

The Visual Object and Space Perception (VOSP) battery (Warrington & James, 1991) taps a range of visual perceptual abilities, consisting of a screening test, and 8 other tests. The test was originally devised to discriminate between patients with right and left hemisphere lesions by comparing performance on object perception (4 tests within the battery) and spatial perception (also 4 tests). The screening test is a figure-ground discrimination test where subjects must detect whether a degraded 'X' is present or absent within a square of visual noise. For the present study only 4 other tests from the battery were used, firstly for the sake of brevity, and secondly because they were felt to be most relevant theoretically to the current sample.

The 'Incomplete letter' test involves identifying a series of capital letters which have been degraded, and therefore processes of visual closure, akin to the Gestalt Test. The 'Silhouettes' test presents 15 silhouettes of animals and 15 silhouettes of everyday objects viewed from unconventional perspectives, mainly foreshortened views where depth information is lost, and the main lateral axis is rotated to distort its defining features. The participant must identify the object correctly to score a point in each case. The 'Object decision' test presents 4 silhouettes, including one real object and three 'nonsense figures' which act as distractors. The subject must select the real object, thus rejecting the three nonsense objects. The VOSP merely requires subjects to select the correct object, thus allowing for naming and semantic difficulties as some agnosic and dementing patients show (Kartsounis, 2003; La Rue, 1992). For the present study subjects were also asked to name the object they had selected, to provide more information about types of visual errors made. The 'Progressive Silhouettes' test consists of 2 subtests. For each, a series of silhouettes is shown of the same object starting from a view where the main axis is completely foreshortened, thus hiding defining features. As the series progresses the perspective is rotated so that in the final picture the object is shown in its full lateral, most prototypical, view and all relevant features allowing identification are shown. The subject is asked to identify the object using as few of the pictures as possible, so that low scores indicate rapid identification using less information.

5.1.9.1.2 Suitability for the current sample

As mentioned earlier, the VOSP was designed to assess performance in detail in patients with right or left hemisphere lesions. The test handbook also contains normative data for 200 British adults to the age of 69, and cut-off scores for showing 'impaired' performance are based on these. However work by a group in the US has shown that an age-related

decline is *more* pronounced after 70, and have provided their own norms based on healthy older adults (Bonello et al, 1997; Rapport et al, 1998). They found that for 2 tests, including the Silhouettes test, cut-offs for impaired performance were too high for older adults, and have warned that Warrington & James' (1991) original sample is not suitable for grading performance in those over 70.

Additional work by Rapport et al (1998) however, provided support for the two-factor model of object and spatial perception proposed by Warrington & James, indicating that the 4 tests used in the present study load on an object perception factor, with good internal reliability, whilst the other 4 tests load on a weaker spatial perception factor, thus giving support for the use of the above 4 tests as a valid battery of object perception in older adults.

The VOSP requires spoken responses only and is therefore not demanding for the participant. No motor response or timed responses are needed so the current sample should not be at a disadvantage relative to other older adults in terms of responding. However, there is some evidence that PD patients have difficulties with word-finding, although this is not as severe as in aphasics, nor does it usually involve the loss of the semantic meaning of words as in AD (La Rue, 1992). Therefore the VOSP should provide a relatively pure measure of visual perceptual function. Bonello et al (1997) found no effects for level of education or estimated verbal IQ on performance in their sample. However, as the current sample included patients with some degree of cognitive decline, verbal IQ in terms of word accessibility and semantic abilities might be expected to bear some relationship to performance on the Silhouettes and Progressive Silhouettes tasks, and also on the additional measure of naming ability on the Object Decision task.

As with other tests, errors made on the VOSP were examined. In addition, the screening test, though used by Warrington & James to assess whether the subject had sufficient

lower-level visual ability to complete the test of higher visual function, was used in the present study to assess figure-ground discrimination, which is impaired in PD patients, and which may relate to abilities of contour perception that have been associated with hallucinations in PD (Buttner et al, 1996; Diederich et al, 1999)

5.1.9.1.3 Variables derived for the current study

Following Warrington & James (1991) instructions and their two-factor model, tests were scored firstly with number of correct responses, and a total score across the 4 tests of object perception, with the score for Progressive Silhouettes reversed (see table 5.19 below).

Variable	Poorest score possible	Best score possible
VOSP Shape detection total	0	20
VOSP Incomplete letters total	0	20
VOSP Silhouettes total	0	30
VOSP Object decision total	0	20
VOSP Progressive silhouettes total	20	2
VOSP Object perception total (PS reversed)	0	80

Table 5.19 Visual Object and Space Perception Battery test variables used in the present study

As the VOSP is scored using the number of correct responses out of a total, incorrect responses will therefore be proportional. However the current study distinguished between 'passes' where the subject gave no responses, and errors where they identified an item incorrectly or inappropriately. Similarly to the analysis of logical memory errors, false positives and false negatives on the screening test were scored separately, as were 'confabulations' where an inappropriate shape was detected such as a 'face' or a 'teddy bear'. Incorrect identifications for the Incomplete Letters and Silhouettes test were scored, as were incorrect decisions about the 'real object' on Object Decision and also errors

identifying those objects chosen as real. The variables derived are listed in Table 5.20 below:

Error variables
VOSP Shape detection false positives
VOSP Shape detection false negatives
VOSP Shape detection confabulations
VOSP Incomplete letters incorrect
VOSP Silhouettes incorrect
VOSP Object decision incorrect
VOSP Object decision misidentifications

Table 5.20 Error variables derived for the VOSP battery

5.1.9.2 Pillon's Overlapping Figures Test

5.1.9.2.1 Description

Pillon's (1989) test presents two visual stimuli, each composed of 15 overlapping line drawings of everyday objects. The subject is required to identify the objects as rapidly as possible and the time taken to correctly identify 12 of them is the key score. Pillon found no differences in the time taken for each test, and either the mean or the total is therefore appropriate as a composite score. For the current study a list of 12 words matched for frequency with the pictured items was used as control measure for vocalisation speed (Cousins et al, 2002).

5.1.9.2.2 Suitability for the current sample

Pillon's test was devised primarily as an index of processing speed rather than visual perception per se, because in normal samples it is a test which is easy to complete test. It has been used in non-demented PD samples as an index of bradyphrenia. However, in dementing samples deficits in correctly naming items have been observed. Incorrect identifications may result either from incorrect lexical decisions, i.e. anomia, or from

identifications of part of an object or an composite of two or more overlapping objects . For the current sample the test was considered appropriate as several studies have collected data on timed responses (Pillon et al, 1989; Cousins et al., 1999) and so reference data is available. For the current study the overlapping figures test was used to assess object perception within a complex visual array, i.e. componential processing (see Cousins et al, 1999), which is not tapped by the VOSP. Again the number and type of errors made was analysed to provide information about types of visual errors, and bias towards incorrect part or composite errors, i.e. errors in top-down visual processing.

5.1.9.2.3 Variables derived for the current study

As piloting revealed, some PD patients were unable to identify 12 objects, that is, the criterion used for timed scores. Therefore for analysis of the current sample, time taken to correctly identify 8 of the 15 objects was used. However, the instructions were to name as many objects as possible so that scores for objects correctly named out of a total of 15 for each test, and out of 30 for both tests were also derived (see table 5.21 below).

Variable	Poorest score possible	Best score possible
Reading speed (in secs)	-	-
Overlapping figure A time to 8 (in secs)	-	-
Overlapping figure B time to 8 (in secs)	-	-
Overlapping figure A total objects named	0	15
Overlapping figure B total objects named	0	15
Total figures named OFigs A + B	20	30

Table 5.21 Overlapping figures test variables

Errors scored were:

R) Repetitions of already named items, suggesting an inefficient visual search

A) Anomia; inability to name object, but able to describe its use

M) Misidentification of an object, whether part or whole

In addition, a percentage score for misidentifications in terms of total responses was calculated, thus controlling for reduced overall output in those with the poorest performance.

	Error variables
Raw scores	Overlapping figures: repetition total Overlapping figures: anomia total Total misidentifications OFigs A + B
%age scores	Percentage misidentifications Ofigs

Table 5.22 Error variables derived from the overlapping figures test

5.1.10 Construction

5.1.10.1 WAIS Block Design subtest

5.1.10.1.1 Description of the test

During the block design test participants are required to assemble blocks to make patterns which the experimenter has demonstrated, or which are presented using a visual stimulus. Pattern complexity and number of blocks used increases throughout the test, with 14 items in all, and performance is scored for correct completion and for speed. The test requires participants to progress from 2-block designs, to 4 block designs, to reproducing designs presented on stimulus cards, and eventually 9-block designs, the last two of which change in orientation.

5.1.10.1.2 Suitability for the current study

The block design test is a performance subtest of the WAIS III-R which taps primarily visuoperceptual and visuocontructive abilities, but which also involves a component of non-verbal problem solving (La Rue, 1992). It could be argued that is also reflects a degree of executive involvement in that strategies may be required for more complex designs. Norms available for the performance subtest of the WAIS III-R allow estimates of patient general

intelligence. As the concept of the test is likely to be unfamiliar to most participants it provides a relatively pure measure of fluid intelligence, which is less confounded by level of education.

As such, this test is sensitive to aging effects and particularly to dementia (La Rue, 1992), and has also been found to be impaired in PD patients (Pirozzolo et al, 1982; Azuma et al, 2003). As it requires relatively complex motor manipulation, testing in PD may be confounded, motor impairment is likely that this is reflected mainly in reduced speed in PD patients unless they show frank apraxia. In all analyses for the PD patients, motor severity was covaried.

The visuoperceptual component of the test may also present a challenge for PD patients, especially those with double vision, and this may be reflected to a greater extent in scores than is constructional ability itself. Indeed the prominent visuospatial impairments in PD and DLB (Salmon et al, 1996; Simard et al, 2003)are likely to contribute to documented deficits in visuoconstructive ability (Connor et al, 1998) and visual form perception deficits may be a confound in assessing construction in such patients (Manning, 2003). One drawback of block design is that it is a relatively long test, particularly if time limits are relaxed, and may induce motor and mental fatiguing or boredom. However, after three consecutive failures the test is terminated.

5.1.10.1.3 Variables derived for the present study

Because of concerns over motor slowing affected speed-based scores, the current sample was scored firstly according to speed as the WAIS III-R specifies and secondly for number of designs completed if the completion occurred outside the specified time limit, but within a reasonable length of time. Manning (2003) also recommends that when the test is used

as an assessment of constructional processes, rather than IQ, no time limit should be imposed.

The measures derived from block design for the present study are listed in Table 5.23 below.

Variable	Poorest score possible	Best score possible
Block design total score	0	
Block design number of designs completed	0	14

Table 5.23 Block Design (WAIS –III R) variables used for the present study

5.1.11 Attention

5.1.11.1 Computerised Divided Attention Test

5.1.11.1.1 Description of the test

Walker et al (1999 and Ballard et al, (2002) used a subtest of the CDAT battery to assess attentional function, specifically fluctuations in attention over time. Their test was a simple computerised vigilance task requiring the subject to press a button whenever they saw the number '2' on screen and ignore other numbers. Mean response time gave an indication of speed, and variability of response gave an index of the tendency to fluctuate in attention in terms of response time. The present study used a computerised attention task, which was a divided attention forced choice paradigm, with 2 conditions. In all conditions subjects were presented with a display of four boxes on screen which corresponded to the positions of 4 buttons on the response pad. Subjects were asked to place both hands on the response pad at the beginning of the test. At the start of each trial, the word 'READY' appeared in the centre of the screen for one second, followed by the four boxes. After the four boxes were displayed on screen for a fixed interval of 3 seconds, a random interval of 0-4 seconds followed with the boxes remaining on screen until one of them '"lit up" by filling in, and subjects were asked to press the appropriate button as rapidly as possible. The

order in which the boxes lit up was also random. When a correct response was made the word 'CORRECT' appeared onscreen. When an incorrect response was made a beep was emitted. If the subject made no response within three seconds, the trial ended and the 'READY' screen appeared again. Each condition consisted of 22 trials, of which the first two were discarded, and the remainder used for analysis. Prior to the beginning of the 2 conditions, subjects were given four practice trials under each condition to familiarise themselves with the task.

For both the undivided and divided attention conditions, subjects were required to choose between the four boxes, by pressing the button which corresponded in position to the one highlighted on screen.

For the divided attention condition, the same 4 choice paradigm was used except that the subjects were required to carry out a simultaneous task of reading and repeating aloud a 4-digit string of randomly generated numbers. The 4 digits were presented on screen prior to the boxes, and when the subject had repeated them correctly twice, the experimenter initiated the start of the trial by pressing a button, to control for varying reading speed. The presentation and filling in of one of the boxes was the same as described above for each of the divided attention trials, but the 4 digits remained on screen throughout each trial, and subjects were required to repeat the digits until they made a response by pressing a button. The 4-digit number was different for each successive trial.

5.1.11.1.2 Suitability for the current sample

The test was designed with the current sample in mind, and although vocal and motor responses were required, the undivided attention condition acted as a baseline for motor speed. The vocal response required was not timed and if the voice fatigued to a quiet level this did not affect performance. In addition, as *variability* of response time, rather than

response time itself was of most interest, the use of the coefficient of variation effectively controlled for differences in speed (Walker et al, 1999; Ballard et al, 2002). In addition disease severity was covaried on all raw timed measures.

5.1.11.1.2 Variables derived for the current study

Variables
Mean RT test undivided
Standard deviation RT test undivided
Coefficient of variation RT test undivided
Mean RT test divided
Standard deviation RT test divided
Coefficient of variation RT test divided

Table 5.24 Attention test variables

5.1.12 Psychological Measures

5.1.12.1 Geriatric Depression Scale

5.1.12.1.1 Description

Patient depression was measured using the Geriatric Depression Scale (GDS; Brink et al, 1982; Yesavage et al, 1983). The original version of the GDS used 30 items, but for the sake of brevity the GDS-15 was used in the present study. This version has shown sensitivity and specificity comparable to the full scale (Lyness et al, 1997). Cut-off criteria for the diagnosis of depression using the GDS-15 is a score of 5 or more, with greater scores indicating more depressive symptomatology. Each item requires a simple yes or no answer. For the full scale see Appendix C.

5.1.12.1.2 Suitability for the current sample

This questionnaire was developed specifically as a screening tool for depression in older adults, and was designed to concentrate on cognitive and affective aspects of depression, rather than somatic complaints, and is therefore suited to a sample of patients with a

chronic illness. The scale has also been widely used in studies of depression in Parkinson's Disease as both short and full versions (Meara et al, 1999; Rojo et al, 2003)

5.1.12.1.3 Variables derived for the current study

Variable	Least severe score possible	Most severe score possible
Geriatric Depression Scale – 15 total score	0	15

Table 5.25 Psychological Measures I - Geriatric Depression Scale (see appendix C for items)

5.1.12.2 State Trait Anxiety Inventory - State

5.1.12.2.1 Description

The present study used the State section of the State-Trait Anxiety Inventory (STAI; Spielberger et al, 1983). The STAI-S consists of twenty items, half scored positively for the presence of anxiety, and half requiring reverse scoring (i.e. 'I feel calm'). Each item is scored for severity on a Likert scale of one to four; from 'Not at all' to 'Very much so'. Therefore a higher score indicates more sever anxiety. For the full scale see Appendix C.

5.1.12.2.2 Suitability for the current sample

The STAI has been used in studies of older adults previously (Stanely et al, 1996; 2002, Kabacoff et al, 1997), and the items are phrased in a way that is easy to understand. Although the HADS is more widely used in previous studies of PD patients it tends to conceptualise anxiety as panic-like symptoms, rather than a more generalised anxiety, which the STAI has been used to assess in older adults.

5.1.12.2.3 Variables derived for the current study

Variable	Least severe score possible	Most severe score possible
State Anxiety Inventory total score (STAI-S)	20	80

Table 5.26 Psychological Measures II - Geriatric Depression Scale (see appendix C for items)

5.2 Design

The study was a single phase cross-sectional study designed to identify correlates of hallucinations in a sample of Parkinson's Disease patients to build a linear regression model, and to assess differences between hallucinators and non-hallucinators. A control sample was used for most group comparisons.

5.3 Participants

5.3.1 Parkinson's Disease sample

Parkinson's Disease patients were recruited from Movement Disorder clinics in Liverpool and Wirral, and inclusion criteria were that they had been given a diagnosis of idiopathic Parkinson's Disease by a Neurologist and/or Consultant Geriatrician. Therefore, according to UK Parkisnon's Disease Brain Bank Criteria they displayed two or more of the following clinical symptoms; (i) tremor, (ii) bradykinesia, and (iii) rigidity. Exclusion criteria were; (i) medication-induced Parkinsonism, (ii) suspected AD or Dementia with Lewy Bodies, (iii) Multiple System Atrophy or Progressive Supranuclear Palsy, and (iv) moderate to severe PD dementia indicated by MMSE<16. In addition, those patients who had experienced a major stroke and/or whose motor symptoms emerged following ischaemic disease were excluded.

78 PD patients were recruited with a mean age of 74.4 (± 7.9) and a range from 52 to 93 (Table 5.30). 65.4% of patients were male, in agreement with the two-thirds estimated male prevalence. The mean disease duration was 5.7 (± 5.3) years and ranged from 3 months to 24 years. The mean age at disease onset (taken as time of diagnosis) was 68.4 (± 9.2) and the minimum age at onset was 46, therefore no participants fell into the early onset category of below 40. At phase one, two patients were unmedicated, 69 were on

levodopa (L-Dopa) (either alone or in combination with other drugs) and the remaining 7 were on DA agonists or selegiline as the primary therapy. Table 5.27 shows the characteristics of the Parkinson's Disease sample.

	Mean	Std. Dev.	Range	Min	Max
Age at time of test	74.40	7.88	41.0	52.0	93.0
Age at onset	68.42	9.16	43.0	46.0	89.0
Disease duration	5.73	5.30	23.8	0.3	24.0
Medication duration	5.60	5.41	24.0	0.0	24.0
Total for motor scale UPDRS	21.17	6.75	27.0	8.0	35
Total fluctuations score UPDRS	2.59	2.78	12.0	0.0	12
Years of FT education	10.40	2.98	14.0	6.0	20
MMSE total score	26.34	3.10	14.0	16.0	30
Full NART equivalent score	28.19	11.17	40.0	8.0	48
Mill Hill Vocabulary total score	15.04	3.29	18.0	2.0	20
Geriatric Depression Scale total	4.97	3.09	14.0	0.0	14
State Anxiety Inventory total	40.47	10.02	45.0	24.0	69
Elder Impairment Scale total	43.98	13.21	52.0	23.0	75

Table 5.27 Descriptive statistics for clinical variables for the PD group for the main study

Participants were divided into three groups according to their experience of hallucinations; a non-hallucinators group consisted of 28 patients with no history of hallucinations, an 'Unusual perceptual experiences' group consisted of 15 patients with a history of infrequent and 'minor' hallucinations which were often poorly defined (see Fenelon et al, 2000), and a hallucinators group consisted of 35 patients wtith complex hallucinations ior frequent illusions of more than one type (see Table 5.28). Chapter 6 detials the frequency of both complex and minor hallucinations in the sample.

Group	Description	N
Non-hallucinators	No history of minor or complex hallucinations	28
Unusual perceptual experiences	Infrequent or poorly defines minor hallucinations (illusions of passage, presence, movement or object illusions)	14
Halucinators	Complex hallucinations or frequent minor hallucinations of more than one type	35

Table 5.28 Description of three PD groups according to experience of hallucinations

5.3.2 Control sample

31 older adults were recruited as controls using a local radio advertisement, and the University of Liverpool Department of Psychology control panel. They were selected to be of a similar age range to the PD group. Their characteristics are described in Table 5.29. Although some members of the control panel had taken part in similar studies, care was taken to screen out those who had used the same tests. Exclusion criteria were; (i) gross visual impairment and/or deafness which would not allow fair testing to take place, (ii) a history of neurological impairment, (iii) a diagnosed sleep disorder, (iv) dementia, (v) epilepsy, (vi) diabetes, and (vii) a movement disorder of any kind.

	Mean	Std. Deviation	Range	Minimum	Maximum
Age at time of test	70.90	5.59	25	56	81
Years of FT education	11.58	3.37	12	7	19
MMSE total score	28.87	1.02	4	26	30
Full NART equivalent score	33.55	11.30	42	8	50
Mill Hill Vocabulary total score	16.90	2.74	11	11	22
Geriatric Depression Scale total	1.65	1.89	8	0	8
State Anxiety Inventory total	32.32	8.21	33	20	53

Table 5.29 Descriptive statistics for clinical variables for the control group for the main study

5.4 Ethical Considerations

Approval for the study was obtained from Liverpool, Sefton & Wirral Health Authorities, with emphasis given to participants about the confidential nature of the study. Participants were told that they would be identified on all test results, transcripts, and data files by a code number only. Personal details were held on a separate file. Where interviews were recorded, tapes were transcribed and erased within six weeks. Consent was sought from both patient, and where possible caregiver, although exclusion of those with a MMSE score of lower than 16 minimised problems with obtaining consent from dementing patients. In addition, participants were told that they could take a rest from testing

whenever they wanted, and that they were not obliged in any way to answer all questions or to continue with testing if they felt unable. In accordance with the University of Liverpool Department of Psychology Ethics Committee, controls were also given an information sheet, and full consent was obtained.

5.5 Procedure

5.5.1 Parkinson's Disease sample

PD patients and their caregivers were interviewed at home to minimise problems with access and comfort during testing due to disability. The test protocol for the main study was designed to be carried out during two visits of approximately two hours each, and in most cases the second visit took place 5-7 days after the first. In some cases PD patients required a third or fourth visit to complete the testing, but care was taken to order tests so that clinical details and global cognitive measures were completed on the first visit, delay between the second and third recall trials of the Logical memory test was no longer than one week, and that sleep diaries and actigraphic measures were commenced on the first visit. The test protocol for the PD patients is shown below in Table 5.30.

5.5.2 Protocol/ Measures

Visit 1
Explanation of study and completion of Consent form
Details and medical history
UPDRS
MMSE
NART
Mill Hill
Logical memory I
Unusual experiences interview (Caregiver QUE/sleep)
Logical memory II
Actiwatches issued
Sleep diaries issued
Visit 2
Actiwatches collected
Sleep diaries collected
Logical memory IV
NART
Mill Hill
VOSP battery tests
Overlapping figures test
Verbal fluency
Attention battery
Trailmaking (if time)
Block design (if time)
Caregiver interview
Questionnaires issued

Table 5.29 Protocol and measures for PD group

5.5.2 Control sample

Controls were tested on one occasion at the Department of Psychology, University of Liverpool. The QUE scales and related sleep interview were administered in the form of a self-report questionnaire. The test protocol is shown below in Table 5.31

Visit 1
Explanation of study and completion of Consent form
Medication details and medical history
Sleep habits and unusual experiences questionnaire (QUE)
Logical memory I
MMSE
NART
Mill Hill
VOSP battery tests
Overlapping figures test
Logical memory II
Attention battery
Actiwatches issued
Sleep diaries issued

Table 5.30 Protocol and measures for control group

As can be seen from the protocols, the controls did not complete the verbal fluency tests, the Trail making test or Block Design. This was because of time constraints and the fact that there is a good deal of normative data for these tests in an elderly population, or in Parkinsonian populations. The sleep diaries and actiwatches were returned the following week to the University by the controls.

CHAPTER 6

UNUSUAL PERCEPTUAL EXPERIENCES IN PD

- SCALE PROPERTIES AND ASSOCIATION WITH CLINICAL VARIABLES.

6.0 Strategy of analysis

For both the pilot study and the main study, the relationship amongst reported sleep symptoms and 'unusual perceptual experiences' will be examined using a factor analytic approach. The internal reliability of derived factors will be assessed using Cronbach's alpha coefficient. Factor scores will be correlated with one another and with disease-related variables with the specific aim of examining which types of sleep symptoms are related to hallucinations, once the confounding factor of disease severity is removed. Results will be compared for the two studies, the methodological limitations of each discussed, and the stability and generalisability to a wider Parkinson's Disease population assessed.

6.1 Pilot study

The pilot study was conducted to (i) investigate factor structure of unusual sleep and perceptual symptoms and (ii) to assess reliability and validity of a questionnaire measure of these symptoms. The participants used were a separate sample to those who took part in the main study. Questionnaires were obtained for a total of 115 patients. Nine were competed by the caregiver (CG) and the remaining 106 by the patients. In addition, 40 CGs also completed a questionnaire specific to caregiving.

6.1.1 Demographic variables for pilot participants

60.4 % of the patients were male, which is consistent with the two-thirds male prevalence in Parkinson's Disease in the UK. Age ranged from 38 to 91 although, the majority (62%) of patients were 65 or older. Mean disease duration was 7.6 years (± 5.8) although there was a large range (4 months to 28 years). Only two patients were unmedicated, 103 were on levodopa (L-DOPA) (and many also on additional drugs including DA agonists) and the remainder receiving either DA agonists or selegiline as the major therapy.

Total score on the ADL scale of the UPDRS ranged from 3 to 36 out of a possible total of 52, with a mean of 16.8 (± 7.3) (Table 6.1). Where ratings were also obtained from the CG there was good agreement ($r = 0.79$, $p < 0.001$) with the mean falling at 18.9. A difference calculated between the two ratings was less than 7 points for all but 3 dyads; less than one standard deviation from the overall mean. Therefore, self and informant ratings appeared to have good agreement, supporting the use of self-report ADL scales for collecting data on disease severity, although of course the ratings were subjective.

	Range	Minimum	Maximum	Mean	Std. Deviation
Age at time of test	53.0	38.0	91	66.03	10.00
Age at onset	47.0	30.0	77	58.44	9.97
Disease duration	27.8	0.3	28	7.60	5.76
Medication Duration	26.0	0.0	26	7.35	5.89
Total UPD score	33.0	3.0	36	16.83	7.33

Table 6.1 Descriptives for clinical variables for pilot study

6.1.2 Properties of QUE scales

Of primary interest was the frequency with which patients experienced sleep-related, hallucinatory, and other 'unusual' symptoms described in the questionnaire, and whether they appeared characteristic of a wider PD population.

6.1.2.1 Individual items

The number of patients experiencing symptoms during the previous month ranged from 3.7% for sleep walking to 81.8% for sleep fragmentation. The most frequent sleep problems were sleep fragmentation, vivid dreams (experienced by 49.1% of patients), and motor activity during sleep (experienced by 47.7%) (Table 6.2). The most frequent unusual experiences were peripheral movement (46.8% of patients) and elementary visual hallucinations (30.9%). Visual hallucinations were the most frequent complex hallucination (experienced by 23.2% of patients).

Item	% age at all	Median	Not at all	1-2 times a month	Weekly	Most days	Every day
Sleep fragmentation	81.8	3	20	19	11	37	23
Hypnogogic imagery	29.4	0	77	10	9	7	6
Vivid dreams	49.1	0	56	23	13	11	7
Nightmares	27.5	0	79	18	7	2	3
Night terror/ panic	20.0	0	88	14	4	3	1
Confusion/disorientation	31.5	0	76	23	6	4	2
Sleeptalking	41.4	0	65	21	11	10	4
Myoclonus	47.7	0	57	16	17	7	12
Sleepwalking	3.7	0	105	2	1	0	1
Spots/ zigzags	30.9	0	76	20	5	3	6
Flashing lights	17.1	0	92	13	4	0	2
Patterns moving	29.5	0	79	17	9	3	4
Peripheral movement	46.8	0	59	21	16	8	7
Misrecognition object	24.1	0	85	12	8	5	2
Illusion of presence	22.3	0	87	14	6	3	2
Déjà vu	22.5	0	86	15	6	4	
Derealisation	25.2	0	83	14	7	5	2
Misrecognition person	13.6	0	95	5	9	1	
Flashbacks shock	5.5	0	103	4	0	1	1
Interaction with vivid memories	4.5	0	105	4	0	1	0
Complex visual hallucination	23.2	0	86	12	6	5	3
Auditory hallucination	12.6	0	97	6	6	2	
Tactile hallucination	19.5	0	91	9	7	5	1
Olfactory hallucination	15.2	0	95	10	6	0	1

Table 6.2 Frequencies for QUE items for pilot study

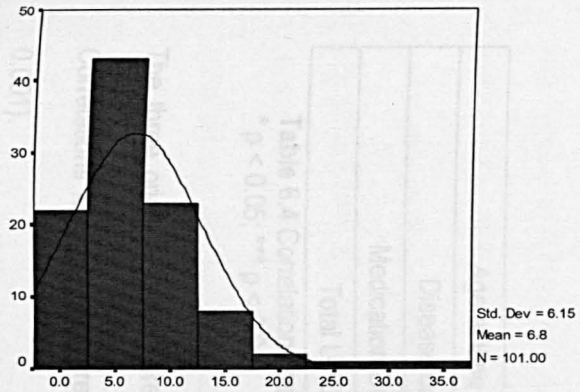
Some questionnaire items were reported by fewer that 10% of respondents, namely sleepwalking, 'flashbacks' and interaction with memories. However, these symptoms are less likely to be reported by patients than caregivers since by their very nature they are experienced by patients who are asleep at the time or may have some degree of confusion. Given that CG reports were not obtained for all patients, it is possible that these kinds of symptoms are underreported.

6.1.2.2 Original scale properties

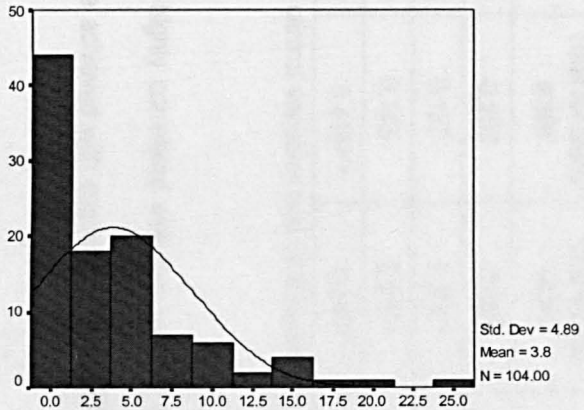
Total scores for each of the original scale were highly skewed (see Figures 6.1, 6.2 and 6.3). All three original scales were non-normally distributed ($p < 0.026$ or less) using the one-sample Kolmogorov-Smirnov test (Table 6.3).

	Range	Median	Mean	SD	Kolmogorov-Smirnov Z	P value for K-S test	$Z_{skewness}$
Total for sleep scale	0-35	5	6.81	6.15	1.47	0.026	7.808
Total for UE scale	0-24	2	3.84	4.89	2.37	0.000	7.760
Total for hallucination scale	0-10	0	1.22	2.29	3.60	0.000	9.628

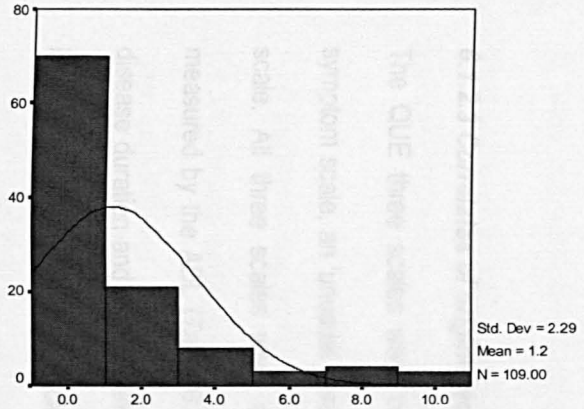
Table 6.3 Distributions and skewness for QUE summed scores for pilot study



Total for sleep scale



Total for UE scale



Total for Hallucination scale

Figures 6.1 (top left), 6.2 (left), 6.3 (above) Distribution of summed scores for original scales. All three summed scale scores are skewed, although the sleep scale is least so. The UE and hallucinations scales however, show that the modal score is zero or one.

However, acceptable alpha coefficients were derived for these scales; for the sleep scale α = 0.79 (which rose to ▯ = 0.80 if the sleepwalking item was excluded), for the UE scale α = 0.79 (which rose to ▯ = 0.81 if flashbacks were included), and for the hallucinations scale α = 0.73.

6.1.2.3 Correlates of original scales

The QUE three scales were conceived originally as distinct entities; a 'sleep-related' symptom scale, an 'unusual perceptual experiences' scale, and a 'complex hallucinations' scale. All three scales were significantly correlated with disease motor severity as measured by the ADL (Table 6.4). The UE and hallucination scales also correlated with disease duration and medication duration, thus disease related variables appear to be an important predictor of experiencing such symptoms. Age however was not correlated with any scores, although this may be due to the fact that older widowed patients have no CG to report sleeptalking or motor activity during sleep, if the patient is unaware of these.

	Total for sleep scale	Total for UE scale	Total for Hallucination scale
Age at time of test	-0.203	-0.069	0.057
Disease duration	0.137	0.200*	0.212*
Medication Duration	0.145	0.211*	0.230*
Total UPD score	0.415***	0.543***	0.480***

Table 6.4 Correlations between clinical variables and QUE scale summed scores
* $p < 0.05$; *** $p < 0.001$

The three original scales were also highly correlated with one another (see table 6.4). Correlations for summed scores were achieved with coefficients $r > 0.58$ or greater ($p < 0.001$).

	Total for sleep scale	Total for UE scale
Total for UE scale	0.68***	
Total for Hallucination scale	0.59***	0.75***

Table 6.5 Correlations between QUE scale summed scores *** $p < 0.001$

At issue was whether the separate scales were measuring one or more factors, and whether these factors had specific and distinct associations with disease related or clinical variables. The structure of the scales were examined using factor analysis.

6.1.3 Differentiating types of sleep and hallucinatory symptoms

6.1.3.1 Unusual perceptual experiences and hallucinations

Items on UPE and hallucinations scales were pooled, and individual items reported by fewer than 10% of patients were removed. Excluded items were 'flashbacks' and 'interaction with vivid memories'. A factor analysis with varimax rotation yielded 4 factors with an eigenvalue of >1, which together accounted for 67.84 % of the total variance. Factor one accounted for 42.75% of the variance and was interpreted as the archetypal experience of hallucinations and illusions/UPE in Parkinson's Disease, and was consistent with Fenelon et al's (2000) classification. Table 6.6 shows the items which loaded onto factor one at 0.55 or greater, these were; (i) patterns moving, (ii) complex visual hallucinations, (iii) peripheral illusions, (iv) object illusions, and (iv) illusions of presence. Elementary hallucinations, i.e. flashing lights and elementary shapes, were also loaded onto this factor, although the loading was only 0.50 for flashing lights. In addition, spots/zigzags also loaded at 0.50 onto factor 4 and therefore was not unique to factor one.

	I	II	III	IV
Visual hallucinations				
Patterns moving	**0.807**	0.068	0.193	0.060
Complex visual hallucination	**0.736**	0.142	0.138	0.195
Peripheral movement	**0.693**	0.367	0.195	0.046
Misrecognition object	**0.643**	0.251	0.424	0.078
Illusion of presence	**0.636**	0.278	0.399	0.076
Spots/ zigzags	0.593	-0.002	-0.161	0.501
Flashing lights	0.519	0.192	0.224	0.027
Other hallucinations				
Tactile hallucination	0.222	**0.866**	0.242	0.067
Olfactory hallucination	0.201	**0.858**	0.091	0.133
Déjà vu/ derealisation				
Déjà vu	0.228	0.071	**0.774**	0.215
Derealisation	0.322	0.262	**0.748**	0.022
Miscellaneous				
Misrecognition person	-0.054	0.032	0.390	**0.817**
Auditory hallucination	0.353	0.371	-0.012	**0.606**

Table 6.6 Rotated component matrix for UPEs and hallucinations
Figures in bold represent loadings above 0.600, figures in grey loadings below 0.500

The second factor accounted for 9.0% of the variance appeared to represent complex hallucinations in other modalities, including tactile and olfactory hallucinations. Factor three accounted for 8.4% of the variance and included déjà vu and derealisation, which fall within the spectrum of 'normal', though infrequent, experience, and therefore may not be particularly representative of PD patients. The fourth factor, accounted for 7.8% of the variance and appeared to be a miscellaneous factor containing items, 'misrecognition of person', 'auditory hallucinations', and 'spots or zigzags'.

Alpha coefficients for factor one improved on those obtained for the scale as a whole. For items loading uniquely on factor one at > 0.55, $\alpha = 0.86$. The second factor obtained a Cronbach's alpha of 0.80, for factor three and for factor four $\alpha = 0.49$. For the following

analysis the correlates of factor one only were examined as this appeared consistent with the archetypal experience of hallucinations in PD, which accounted for a large proportion of the variance and obtained a good alpha coefficient.

6.1.3.2 Sleep symptoms

Repeating the same process with the sleep-related items and excluding sleepwalking (frequency is less than 10%), two factors were obtained with a varimax rotation accounting for 60.9% of the variance (Table 6.7). The first factor 'altered dream events' (ADE) accounted for 46.4 % of the variance, and the second factor 'sleep activity' (SA) accounted for 14.4%.

	I	II
Altered dream events		
Nightmares	**0.868**	0.134
Hypnogogic imagery	**0.811**	0.178
Night terror/ panic	**0.752**	0.109
Vivid dreams	**0.714**	0.375
Confusion/disorientation	**0.581**	0.270
Sleep activity		
Myoclonus	0.135	**0.859**
Sleeptalking	0.282	**0.727**
Waking many times	0.141	**0.621**

Table 6.7 Rotated component matrix for sleep symptoms
Figures in bold represent loadings above 0.600, figures in grey loadings below 0.500

Internal reliability was high for the ADE factor (= 0.84) but was weaker for the SA factor (= 0.64).

6.1.3.3 Characteristics of derived measures

Factor scores were calculated for both sleep factors and for hallucinations factors. In addition, a summed score of the items loaded on factor one was calculated giving a

possible range of 0-20. Although for the summed score weightings provided by the factor score were lost, the score was specific to the five most highly loaded items only and also had the advantage of being reproducible in further studies and by clinicians.

The characteristics of the derived factors were examined as scores for individuals, revealing skewing for both factor scores and for the summed total (Table 6.8). Skewing most likely arose from the fact that medians were low, although such patterns of distribution are inherent in studies quantifying low-baseline or 'unusual' symptoms.

	Range	Median	Mean	SD	Kolmogorov-Smirnov Z	P value	$Z_{skewness}$
Altered dream phenomena factor	5.23	-0.29	0.00	1.02	2.00	0.00	10.17
Sleep activity factor	4.52	-0.17	-0.04	0.97	0.97	0.31	2.74
VH factor	5.29	-0.31	-0.04	0.88	1.99	0.00	7.50
VH factor summed score	20.00	1.00	2.75	4.04	2.61	0.00	8.96

Table 6.8 Distributions and skewness for derived factor scores and summed scores

6.1.3.4 Correlates of sleep factors with other variables

To address the question of whether the distinct sleep factors had different concomitants, factor scores were calculated and correlated with clinical variables, and with the factors derived from the UE and hallucinations items.

The altered dreams events factor correlated with disease severity as measured by the total ADL score and all original scales (Table 6.9). The sleep activity factor correlated with overall severity and also with disease duration and medication duration, as well as all original scales.

	VH factor	VH factor summed score	Age at time of test	Disease duration	Medn Duration	Total UPD score
Altered dream events factor	0.279**	0.438***	-0.121	-0.047	-0.031	0.217*
Sleep activity factor	0.269**	0.313**	-0.137	0.274**	0.270**	0.374***
VH factor		0.891***	0.111	0.216*	0.227*	0.489***
VH factor summed score			-0.014	0.268	0.279	0.500

Table 6.9 Correlations between clinical variables and derived summed and factor scores Shown are correlation coefficients (Pearson's) * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Both also correlated significantly with the VH factor score, and the summed score of the 4 items most consistently associated (object illusions, illusions of presence, complex visual hallucinations and patterns moving) (Table 6.10).

	ADE factor	SA factor
VH factor	0.279**	0.269**
VH factor summed score	0.438***	0.313**

Table 6.10 Correlations between sleep and hallucinations factors and summed scores Shown are correlation coefficients (Pearson's) * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

In order to uncover the association between the two sleep factors and hallucinations score *independently* of disease severity, ADL score and disease duration were covaried using a partial correlation (Table 6.11).

	ADE factor	SA factor
VH factor	0.209*	0.105
VH factor summed score	0.408***	0.147

Table 6.11 Partial correlations between sleep and hallucinations scores controlling for severity and disease duration. Shown are partial correlation coefficients (Pearson's). * $p < 0.05$; *** $p < 0.001$

6.1.4 Summary

The factor analytic approach revealed specific clusters of symptoms; (i) an 'altered dream events' factor, (ii) a 'sleep activity' factor, and (iii) a 'visual hallucinations' factor. Both sleep factors were associated with disease severity, and are therefore expected to become more likely as an individual progresses through the disease. However, the 'altered dream events' factor was associated with a visual hallucinations score *independently of disease severity*, whereas the 'sleep activity' factor was not.

6.1.4.1. Some limitations of the questionnaire approach used in the pilot study

The pilot study raised a number of methodological concerns; (i) statistical, (ii) use of self-report scales, and (iii) nature of the sample.

Firstly, internal validity may be affected by the fact that it is difficult to quantify relatively infrequent or low baseline events. As many of the symptoms were relatively rare, median scores for most items and for summed scores were very low. For example, the median score for the VH summed score was 1 (from a possible range of 0-16). This raises the possibility that correlations between this and other variables are inflated simply because so many people scored zero on these measures. Although a factor analytic approach avoids this problem to some extent by increasing range and allowing deviation *below* zero, the possibility that those items which were most rare were associated by default cannot be ignored. However, very rare items (less than 10%) were excluded.

To assess whether the model was a good fit for *all* of the data, or for only for those individuals with relatively low hallucination scores, a linear regression was performed, with VH factor summed score as the outcome variable. A forced entry method was used entering ADL scale score into the regression model which accounted for 25% of the overall

variance (R = 0.50, R^2 = 0.25). To assess the additional value of the ADE factor, ADE factor score was entered second resulting in an R value of 0.603 (R^2 = .364). Both steps added significantly to the model and both β values were significantly different from zero ($p < 0.001$ for both predictors). In addition, confidence intervals for both were above zero, and so the model would appear to be generalisable to a wider PD population.

However, residuals failed the K-S test for normality of distribution, thus violating the assumption of homoscedasticity i.e. that residuals are equal at all levels of the predictor variable. This point is well illustrated by Figure 6.4, where a 'funnelling' of cases is apparent, with greater residuals for those cases with higher predicted values. An examination of outliers with residuals of greater than two showed that the predicted value for VH summed score underestimated the actual value for several patients who scored highly on the summed score. In other words, the model appeared to be serving those who *do* show hallucinatory phenomena poorly, with greater residuals at that end of the scale.[1] An examination of outliers and residuals revealed two cases with residuals of greater than three (which were therefore not well represented by the model) and further three cases which were exerting excessive leverage over the model (centred leverage value >0.78 for 2 predictors and 115 cases).

Similar problems with outliers and heteroscedasticity were found when predicting the VH factor score, ADL scale, and ADE scores. In summary, the relatively low prevalence of UE and ADE symptoms in this sample led to skewing of scores, with many people scoring zero on both scales, thus compressing variance at one end of the scale. This compromises the generalisability of the model when applying it to a more impaired or more symptomatic population.

Although skewed distributions are likely to be inherent in studies of low-baseline events, extending the range of scores may help to raise medians and reduce skewing. For the main study it was therefore decided to extend the period considered from one to three months. This introduced an extra scale point between 'monthly' and 'never'. This should have the effect of improving the stability of correlations by reducing the number of people scoring zero.

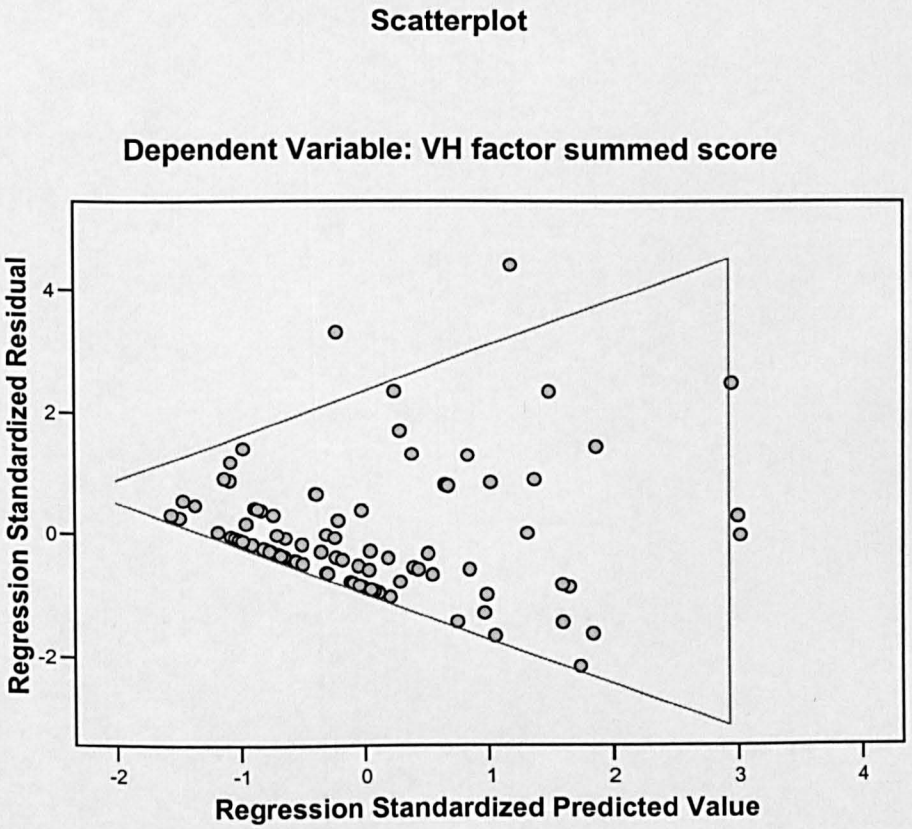


Figure 6.4 Scatterplot of standardised predicted values against studentised residuals

A second problem which may compromise internal validity is the nature of a self-report questionnaire study. This raises a number of issues, of which 'reporting-bias' is key. Those

individuals who answered yes to one item may be more likely to answer yes to all others, particularly in the context of unusual or stigmatising symptoms. Willingness to report such unusual experiences may well be related to certain personality traits, and so correlations between items will be artificially inflated for some individuals, and reduced for others.

For the main study it was decided to administer items on the QUE as part of a semi-structured interview, allowing clarification of the meaning of items. More detailed description of experiences would therefore be obtained and an experimenter rating made as to whether those reported met criteria for presence of the item. Motor symptoms would be assessed for the main study using a clinical examination of motor abilities, giving a more objective measure free from patient or caregiver reporting bias.

Thirdly, in terms of external validity, the sample was largely recruited at local branches of the PD Society and may therefore represent a less impaired group of patients. Those visiting such meetings may be more likely to have access to private transport, be less disabled, and less likely to experience stigmatising or socially 'unacceptable' symptoms, such as hallucinations or excessive somnolence. They may also have more knowledge of Parkinson's symptoms and possibly personality traits of higher extroversion and openness to experience. These may all influence experience or reporting of sleep-related and hallucinatory symptoms.

For the main study patients were recruited via clinician referral from movement disorder clinics in the North West. This would impose more stringent criteria in terms of diagnosis, and those patients with suspected DLB, PSP, MSA, or severe dementia could be avoided. It would also allow access to those patients who were effectively housebound, had access to fewer services, and those in nursing homes.

Lastly it was clear from the limited interviews carried out during the pilot study that daytime sleepiness and fatigue were prominent problems for PD patients and should be included in the assessment. It is possible that daytime sleepiness was associated with clinical variables and hallucinatory symptoms in some pattern other than SA or ADE. Motor activity during sleep, for example, was so extreme in some patients that caregivers or patients had been injured. An extra item assessing this RBD type behaviour was therefore added.

The flaws described may well have compromised the internal validity of the pilot study model and its generalisability to other PD patients, but methodological changes for the main study were designed to address these problems. Despite flaws, the pilot study revealed the benefit of taking a factorial approach rather than (i) assuming all 'unusual' symptoms to be homogenous, (ii) looking for specific patterns of associations for each symptom cluster, and (iii) covarying major predictors, such as disease severity.

6.2 Main study

6.2.1. Patient Demographics

78 PD patients were recruited with a mean age of 74.4 (± 7.9) and a range from 52 to 93 (Table 6.12). 65.4% of patients were male, in agreement with the two-thirds estimated male prevalence. The mean disease duration was 5.7 years (± 5.3) and ranged from 3 months to 24 years. The mean age at disease onset (taken as time of diagnosis) was 68.4 (± 9.2) and the minimum age at onset was 46, and therefore no participants fell into the 'early-onset' category of below 40. At phase one, two patients were unmedicated, 69 were on levodopa (L-DOPA) (either alone or in combination with other drugs) and the remaining 7 were on DA agonists or selegiline as the primary therapy.

The main study used the motor severity section of the UPDRS to assess disease severity giving a possible range of 0 to 52 points. Scores ranged from 8 to 35 with a mean of 21.2 (± 6.8). The 'fluctuations' score was derived by summing item scores on the complications of therapy section of the UPDRS, with a possible total of 20. The mean score was 2.6 (± 2.8) and the median 2, indicating that response fluctuations were experienced only by a subgroup of patients.

	Mean (± SD)	Range
Age at time of test	74.40 (7.88)	52.0 – 93.0
Age at onset	68.42 (9.16)	46.0 – 89.0
Disease duration (years)	5.73 (5.30)	0.3 – 24.0
Medication duration (years)	5.60 (5.41)	0.0 – 24.0
Total for motor scale UPDRS	21.17 (6.75)	8.0 – 35.0
Total fluctuations score UPDRS	2.59 (2.78)	0.0 – 12.0

Table 6.12 Descriptive statistics for clinical variables for the main study

6.2.2.1 Individual items

Frequencies for QUE items were considered for the last 3 months and the range of scores was from 0-5 for each item rather than 0-4 as discussed in the previous section. This allowed for an extra level on the scale for 'once during the last 3 months'. Consequently higher medians were achieved than for the pilot study.

Item	% age at all	Median	Not at all	1-2 times	1-2 month	1-2 week	Most days	Daily
Physical fatigue	89.5	3	8	6	8	21	21	12
Drowsy in day	96.1	4	3	3	5	9	29	28
Naps during day	92.2	4	6	2	4	12	29	24
Waking many times	67.5	2	25	12	5	4	12	19
Hypnogogic imagery	13.0	0	67	3	1	3	1	2
Vivid dreams	37.7	0	48	5	7	14	0	3
Nightmares	26.0	0	57	13	3	3	0	1
Nightmares	26.0	0	57	13	3	3	0	1
Night terror/ panic	9.1	0	70	2	5	0	0	0
Confusion/disorientation	46.8	1.5	41	7	17	9	3	0
Sleeptalking	52.7	2	35	2	14	16	7	0
Motor activity during sleep	58.7	0	31	6	10	17	8	3
Injury during sleep	27.3	0	56	11	9	0	1	0
Sleepwalking	5.2	0	73	2	1	0	1	0
Spots/ zigzags	20.8	0	61	7	4	3	1	1
Flashing lights	19.5	0	62	5	5	3	1	1
Patterns moving	36.8	2	48	4	10	7	3	4
Peripheral movement	68.4	0	24	8	7	27	5	5
Misrecognition object	23.7	0	58	3	7	4	2	2
Illusion of presence	35.5	0	49	3	13	6	1	4
Deja vu	13.3	0	65	6	3	1	0	0
Derealisation	16.0	0	63	6	4	1	0	1
Misrecognition person	8.1	0	68	3	2	0	1	0
Flashbacks shock	0.0	0	75	0	0	0	0	0
Interaction with vivid memories	1.3	0	74	0	0	0	1	0
Complex visual hallucination	23.7	0	58	5	1	8	3	1
Auditory hallucination	10.5	0	68	3	4	1	0	0
Tactile hallucination	25.0	0	57	4	9	4	1	1
Olfactory hallucination	6.6	3	71	2	2	1	0	0

Table 6.13 Frequencies for QUE items for main study

6.2.2 Factor structure of sleep and hallucinatory items for the main study

As with the pilot study, QUE scales were examined factor analyses conducted to detect smaller clusters of symptoms. The stability of the factor solutions for the pilot study was therefore assessed using this (slightly smaller) sample.

6.2.2.1 Unusual perceptual experiences and hallucinations

In keeping with the findings of the pilot study, items from the UE and hallucinations scales were pooled and those with frequencies of less than 10% excluded. Excluded items were misrecognition of people, 'flashbacks', and interaction with vivid memories. Varimax rotation yielded a 4 factor solution accounting for 66.52% of the variance (Table 6.14). The first factor had loadings of > 0.550 for object illusions, illusions of presence, complex visual hallucinations, and patterns moving, accounting for 42.75% of the total variance, and consistent with the study by Fenelon et al (2000). Déjà vu was also loaded on this factor although with a loading of under the criterion of 0.55. Internal consistency of the scale was acceptable at Cronbach's α = .84.

	I	II	III	IV
Visual hallucinations				
Misrecognition object	**0.860**	0.106	0.011	0.074
Complex visual hallucination	**0.828**	0.024	0.084	0.033
Patterns moving	**0.771**	0.101	0.093	0.164
Illusion of presence	**0.699**	0.273	0.045	-0.082
déjà vu	0.542	-0.460	0.171	-0.094
Elementary VH				
Flashing lights	0.315	**0.803**	-0.017	0.015
Spots/ zigzags	0.032	**0.701**	0.320	0.009
Tactile/ peripheral				
Tactile hallucination	0.053	0.164	**0.812**	-0.119
Peripheral movement	0.438	0.074	0.566	-0.071
Derealisation				
Derealisation	0.135	0.060	-0.133	**0.903**
Auditory hallucination	0.453	0.332	-0.481	-0.376

Table 6.14 Rotated component matrix for UPEs and hallucinatory symptoms
Figures in bold represent loadings above 0.600, figures in grey loadings below 0.500

6.2.2.2 Sleep symptoms

Items from the sleep scale underwent a factor analysis with varimax rotation. These included new items; (i) 'daytime drowsiness', (ii) 'daytime napping', and (iii) 'RBD type behaviour resulting in injury'. Low frequency items excluded were 'sleepwalking' and' panic/terror during the night'. A four factor solution accounted for 65.12% of the total variance. The fatigue item was excluded as it pertained to physical symptoms rather than sleep and so may have introduce extra variance into the model. A second three factor solution accounted for 57.45 % of the total variance (Table 6.15). The first and strongest factor 'sleep activity', accounted for 22.96% of the total variance ('sleeptalking', 'motor activity during sleep', and 'RBD resulting in injury). The second factor was made up of the new items 'daytime drowsiness' and 'daytime napping', accounting for 19.68% of the variance. The third factor was interpreted as 'altered dream events' and accounted for 14.63 % of the variance. It had some overlap with the altered dream events factor from the pilot study including confusion/disorientation, vivid dream, nightmares and hypnogogic imagery (the latter loading at < 0.55), but also contained sleep fragmentation which had been loaded onto the sleep activity factor in the pilot study. In terms of internal reliability the sleep activity factor had a Cronbach's α of 0.65, and for the daytime sleep factor α = .92. The altered dream events factor however showed poorer reliability, (α = 0.53, rising to 0.54 if sleep fragmentation was excluded).

	I	II	III
Sleep activity			
Sleeptalking	**0.812**	0.140	0.014
Injury during sleep	**0.744**	0.052	-0.021
Motor activity during sleep	**0.743**	-0.058	0.106
Daytime sleepiness			
Drowsy in day	0.095	**0.951**	-0.028
Naps during day	0.015	**0.946**	-0.024
Altered dream events			
Confusion/disorientation	0.015	0.037	**0.647**
Vivid dreams	0.381	-0.183	**0.614**
Sleep fragmentation	-0.100	0.215	**0.606**
Nightmares	0.287	-0.064	**0.575**
Hypnogogic imagery	-0.090	-0.131	0.541

Table 16.5 Rotated component matrix for sleep symptoms for main studies
Figures in bold represent loadings above 0.600, figures in grey loadings below 0.500

The factors obtained for UPEs and hallucinations and for sleep items supported those from the pilot study. The similarity of concomitant variables for these factors was subsequently examined.

6.2.2.3 Characteristics of derived measures

Of the sleep factors, altered dream events was significantly correlated with disease severity as measured by the motor section of the UPDRS ($r = 0.36$, $p < 0.01$), although sleep activity was not. Neither was correlated with disease duration. The daytime sleepiness factor was not correlated with either severity or duration, but was associated with age ($r = 0.249$, $p = 0.032$). As with the pilot study VH factor scores and summed scores were correlated with severity.

	Mean (±SD)	Range	Median	Kolmogorov-Smirnov Z	Asymp. Sig. (2-tailed)	$Z_{skewness}$
Sleep activity factor	-0.01 (0.99)	4.83	-0.30	1.25	0.09	3.12
Daytime sleep factor	0.01 (1.00)	4.11	0.29	1.48*	0.02	-4.53
Altered dream events factor	-0.02 (0.96)	4.26	-0.16	0.80	0.54	3.11
VH factor	-0.01 (1.00)	5.44	-0.38	1.50*	0.02	7.33
Summed score VH factor	3.20 (4.57)	0-20	2	2.11**	0.00	7.09
Summed score 5	5.14 (5.41)	0-25	4	1.49*	0.02	5.74

Table 16.6 Distributions and skewness for derived measures for main study

6.2.2.4 Correlates of the sleep factors – replication of the pilot study

Both SA and ADE were associated with a summed score of the VH factor, and (almost significantly) with VH factor scores. However, when disease severity was covaried in a partial correlation, only SA remained significantly correlated ($r = 0.267$, $p < 0.05$; $r = 0.248$, $p = 0.05$). Discrepancies between findings in the pilot study and main study may have been to some extent explained by methodological differences, as discussed below.

	VH factor	VH factor summed score	Age	Disease duration	Medn duratn	UPDRS motor scale total	Total fluct score
Sleep activity factor	0.226	0.233*	-0.227	-0.011	-0.006	-0.100	0.072
Daytime sleep factor	0.050	0.093	0.249*	0.074	0.086	0.177	-0.033
Altered dreams factor	0.206	0.253*	0.211	0.089	0.084	0.358**	-0.067
VH factor		0.952***	-0.042	0.019	-0.005	0.173	0.070
VH factor summed score			0.011	0.092	0.073	0.246*	0.102

Table 16.7 Correlations between sleep and hallucinations factor and summed scores and clinical variables. Shown are correlation coefficients (Pearson's) * $p < 0.05$; ** p , 0.01; *** $p < 0.001$

6.2.3 Possible sources of discrepancy between pilot and main study results

The general factor structure was similar between the pilot and main studies, and therefore may be relatively stable across a wider Parkinson's population. However, equivalent factors were correlated with different clinical and disease-related variables in the two studies. The following section discusses possible sources of variation and discrepancy between the two studies. Where possible, hypotheses about sources of discrepancy are tested empirically by a series of reanalyses of data from the pilot study and the main study.

Firstly, it is likely that adding extra items, two of which formed a new factor, changed the integrity of the overall factor structure by adding new variance. This can be verified by analysing data from the main study using only the items included in the pilot study (see section 6.2.3.2). The extended range for each item (i.e. from 0-5 rather than 0-4) may have revealed a set of associations for low frequency items that were previously undetected. Replicating the pilot study with the original scale of 0-4, by collapsing the lowest two levels may address this (see section 6.2.3.3).

Secondly, participants were recruited by different means; *via* a referring consultant or from a movement disorders clinic for the main study, and from local branches of a support group for the pilot study. It is likely that the branch subject pool contained less disabled, more outgoing people, who may have had more knowledge of PD symptoms which could have influenced reporting bias. The clinic subject pool may have included more disabled people who might experience a greater degree of stigmatising or 'embarrassing' symptoms than those who attended meetings and social events. Because different severity measures were used it is not possible to directly compare disability levels. Levels of 'unusual experiences' however can be assessed with rescored scales and medians (see section 6.2.3.3).

Thirdly, differences in administration of the QUE items may have also had an effect of patterns of association. The fact that the questions were experimenter administered on the main study introduces an extra level of stringency, and the experimenter's own interpretation and bias. It was possible (in most cases) to elicit some descriptive detail about the symptoms experienced and assess whether they were describing the symptom in question. One example of how self-report and experimenter interpretations differed is that several patients reasoned that they must have been experiencing vivid dreams even though they could not recall them because they had been sleep talking or moving during sleep. However, recall was part of the criteria for having experienced vivid dreams at interview, and therefore the self-report symptoms may have contained a different pattern of associations. Administering both the self-report and clinical interview versions of the QUE to the same patients would have allowed direct comparisons, but this was not done, and would have neglected those patients too disabled to complete a paper and pencil questionnaire and without a caregiver.

Finally, the two studies also used different measures of disease severity. The pilot study used a self-reported 'activities of daily living' scale, while the main study utilised an experimenter administered clinical assessment of motor symptoms. It is possible that patients' own self-report of motor severity may have been compromised by cognitive impairment and/or lack of insight, depression and negative outlook, although it must be noted that patient and caregiver ratings were highly correlated for the pilot study. It is also possible that the two scales were tapping different motor aspects of PD, with more weighting on the clinical examination given to certain aspects of motor performance such as amplitude of movement which are too subtle for inclusion on the ADL scale, as this measure pertains to symptoms which have a direct effect on functional ability and quality of life. There is however considerable overlap in the items on the two scales and so

examining the associations with certain types of motor problems across studies may be revealing (see section 6.2.3.5).

One critical aspect of a self-report measure of motor severity is that it is influenced by personality characteristics of the participant and by a general reporting bias, or differences in awareness of, or attention to, physical symptoms. This may mean that there is much shared variance between the ADL scale and other self-report symptoms that is attributable to a reporting bias. Given that the sleep activity items for the pilot study were essentially nocturnal motor problems it may have been that there was a common tendency to report these sorts of physical symptoms, especially as these are directly observable by the caregiver. However, altered dream event items and hallucinatory symptoms may be conceptualised as 'mental' or 'internal' rather than physical, and so reporting may be subject to other influences such as willingness to admit to 'unusual' symptoms, a greater awareness of cognitive processes and/or suggestibility. Variance from this hidden variable may obscure the true relationship between hallucinations, the two sleep factors and the ADL scale. For this reason a clinical assessment would remove the influence of patient or caregiver reporting bias. However, without measures of social desirability, or suggestibility it is not possible to gauge the effect of reporting bias.

6.2.3.1 Further reanalysis and manipulations of the data

To investigate possible sources of discrepancy between the two studies four re-analyses were attempted, each time manipulating one aspect of the data to test the above hypotheses about the discrepant findings.

6.2.3.2 Re-analysis 1 - Using the same items as the pilot (excluding new items)

To assess whether the addition of three new items on the sleep scale for the main study were responsible for the different pattern of associations, a re-analysis was performed where only the items included in the pilot study sleep scale were included. If the correlates of the factors derived from the re-analysis were similar to that of the pilot study, i.e. only 'ADE' correlated with hallucinations scores once severity was covaried, then it would be likely that adding the new items was responsible for the discrepancy. To test this hypothesis a two factor solution using varimax rotation was deliberately extracted from the eight QUE items used in the pilot study. This accounted for only 46.37% of the variance and although items loaded in the same pattern as before, sleep fragmentation was included in the ADE factor. ADE (including sleep fragmentation) accounted for 29.2% of the variance, SA for 17.2%.However, sleep activity still correlated significantly with the hallucinations score, whereas altered dream events did not (Table 6.18). Only ADE correlated with motor severity, and sleep activity correlated negatively with age.

	'Pilot' summed score	VH factor score	Age at time of test	Disease duration	UPDRS Motor scale total	UPDRS fluct score total
ADE factor score	0.144	0.110	0.152	0.063	0.268*	0.016
SA factor score	0.293*	0.263*	-0.267*	0.042	-0.074	0.110
'Pilot' summed score		0.935***	0.055	0.057	0.230	0.043
VH factor score			-0.042	0.019	0.173	0.070

Table 16.8 Correlations between sleep and hallucinations summed and factor scores and clinical variables.
Shown are correlation coefficients (/Pearson's) * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Partialling out severity and disease duration left only SA significantly correlated with VH score (Table 6.19). The replication using the same items as the pilot shows a largely

similar factor structure, although the pattern of associations is not the same. Therefore, the introduction of the new items did not seem to be responsible for the discrepancy between the two studies.

	ADE factor	SA factor
'Pilot' summed score	.214	.342**
VH factor	.139	.273*

Table 6.19 Partial correlations between sleep and hallucinations scores controlling for motor severity score and disease duration
Shown are partial correlation coefficients (Pearson's) * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

6.2.3.3 Re-analysis 2 - Using the same items as the pilot rescored as 0-4

To assess the effect of extending the range for each item in the main study, the QUE items from the main study were rescored to give a range of 0-4 by collapsing 0 and 1 into 0, and the remaining levels were recoded (Table 6.20). It was clear that the interview imposed some extra stringency on reporting of symptoms as several items were less prevalent in the main study, including 'déjà vu', 'derealisation', 'olfactory hallucinations'. However, key variables loading on the VH factor, and sleep items other than fragmentation were not significantly different. Therefore it was not apparent that the main study population experienced more 'unusual' symptoms than their counterparts in the pilot which is counter to the hypotheses that patients would be more willing to admit to 'unusual' or stigmatising symptoms at interview.

QUE item	Pilot study		Main study		Kolg.-Smirnov Z
	%age at all	Median	%age at all	Rescored median	
QUE Waking many times	81.8	3	51.9	1	-2.396*
QUE Hypnogogic imagery	29.4	0	9.1	0	-3.241**
QUE Vivid dreams	49.1	0	31.2	0	-2.347*
QUE Nightmares	27.5	0	9.1	0	-3.014**
QUE Night terror/ panic	20.0	0	6.5	0	-2.662**
QUE Confusion/disorientation	31.5	0	37.7	0	-0.901
QUE Sleeptalking	41.4	0	50.0	0	-1.022
QUE Movement during sleep	47.7	0	50.7	1	-0.181
QUE Sleepwalking	3.7	0	2.6	0	-0.407
QUE Spots/ zigzags	30.9	0	11.7	0	-2.993**
QUE Flashing lights	17.1	0	13.0	0	-0.690
QUE Patterns moving	29.5	0	31.6	0	-0.458
QUE Peripheral movement	46.8	0	57.9	1	-1.848
QUE Misrecognition object	24.1	0	19.7	0	-0.696
QUE Illusion of presence	22.3	0	31.6	0	-1.435
QUE Déjà vu	22.5	0	5.3	0	-3.192**
QUE Derealisation	25.2	0	8.0	0	-3.004**
QUE Misrecognition person	13.6	0	4.1	0	-2.153*
QUE Flashbacks shock	5.5	0	0.0	0	-2.060*
QUE Interaction with vivid memories	4.5	0	1.3	0	-1.189
QUE Complex visual hallucination	23.2	0	17.1	0	-0.837
QUE Auditory hallucination	12.6	0	6.6	0	-1.409
QUE Tactile hallucination	19.5	0	19.7	0	-0.090
QUE Olfactory hallucination	15.2	0	3.9	0	-2.453*

Table 6.20 Percentage prevalence, medians and differences using Kolgomorov-Smirnov Test for rescored QUE items from main study data.

Forcing a two factor solution using varimax rotation using rescored items, the integrity of the original factors was compromised, and the 'sleep activity' factor (28.6% of the variance) now contained the item 'vivid dreams', and 'sleep fragmentation' again loaded on the ADE factor (17.78% of the variance). A VH factor score derived from a factor analysis on the rescored items correlates significantly with the first factor ($r = .236$, $p = .047$) but not with the second factor, which correlated with UPDRS motor severity score. A partial correlation

covarying disease duration and severity leaves Factor 1 (predominantly SA items) significantly correlated with VH factor score ($r = .240$, $p = .047$) but not Factor 2.

It is clear that the extra range (i.e. 0-5) for the main study allowed a more stable factor structure, accounting for more of the overall variance, and allowing patterns of association to be teased out. However, it is also clear that simply compressing the scale for the reanalysis does not change the overall discrepancy in patterns of association between the two studies.

6.2.3.4 Reanalysis 3 - Excluding sleep fragmentation (both datasets scored 0-4)

'Sleep fragmentation' was a high frequency item which may not have allowed discrimination between individuals as it was so prevalent. It was associated with different factors in the two studies but may have done so in an arbitrary way as it loaded onto the weaker factor in both studies and in all reanalyses. It may therefore be revealing to exclude it and examine the factor structures without it.

For the pilot study the original factor structure was stable even with the removal of sleep fragmentation, and together the factors accounted for 66.38% of the model's variance, therefore removing sleep fragmentation strengthened the model (Table 6.21). However, the integrity of the factor structure for the main study was compromised, and the vivid dreams item loaded on the SA factor instead of ADE (Table 6.22). The model accounted for 50.6% of the overall variance.

	I	II
QUE Hypnogogic imagery	**0.785**	0.228
QUE Vivid dreams	**0.672**	0.460
QUE Nightmares	**0.848**	0.197
QUE Night terror/ panic	**0.783**	0.049
QUE Confusion/disorientation	**0.631**	0.172
QUE Sleeptalking	0.251	**0.794**
QUE Motor activity during sleep	0.110	**0.900**

Table 6.21 Factor structure for the pilot study excluding sleep fragmentation

	I	II
QUE Nightmares	**0.790**	0.180
QUE Night terror/ panic	**0.758**	0.014
QUE Confusion/ disorientation	**0.562**	-0.046
QUE Hypnogogic imagery	0.315	0.119
QUE Vivid dreams	0.451	**0.578**
QUE Sleeptalking	0.039	**0.772**
QUE Motor activity during sleep	0.007	**0.866**

Table 6.22 Factor structure for the main study excluding sleep fragmentation

6.2.3.5 Reanalysis 4 – Exploration of motor scales and relationship to sleep and hallucinations

The two studies used different sections of the Unified Parkinson's Disease Rating Scale to assess motor severity. The pilot used an 'activities of daily living' scale specific to Parkinsonian motor symptoms, while the main study used the motor severity and complications of therapy sections. Although assessing motor severity in different ways, there is considerable overlap of items. For each study the factor structure of the motor scales was examined, and then related to other clinical variables, sleep factors, and the hallucinations factor.

The 13 items of the pilot study ADL scale were scored 0-4 and yielded 4 factors using a varimax rotation, together accounting for 60.92% of the variance (Table 6.23). 'Dexterity' was the strongest factor accounting for 31.3% of the variance and relating to difficulty carrying out everyday tasks requiring dexterity. An 'ambulatory' factor accounting for 10.9% described difficulty getting about, and a 'swallowing' factor was less clearly defined but also contained speech, though loading at < 0.600. Tremor as a single-item factor accounted for

9.3% of the variance, and two items, handwriting and salivation were not strongly loaded on any factor.

	I	II	III	IV
Dexterity				
UPD Cutting food	**0.838**	-0.025	0.065	0.213
UPD Dressing	**0.813**	0.154	0.071	0.070
UPD Personal care	**0.669**	0.331	0.084	-0.189
UPD Turning in bed	0.543	0.459	0.087	-0.209
Ambulatory				
UPD Freezing	0.184	**0.759**	0.234	-0.005
UPD Walking	0.011	**0.756**	-0.193	0.178
UPD Falling	0.257	**0.632**	0.368	0.015
Swallowing				
UPD Swallow/choke	0.027	-0.016	**0.785**	0.150
UPD Parasthesiae	0.012	0.114	**0.631**	0.017
UPD Speech	0.370	0.153	**0.579**	-0.325
Tremor				
UPD Tremor	0.056	0.074	0.080	**0.885**
UPD Saliva	0.440	0.023	0.442	0.227
UPD Handwriting	0.423	0.226	0.361	0.396

Table 6.23 Rotated component matrix for UPDRS ADL scale items
Figures in bold represent loadings above 0.600, figures in grey loadings below 0.500

The ambulatory factor correlated with age ($r = .251$, $p = .014$) and both ambulatory and dexterity correlated with disease (and medication) duration ($r = .371$, $p < .001$; $r = .252$, $p = .010$). Correlations with QUE factors are outlined in Table 6.24

	Age	Disease duration	Medcn duration	Altered dream events factor	Sleep activity factor	VH factor	VH factor summed score
Dexterity factor (ADL)	0.021	0.252*	0.283**	-0.023	0.220*	0.316**	0.292**
Ambulatory factor (ADL)	0.251*	0.371***	0.357***	0.194	0.154	0.243*	0.231*
Speech factor (ADL)	-0.083	0.134	0.120	0.358***	0.241*	0.382***	0.406***
Tremor factor (ADL)	0.095	0.021	0.016	-0.089	0.205*	0.049	0.130

Table 6.24 Correlations between ADL scale factors and clinical, sleep and hallucinatory variables Shown are correlation coefficients (Pearson's) * $p < 0.05$; ** p , 0.01; *** $p < 0.001$

For the main study, 20 items scored 0-4 were used from the motor examination and complications of therapy sections. Those items scored 0 or 1 were left out of the factor analysis. A six factor solution was obtained from varimax rotation, accounting for 69.2 % of the variance (Table 6.25). The strongest factor (29.0% of the variance) appeared to represent an 'ambulatory' factor including gait, standing, falling, posture and balance. A second 'dexterity' factor (13.7% of the variance) contained items largely related to manual dexterity, and a third (8.8% of the variance) represented dyskinesias. A 'face' factor including facial expression and speech accounted for 6.9% of the variance, two tremor items comprised a 'tremor' factor (5.6% of the variance) and 'Offs and freezing' together comprised the final factor (5.2% of the variance).

	I	II	III	IV	V	VI
Ambulatory						
UPD Gait	**0.780**	0.309	0.045	0.104	0.133	-0.050
UPD Falling	**0.720**	0.082	-0.154	0.197	0.022	0.263
UPD Postural stability	**0.713**	0.138	0.237	0.187	0.085	0.023
UPD Standing	**0.705**	0.364	-0.019	-0.059	0.181	0.270
UPD Posture	**0.656**	0.239	0.038	0.278	0.050	-0.063
Dexterity						
UPD Pron/Sup	0.216	**0.781**	0.027	0.164	0.207	-0.008
UPD Leg agility	0.211	**0.682**	0.124	-0.244	-0.033	0.163
UPD Open/close	0.154	**0.672**	0.163	0.204	0.393	-0.090
UPD Finger taps	0.245	**0.663**	-0.045	0.343	0.093	-0.016
UPD Bradykinesia	0.366	**0.630**	-0.052	0.250	-0.091	0.028
UPD Rigidity	0.056	0.535	-0.238	-0.022	-0.042	0.078
Dyskinesias						
UPD Propoprtion dyskinesias	0.076	0.025	**0.922**	0.102	-0.031	0.153
UPD Disability dyskinesias	0.079	-0.005	**0.916**	0.031	-0.042	0.076
UPD Painful dyskinesias	-0.039	-0.077	**0.753**	-0.162	-0.098	0.074
Speech						
UPD Speech	0.288	0.063	0.045	**0.839**	0.039	0.082
UPD Facial expression	0.288	0.298	-0.109	**0.723**	-0.143	0.221
Tremor						
UPD Resting tremor	0.103	0.117	-0.085	-0.189	**0.850**	-0.045
UPD Action tremor	0.131	0.047	-0.096	0.116	**0.844**	0.067
'Offs' and freezing						
UPD Proportion offs	-0.066	-0.045	0.249	0.170	0.058	**0.776**
UPD Freezing	0.286	0.157	0.068	0.031	-0.046	**0.755**

Table 6.25 Rotated component matrix for motor severity and complications of therapy items
Figures in bold represent loadings above 0.600, figures in grey loadings below 0.500

At least three factors (ambulatory, dexterity and tremor) seemed to have overlap with the ADL scale factors, supporting the use of the self-report ADL scale in terms of its conceptual consistency with the clinical examination. These similarities allow some degree of comparison of patterns of association between the two studies.

As with the pilot study, the ambulatory factor correlated with age, and ambulatory, dyskinesias and offs/freezing factors all correlated with disease duration and medication

(Table 6.26). This is consistent with the fact that dyskinesias and offs emerge over time as complications of medication. Similarly, the ambulatory factor also correlated with VH and offs/freezing scores. Tremor, however, correlated with ADE, whereas it had previously only been associated SA in the pilot study. Neither daytime sleepiness nor sleep activity correlated with any motor factors. Therefore there was no consistent pattern of association between equivalent sleep factors and motor symptom factors.

	Age	Disease duration	Medication duration	Sleep activity factor	Daytime sleep factor	Altered dreams factor	VH factor	VH factor summed score
Ambulatory factor	0.334**	0.280*	0.279*	-0.097	0.007	0.218	0.207	0.245*
Dexterity factor	0.176	0.124	0.111	-0.142	0.119	0.212	0.125	0.146
Dyskinesia factor	-0.087	0.330**	0.335**	0.021	-0.163	-0.061	0.001	-0.024
Face factor	0.084	0.008	0.017	0.105	0.205	0.083	0.041	0.096
Tremor factor	0.066	-0.026	-0.049	0.067	0.018	0.320**	0.041	0.108
Off/freezing factor	-0.200	0.370**	0.372**	0.207	0.082	0.033	0.178	0.256*

Table 6.26 Correlations between UPDRS scale factors and clinical, sleep and hallucinatory variables for main study. Shown are correlation coefficients (Pearson's) * $p < 0.05$; ** p , 0.01

Summary

The re-analyses detailed above showed that the addition of new items and the extension of the range for items could not explain the discrepancies between the two studies alone. However, re-analysis 2 suggested that the interview method may have imposed greater stringency which led to lower reported frequencies for the ADE factor and for some unusual experiences. Re-analysis 3 where the sleep fragmentation item was removed showed that for the main study the factor structure was unstable and questioned the concreteness of the division into ADE and SA alone. Finally, although the ADL scale used

for the pilot and the motor severity scale used for the main study had comparable factors, the correlates of those factors in terms of sleep and hallucinations were different. Without the benefit of having both self-report and interview data for the same patients, and without a measure of personality variables such as suggestibility or social desirability it is difficult to pinpoint the source of discrepancy if in fact it is methodological. It is possible of course that the two samples, obtained from different sources, did in fact display a different structure of symptoms. Such a difference may be due to the fact that quantifying low frequency events will always present problems of replicability unless very large samples are used.

The following chapters will examine the wider concomitants of hallucinations and UPEs beyond other self-report symptoms and disease-related variables. Two approaches to the question of what predicts hallucinations will be used; a multiple regression approach using a factor score or summed score as the outcome variable, and a group comparisons approach also utilising logistic regression which will bypass the problem of non-parametric predicted scores. The role of; (i) clinical variables (such as global cognition, IQ, and depression), (ii) 'normal' sleep variables (such as sleep duration, efficiency and, daytime sleepiness), (iii) specific cognitive abilities (such as visual object recognition), and (iv) memory and executive processes, in the genesis of hallucinations will be examined.

CHAPTER 7

CLINICAL CONCOMITANTS OF HALLUCINATIONS

The previous chapter addressed the association *within* the spectrum of 'unusual' symptoms and also *between* such symptoms and disease-related variables. This chapter examines the wider clinical concomitants of hallucinations including disease-related variables, global cognition, IQ psychological measures of anxiety and depression and behavioural impairment. Additional chapters will examine sleep-related concomitants and specific cognitive abilities and deficits, beyond the self-reported symptoms of the previous chapter.

7.0 Strategy of analysis

As discussed earlier, the majority of studies investigating hallucinations in Parkinson's Disease have used a between subjects group comparisons approach, identifying those variables on which hallucinating patients perform more poorly or display different characteristics to non-hallucinating controls. Limitations of this approach have included the failure to control for the most robust predictors, such as disease severity, and the failure to address the relative value of variables in terms of significant contributions to a predictive model beyond key predictors such as disease severity and general cognitive decline. For this reason, once group differences have been established, where appropriate further comparisons will use analysis of covariance to examine the additional effect of other predictors. A multiple regression using the hallucinations scores derived in the previous chapter will assess the contribution of variables to a model predicting severity/frequency of current hallucinations, rather than simply considering hallucinations as a dichotomous variable. The current study will also compare performance of hallucinating and non-

hallucinating PD patients with age-matched controls to assess the degree of sleep and cognitive deficits in terms of a healthy ageing population.

7.1 Descriptives for clinical variables

As described in the previous chapter, 78 patients diagnosed with idiopathic Parkinson's Disease displayed the following characteristics on clinical variables (Table 7.1):

	Mean	Std. Dev.	Range	Min	Max
Age at time of test	74.40	7.88	41.0	52.0	93
Age at onset	68.42	9.16	43.0	46.0	89
Disease duration	5.73	5.30	23.8	0.3	24
Medication duration	5.60	5.41	24.0	0.0	24
Total for motor scale UPDRS	21.17	6.75	27.0	8.0	35
Total fluctuations score UPDRS	2.59	2.78	12.0	0.0	12
Years of FT education	10.40	2.98	14.0	6.0	20
MMSE total score	26.34	3.10	14.0	16.0	30
Full NART equivalent score	28.19	11.17	40.0	8.0	48
Mill Hill Vocabulary total score	15.04	3.29	18.0	2.0	20
Geriatric Depression Scale total	4.97	3.09	14.0	0.0	14
State Anxiety Inventory total	40.47	10.02	45.0	24.0	69
Elder Impairment Scale total	43.98	13.21	52.0	23.0	75

Table 7.1 Descriptives for clinical variables for PD patients only

The correlations shown in table 7.2 suggest an association between MMSE and age, as would be expected, and between years of education, MMSE, current and premorbid IQ. Unsurprisingly, there were also highly significant associations between the three cognitive variables; MMSE, premorbid and current IQ. There was also a relationship between cognition and depressive symptomatology, with scores on the GDS being negatively correlated with MMSE scores and current IQ, suggesting motivational factors may have affected cognitive performance.

	Years of FT education	MMSE total score	Mill Hill Vocabulary total score	Full NART equivalent score	Geriatric Depression Scale total	State Anxiety Inventory
Age at time of test	-0.052	-0.334**	0.116	0.014	0.148	-0.180
Years of FT education		0.371**	0.519***	0.558***	-0.223	-0.114
MMSE total score			0.447***	0.443***	-0.346**	-0.222
Mill Hill Vocabulary total score				0.689***	-0.276*	-0.146
Full NART equivalent score					-0.184	-0.021
Geriatric Depression Scale total						0.625***

Table 7.2 Correlations between clinical variables for Parkinson's patients only * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Thirty one gender matched control patients were tested. Performance on clinical measures for controls are shown in Table 7.3.

	Mean	Std. Deviation	Range	Minimum	Maximum
Age at time of test	70.903	5.588	25	56	81
Years of FT education	11.581	3.374	12	7	19
MMSE total score	28.871	1.024	4	26	30
Full NART equivalent score	33.548	11.298	42	8	50
Mill Hill Vocabulary total score	16.903	2.737	11	11	22
Geriatric Depression Scale total	1.645	1.889	8	0	8
State Anxiety Inventory total	32.323	8.207	33	20	53

Table 7.3 Descriptives for clinical variables for controls

Correlations between clinical variables for controls showed the expected associations between years of education and premorbid and current IQ ($r = 0.654$, $p < 0.001$; $r = 0.591$, $p = 0.001$), and between premorbid IQ and MMSE ($r = 0.479$, $p < 0.01$). There was however no relationship between age and MMSE ($r = 0.085$, p = NS) however, as all

controls were chosen to be cognitively intact there was a relative small range of scores on the MMSE.

7.2 Comparisons between PD patients and controls

Despite attempts to match for age the control group was significantly younger ($t = 2.251$, $p < 0.05$), although means for both groups were between 70 and 75. There was no difference in years of full-time education, although premorbid IQ as measured by the NART was significantly lower in the Parkinson's group ($t = -2.230$, $p < 0.05$). However, a negative effect of double vision and speech problems on NART scores cannot be ruled out in the Parkinson's group. Because of group differences in age and premorbid IQ, cognitive data were analysed using ANCOVA to determine whether these variables were statistically significant covariates. Score on the Mini Mental State Examination was significantly lower for the PD group independent of both age and premorbid IQ ($F = 8.829$, $p < 0.001$).

There were also significant differences on the Geriatric Depression Scale and the State Anxiety Inventory with PD patients scoring more highly ($t = 6.491$, $p < 0.001$; $t = 3.856$, $p < 0.001$).

7.3 Concomitants of hallucinations

7.3.1 Group comparisons on clinical variables

As described in the methods section, Parkinson's patients were assigned to one of three groups according to their experience of unusual perceptual experiences and hallucinations, reported by themselves at interview, or by their CG. Groups, including control participants were compared on all clinical variables using one-way ANOVA as most variables were normally distributed.

	Means (SD)				
	Non-hall	UPE	Hall	Controls	F
Age at time of test	71.82 (± 7.46)	77.64 (± 8.81)	75.14 (± 7.40)	70.90 (±5.59)	4.069**
Years of FT education	10.83 (± 3.05)	10.63 (± 2.77)	9.96 (± 3.03)	11.58 (±3.37)	1.262
MMSE total score	27.93 (± 1.90)	26.57 (± 2.65)	25.03 (± 3.45)	28.87 (±1.02)	14.891***
Mill Hill Vocabulary total score	16.00 (± 2.00)	14.92 (± 2.91)	14.29 (± 4.09)	16.90 (±2.74)	4.019*
Full NART equivalent score	29.70 (± 12.07)	24.62 (± 8.85)	28.36 (± 11.21)	33.55 (±11.30)	2.261
Geriatric Depression Scale total	4.64 (± 2.70)	5.14 (± 3.80)	5.14 (± 3.09)	1.65 (±1.89)	10.100***
State Anxiety Inventory total	41.32 (± 10.57)	37.09 (± 8.03)	41.32 (± 10.42)	32.32 (±8.21)	5.532**

Table 7.4 Group comparisons between controls and 3 PD groups on clinical variables. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Bonferroni post-hoc tests identified the significant difference in age to be between controls and the UPE group only so there was no clear effect of age for hallucinating status. MMSE was found to be significantly reduced in hallucinating patients as compared to controls and non-hallucinating PD patients ($F = 14.89$; $p < 0.001$) (See Figure 7.1). Scores for the UPE group fell between those for hall and NH. ANCOVA confirmed that this effect was significant even after age, premorbid IQ and depression were covaried ($F = 10.139$, $p < 0.001$).

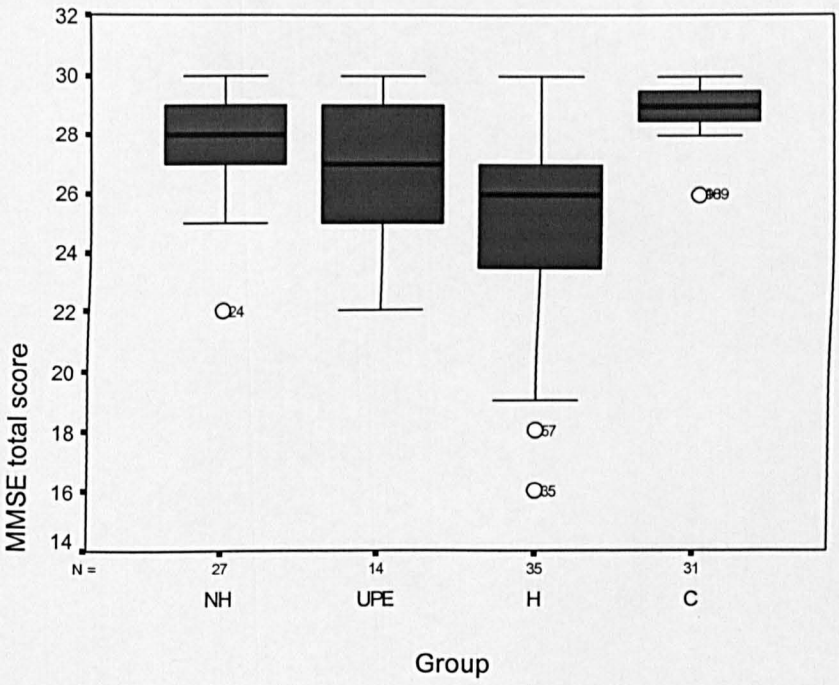


Figure 7.1 Boxplots for MMSE score by group

Chi-square comparisons revealed that a near significant difference in the number of patients in the hallucinating group who attained scores on the MMSE that fell below the 24/30 cut-off which is indicative of dementia ($\chi^2 = 5.434$, $p = 0.066$). Data from the control group was not included in this analysis as controls were chosen on the basis that they were not cognitively impaired.

MMSE score	Non-hall	UPE	Hall	Controls
24 +	26	11	26	31
23 or less	1	3	9	0

Table 7.5 Frequencies of patients scoring below cut-off on MMSE

Current IQ as measured by the Mill Hill vocabulary test was also reduced in hallucinating patients, although post-hoc test revealed this was significantly lower only compared to the age-matched control group ($F = 4.019$; $p < 0.05$). This effect remained significant after age, premorbid IQ and depression were covaried ($F = 3.184$, $p < 0.05$). There were no

significant differences in premorbid IQ however, when comparisons were made across the four groups (F = 2.261, p = 0.086).

Scores on the GDS were significantly lower for all PD patients compared with controls (F = 10.000; p < 0.001), but no differences between the three PD groups were evident. Similarly, state anxiety scores were also lower for hallucinating and non-hallucinating patients as compared to controls (F = 5.532; p = .002), although not for the UPE group.

7.3.2 Group comparisons of disease-related variables

	Means (SD)			
	Non-hall	UPE	Hall	F
Disease duration	4.43 (±4.81)	7.41 (±6.45)	6.15 (±5.12)	1.635
Medication duration	4.37 (±4.86)	7.25 (±6.56)	5.98 (±5.31)	1.436
Total for motor scale UPDRS	18.00 (±5.77)	21.71 (±5.34)	23.49 (±7.11)	5.853**
Total fluctuations score UPDRS	1.71 (±2.89)	3.07 (±2.59)	3.12 (±2.66)	2.284
Ambulatory factor - UPD	-0.41 (±0.92)	0.35 (±0.83)	0.12 (±0.99)	3.558*
Dexterity factor - UPD	-0.19 (±1.03)	-0.18 (±1.09)	0.19 (±1.01)	1.147
Dysk/Rigid factor - UPD	-0.08 (±1.03)	0.31 (±0.94)	0.07 (±1.07)	0.594
Face/speech	-0.19 (±0.97)	-0.30 (±0.95)	0.22 (±0.93)	1.994
Tremor factor - UPD	-0.08 (±0.74)	0.59 (±1.07)	0.06 (±1.09)	1.930
Off/freezing factor - UPD	-0.38 (±0.91)	0.13 (±0.84)	0.20 (±0.91)	3.339*

Table 7.6 Group comparisons between 3 PD groups on disease-related variables
* $p < 0.05$; ** $p < 0.01$

No differences in disease duration or duration of medication were apparent between the PD groups. However, the total score for the UPDRS motor scale (worst side) was significantly higher in the hallucinating, than the non-hallucinating group (F = 6.624; p <0.01). Scores for the UPE group fell between those for the other two groups.

Comparison of factor scores on the UPDRS for chosen items revealed a significant difference between hallucinators and non-hallucinators on the Off/freezing factor (F = 3.415; p < 0.05), post-hoc tests showed that hallucinators scored more highly on this factor. Although ANOVA also indicated differences on the ambulatory factor, the effect

was not strong enough for differences on Bonferroni's post-hoc test for multiple comparisons.

7.3.3 Relationship between disease-related and clinical variables

	Medication duration	Total for motor scale UPDRS	Total fluctuations score UPDRS	Ambulatory factor - UPD	Dexterity factor - UPD	Dysk/Rigid factor - UPD	Face/speech	Tremor factor - UPD	Off/freezing factor - UPD
Disease duration	0.997***	0.260*	0.488***	0.274*	0.116	0.337**	0.026	-0.004	0.367**
Medication duration		0.251*	0.499***	0.274*	0.103	0.342**	0.034	-0.029	0.370**
Total for motor scale UPDRS			0.070	0.535***	0.706***	0.022	0.243*	0.386**	0.070
Total fluctuations score UPDRS				0.053	-0.023	0.839***	0.041	-0.021	0.448***

Table 7.7 Correlations amongst motor variables. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Disease and medication duration were related to the total UPDRS motor scale and more strongly to the fluctuation score. They were also correlated with dyskinesias and the off/freezing factors, and to a lesser degree to the ambulatory factor.

	Age at time of test	Years of FT education	MMSE total score	Mill Hill Vocab total score	Full NART equivalent score	Geriatric Depression Scale total	State Anxiety Inventory total
Disease duration	0.030	-0.026	-0.036	-0.062	0.035	0.049	-0.182
Medication duration	0.038	-0.031	-0.039	-0.072	0.037	0.034	-0.180
Total for motor scale	0.347**	-0.305*	-0.472***	-0.300*	-0.208	0.233	0.069
Total fluctuations score	-0.162	0.037	-0.024	-0.133	-0.083	-0.045	0.045
Ambulatory factor	0.354**	-0.222	-0.311**	-0.120	-0.157	0.197	0.067
Dexterity factor	0.179	-0.183	-0.269*	-0.175	-0.136	0.185	0.061
Dysk/Rigid factor	-0.094	0.091	-0.025	-0.097	-0.057	-0.052	0.155
Face/speech factor	0.044	-0.048	-0.172	-0.230	-0.032	-0.136	-0.018
Tremor factor	0.038	-0.037	-0.164	-0.124	-0.073	0.089	-0.050
Off/freezing factor	-0.199	-0.126	0.009	-0.024	-0.078	0.080	-0.119

Table 7.8 Correlations between clinical and disease-related variables for PD patients only. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

An unexpected relationship between age and motor scale score ($r = 0.347$; $p < 0.01$) was largely explained by correlations between age and the ambulatory factor ($r = 0.334$; $p < 0.01$) (Table 7.8), which accounted for the greatest proportion of the variance in the 6 factor solution. This relationship between motor symptoms and age may also be explained by the fact that those patients treated by dopamine agonists were significantly younger than those treated by levodopa and COMT inhibitors alone ($t = 5.355$, $p < 0.001$). Such differences can be accounted for by prescribing guidelines for DA receptor agonists as the primary therapy for younger patients and a lack of tolerance of DA receptor agonists in older patients. However, it is likely that frailty caused by age and comorbid problems such as arthritis may have affected performance items loading on the ambulatory factor such as standing up, posture and frequency of falling.

A significant correlation ($r = -0.472$; $p < 0.001$) between MMSE and motor scale total suggests a decline in general cognitive abilities as the disease progresses. This association was still significant after covarying for age and premorbid IQ in a partial correlation ($r = -0.267$, $p < 0.05$). Accordingly, an association between current IQ and motor scale score was also evident ($r = -0.259$; $p < 0.05$ after covarying age and current IQ). Finally, there were no significant correlations between depression and anxiety and disease-related variables.

7.3.4 Correlations with hallucinations scores

Several tables of multiple correlations are presented in the results chapters. Using multiple comparisons increases the likelihood of finding a significant association at a given alpha-level, and this likelihood increases with the number of correlations performed. Therefore the risk of making a Type I error and finding a statistical association where none exists increases. To prevent this possibility, a greater stringency may be imposed using Bonferroni corrections, where the alpha-level or p value required can be adjusted according to the number of correlations. However, for the present analysis correlations were carried out for exploratory reasons, primarily to identify (i) suitable independent variables for entry into a multiple regression model and (ii) possible covariates for entry into ANCOVA, and were not used as results in themselves. Since multivariate analyses do not carry the same risk of Type I error as multiple correlations, it was felt unnecessary to use Bonferroni corrections in the present analysis.

	Age at time of test	Years of FT education	MMSE total score	Mill Hill Vocab total score	Full NART equivalent score	Geriatric Depression Scale total	State Anxiety Inventory total
VH factor summed score	0.011	-0.058	-0.267*	-0.160	-0.171	0.091	0.103
Visual hallucinations factor	-0.042	-0.038	-0.266*	-0.132	-0.196	0.063	0.112

Table 7.9 Correlations between hallucinations factor and summed scores and clinical variables. * $p < 0.05$

Of all the clinical variables, only MMSE score was significantly associated with hallucinations scores (Table 7.9); cognitive deficit was associated with higher hallucinations scores.

	Disease duration	Medication duration	Total for motor scale UPDRS	Total fluctuations score UPDRS	Ambulatory factor	Dexterity factor	Dyskinesia factor	Face factor	Tremor factor	Off/freezing factor
VH factor summed score	0.092	0.073	0.246*	0.102	0.245*	0.146	-0.024	0.096	0.108	0.256*
Visual hallucinations factor	0.019	-0.005	0.173	0.070	0.207	0.125	0.001	0.041	0.041	0.178

Table 7.10 Correlations between hallucinations factor and summed scores and disease-related variables. * $p < 0.05$

7.3.5 Review of results so far

- Group comparisons comparing hallucinators and non-hallucinators found that total motor scale score, and off periods were significantly greater in hallucinators, and that current IQ and global cognitive status were significantly lower.
- Total score on the UPDRS motor scale, factor score on the off/freezing scale and MMSE also correlated significantly with current hallucination scores.

7.4 Predictive models of hallucinations in PD - clinical variables

The 'medical model' or clinical approach which has dominated investigations of hallucinations in PD emphasises the role of medication, disease-related factors and dementing processes in predicting hallucinations. Indeed disease severity and impaired cognition have been the most robust concomitants of hallucinations in the existing literature. As this study has not attempted to quantify type and dose of medication as a single variable, disease variables and global cognitive status will be considered as the standard medical model of hallucinations in PD. The value of the medical model in terms of variance explained in a multiple regression predicting hallucinations scores.

7.4.1 Multiple regression - predicting frequency or severity of current hallucinations

Correlates of the factor scores and summed scores were MMSE, motor scale score and the off/freezing factor. As the two disease-related variables overlap conceptually and share an item, they were not both entered into the same regression. Both outcome measures were highly skewed as detailed in section 6.2.2.3, but the median of the summed score was 2 and so fewer subjects scored zero than in the pilot study.

The best model was obtained by entering MMSE score and off/freezing factor score as separate steps, to predict the VH factor summed score. The model gave a multiple R of 0.371 (R^2 = 0.137), both steps added significantly to the variance explained and had significant β weights, and the model was significant at p = 0.008. However, when predicting VH factor score MMSE alone gave an R of 0.266 (R^2 = 0.071), and the off/freezing factor score did not add significantly to the variance explained. The off/freezing factor was a more powerful predictor of hallucinations than motor scale score, primarily because less variance was shared with MMSE score, and therefore this motor variable added more value to the model. However, as discussed below the motor scale score may be a more useful variable for further analyses.

The following chapters will extend the model by adding extra variables in an attempt to improve its predictive power. The order in which the variables are added will be based on the extent to which they are supported by existing theory and literature. The first steps will therefore be clinical variables, followed by relevant sleep concomitants, and finally by specific cognitive abilities or deficits. Although the model including off/freezing and MMSE is more powerful than that including MMSE and motor scale score, representing motor severity by one factor is rather narrow. The motor scale score gives a far broader

representation of motor severity, and is therefore a better variable for use as a key covariate, just as MMSE score represents a global non-specific measure of cognitive ability. Adding the off/freezing factor into the model as well would violate the assumption of independence of predictors as an item is shared. Therefore global cognition (MMSE) and disease severity (UPDRS motor scale score) will be entered as the first step, and other variables will need to add to the variance beyond that explained by the two key predictors.

The medical model described, with MMSE and motor scale score entered as a single step gave an R of 0.299 (R^2 = 0.090), which was significant at p = 0.036 when predicting the summed score. Therefore the 'medical model' although strongly supported by the literature has relatively poor value in predicting severity of current hallucinations; only 9% of the total variance was explained. As MMSE and disease severity are likely to increase in a predictable manner as the disease progresses they emphasise the emergence of hallucinations over time. Medication factors can change relatively abruptly as dose and type of medication is altered in response to motor symptoms and the stronger predictive value of the off/freezing factor may reflect the importance of medication related factors in predicting hallucinations.

CHAPTER 8

SLEEP PATTERNS AND THEIR RELATIONSHIP WITH HALLUCINATIONS

8.0 Strategy of analysis

The following chapter examines sleep in controls and PD patients using three different methodologies; an interview on 'average' or routine sleep patterns for the previous three months, a diary of sleep parameters kept for several days, and actigraphic records of rest-activity rhythms kept over the same period. These methods were not entirely independent and diary records were used in conjunction with experimenter decision based on activity levels for setting sleep and wake times for the actigraphic analysis. Key variables collected by the three methods included nocturnal sleep variables (sleep latency, time asleep at night, time awake during the night, measures of sleep efficiency and subjective ratings of sleep quality), daytime sleep variables (a clinical rating of sleepiness, time spent napping during the day, number of naps per day) and also rest-activity rhythms derived from the actigraphic data to give an indication of circadian rhythm.

The analysis proceeded as follows:

1. Use of hypnotic medication, experiences of unusual sleep symptoms and sleep patterns assessed by the three methods was compared for PD patients and controls, using chi-square and t-tests. This comparison addressed whether the sleep symptoms experienced by Parkinson's patients are characteristic of the disease or rather of old-age alone.
2. The validity of the three methods was examined to gauge their reliability for assessing sleep disturbance in Parkinson's Disease. In particular, the validity of using actigraphy in a population with movement disorder was examined. Internal consistency of each method, and consistency between methods were assessed via correlation analysis. Equivalent

variables were compared across the three methods and where significant differences were found, discrepancies were calculated for each individual. Discrepancies were then correlated with global cognition which may have affected reliability of self-report or diary records, and with motor symptoms such as tremor or dyskinesia which may have compromised reliability of rest-activity rhythms.

3. Correlates of sleep quality were examined for both groups, and the extent to which poor sleep was related to specific motor symptoms and disease severity assessed.

4. Group comparisons were made to assess sleep parameters across the three PD groups, controlling for factors such as disease severity by using analysis of covariance.

5. The 'medical' model built in chapter 7 using multiple regression is extended to include relevant sleep-related variables. The key investigation was to determine whether sleep-related variables significantly improved the existing model.

8.1 Differences between PD patients and controls on sleep variables

8.1.1 Hypnotic medication

Data on medication revealed that 22 of PD patients used medication which may have affected sleep (other than dopaminergic medication), although only 8 used medication specifically aimed at improving sleep. Within the control group, none used hypnotics although two used antidepressants (see table 8.1)

	Hypnotics	Benzodi-azepenes	Major tranquiliser	Antidep-ressants	Opiates	Herbal remedies	'Drug free'
Control	0	0	0	2	0	1	28
PD	4	2	2	14	1	2	55

Table 8.1 Frequencies of use of medication which may affect sleep

8.1.2 Unusual sleep symptoms

Chapter 6 described occurrences of sleep-related and other unusual experiences for the period of three months prior to interview. Table 8.2 shows how PD patients and controls differed on self-reported sleep symptoms during that period, both on frequencies for each item and summed score totals for the factors derived in chapter 6. PD patients scored significantly higher on daytime sleepiness items and the summed score, sleep activity items (apart from injury during sleep) and the summed score but not on any of the altered dream events items, nor the summed score total. Although PD patients experienced more of the ADE symptoms, medians were low and group comparisons therefore not significant.

	Medians		Kolmogorov-Smirnov Z
	Control	PD	
QUE Physical fatigue	1.5	3	2.059***
QUE Drowsy in day	2	4	2.570***
QUE Naps during day	1	4	2.848***
QUE Waking many times	1	2	1.160
QUE Hypnogogic imagery	0	0	0.603
QUE Vivid dreams	0	0	0.404
QUE Nightmares	0	0	0.463
QUE Night terror/ panic	0	0	0.154
QUE Confusion/disorientation	0	0	1.467*
QUE Sleeptalking	0	1	2.337***
QUE Motor activty during sleep	0	2	1.618*
QUE Injury during sleep	0	0	0.979
QUE Sleepwalking	0	0	0.244
Total for sleep scale	9.5	17	2.198***
Summed score daytime sleepiness	2	8	2.816***
Summed score sleep activity	0	3	1.987***
Summed score altered dream events	2	5	1.260

Table 8.2 Medians for PD patients and controls on sleep symptoms and group comparisons using Kolmogorov-Smirnov Z. * $p < 0.05$, *** $p < 0.001$, significant difference between groups

Table 8.3 shows occurrence of similar items over the diary period, and differences between controls and PD patients in terms of no of individuals reporting such symptoms. Significantly more PD patients reported sleep talking and motor activity during sleep, and there was a non-significant trend towards more incidences of confusion and disorientation on waking. Occurrences of nocturnal hallucinations, injury resulting from RBD type activity and sleepwalking were confined to PD patients, though the overall frequency was too low to produce meaningful differences between groups.

		PD	Control	χ^2
Nocturnal hallucinations	No	49	31	NS
	Yes	1	0	
Upsetting dreams	No	46	30	NS
	Yes	5	1	
Night terrors/ panic	No	51	31	
	Yes	0	0	
Confusion/ disorientation	No	42	30	3.745
	Yes	9	1	
Sleep talking	No	42	31	6.145*
	Yes	9	0	
Motor activity	No	33	30	11.138**
	Yes	18	1	
RBD injury	No	48	31	NS
	Yes	3	0	
Sleepwalking	No	49	31	NS
	Yes	2	0	

Table 8.3 No of individuals reporting sleep symptoms during diary period. * $p < 0.05$; ** $p < 0.01$ significant difference between groups

Comparisons using both interview data on the previous three months and diary data over several days indicated that PD patients were more likely to experience 'sleep activity' symptoms, but that altered dream events symptoms were too infrequent to give meaningful differences.

8.1.3. Interview self-reported sleep variables

Several self-report sleep variables were skewed and did not display a normal distribution according to the K-S test, apart from total time asleep per night. For this reason non-parametric methods were used to make group comparisons between them.

	Scored	Direction	PD	Control	t	χ^2
Sleep latency (mins) [1]			<10	<10		0.023
Total time asleep (hrs)			6.32	6.48	0.251	
Total time awake in night (hrs)			1.27	1.23	0.021	
Number of wakenings[a]			2.00	2.00		3.900*
Number of times out of bed[a]			1.00	1.00		0.000
Nocturnal sleep latency (mins) [1]			<10	10-30		1.058
Self-report sleep quality[a]	1 - 5	1 = Very poor 5 = Very good	4.00	4.00		0.080
Number of unplanned naps[a]			2.00	0.50		24.348***
Total daily nap time (hrs)			1.37	0.36	17.346***	
Able to resist sleep in day ?	0 - 4	0 = Not at all 4 = Not sleepy	2.00	2.00		7.692**
Functional impact of sleepiness[a]	0 - 3	0 = No impact 3 = Much impact	0.00	0.00		3.549
Epworth Sleepiness Scale total	0 - 24	Higher = sleepier	8.28	5.16	10.669**	

Table 8.4 Group comparisons between PD patients and controls on self-report sleep variables. [a] Median values given, and χ^2 calculated for Kruskal-Wallis non-parametric test. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

No differences were observed in nocturnal sleep parameters, but PD patients experienced a greater number of naps during the day, spent longer asleep per nap, spent a greater amount of time asleep during the day per day, and also scored more highly on the Epworth Sleepiness Scale (Table 8.4). ANCOVA confirmed that the effects for time slept per day and ESS score were independent of age ($F = 14.973$, $p < 0.001$; $F = 11.761$, $p < 0.01$). In terms of subjective experience the quality of nocturnal sleep was no worse in PD patients than in healthy older adults, but daytime sleepiness was significantly increased.

8.1.4 Sleep diary records

Sleep diaries were completed by 44 PD patients and 31 controls to a reliable standard. Other diaries were incomplete or illegible and were not included in the analysis. For comparisons, mean and median values were obtained for the days recorded (Table 8.5).

	Scored	Direction	PD	Control	t	χ^2
How long awake last night ? (mins)			74.31	60.10	1.043	
How long sleep last night ? (mins)			390.00	397.29	-0.466	
No. of awakenings ?[a]			2.34	1.61		8.376**
No. times out of bed ?[a]			1.80	1.13		7.566**
Sleep quality ?	1 – 5	1 = Very poor 5 = Very good	3.37	3.52	-0.917	
Refreshed ?	1 - 4	1 = Shattered 4 = Refreshed	2.96	3.04	-0.705	
Time spent napping per day (mins)			33.29	11.87	3.610**	
No. of daytime naps per day[a]			0.94	0.35		6.603*
Mean nap time per nap (mins)			27.82	16.24	4.103***	

Table 8.5 Group comparisons of diary records for sleep between PD patients and controls [a] Median values given, and χ^2 calculated for Kruskal-Wallis non-parametric test. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Comparisons using the second means of assessment, sleep diaries, again showed significantly greater levels of daytime napping in PD patients, despite expected under reporting in this group. The effect for total time slept during the day was independent of age using analysis of covariance ($F = 9.003$, $p < 0.01$). There was however also a difference in number of reported nocturnal awakenings, with a greater number of times woken during the night, and a greater number of times out of bed for Parkinson's patients. Although use of ANCOVA is not strictly viable for non-parametric data the effects for both number of awakenings and number of times out of bed were independent of age ($F = 8.345$, $p = 0.005$; $F = 6.617$, $p < 0.05$). This suggests that the diary method may be more sensitive than interview for evaluating nocturnal events which can be quickly forgotten if not recorded the following morning.

8.1.5 Nocturnal actigraphic variables

Data for at least two nights was obtained for 66 patients and for 30 controls. The mean number of nights for which interpretable data was obtained for subjects was 5.26. Parameters derived for each night were averaged across nights to give a mean value for each variable.

Table 8.6 shows mean values for night time variables for control patients and PD patients, and t values derived from comparison.

	Control	PD	t
Assumed sleep (mins)	426.02	436.50	0.720
Actual sleep time (mins)	386.31	399.63	0.926
Actual sleep (%)	90.58	91.68	0.962
Actual wake time (miins)	39.13	36.38	-0.531
Actual wake (%)	9.42	8.32	-0.963
Sleep efficiency	75.67	76.73	0.523
Sleep latency (mins)	43.62	29.74	-2.020
Sleep bouts	29.94	23.39	-2.743**
Wake bouts	29.89	23.39	-2.719**
Mean sleep bout time (mins)	15.35	24.11	4.237***
Mean wake bout time (mins)	1.36	1.58	1.444
Immobile mins	377.87	374.82	-0.192
Immobile time (%)	88.62	85.97	-1.147
Moving mins	48.14	61.69	1.332
Moving time (%)	11.38	14.03	1.147
No. immobile phases	49.06	53.75	0.789
Mean length immobility (mins)	9.74	10.29	0.359
1 Minute immobility	14.96	18.90	1.165
1 Min immobility (%)	26.09	29.40	1.184
Total activity score	6437.97	5675.90	-0.706
Mean activity score	7.68	6.56	-0.872
Mean score in active	80.17	50.40	-2.991***
Fragmentation index	37.47	43.43	1.221
Mean wake score	121.95	65.61	-4.861***

Table 8.6 Group comparisons between controls and PD patients on nocturnal actigraphic indices. *** $p < 0.001$

Significant differences were obtained for number of sleep and wake bouts (greater for controls) and length of wake bouts (greater for PD). Control subjects also showed greater mean activity levels during wake bouts and during the daytime as would be expected for a more physically able population. The finding of greater length of wake bouts is in accordance with the greater number of awakenings and risings in the PD group; length of wake bout may be prolonged by disability if the patient needs to turn over in bed, pull up bed covers or get up to use the toilet.

However, given the nature of actigraphic assessment, group comparisons between healthy non-disabled, and movement disordered patients are confounded by the presence of motor symptoms which limit movement at some points in time and exaggerate it in others., As there was no data collected on motor abilities for controls for use in covariate analysis, and there is no means of varying sensitivity within the software for nocturnal actigraphic analysis, comparisons are of limited validity. It was therefore decided that when comparing extent of nocturnal sleep disruption in hallucinators and non-hallucinators PD patients alone would be used.

8.1.6 Daytime actigraphic variables

Parkinson's Disease can lead to reduced activity levels because of reduced amplitude of movement and disability, or increased activity levels when using wrist monitors because of severe tremors or dyskinesias. The Nap Analysis software for use with actigraphic data allows the experimenter to change the sensitivity of the nap detection algorithm by altering the threshold under which activity is assumed to represent sleep. This feature allowed the sensitivity to be adjusted for each Parkinson's patient according to overall activity levels during the day, and relative to activity levels for controls. A default sensitivity of 10 activity counts per epoch was used for control patients (a count of <10 for 10 successive epochs

marked sleep onset). Mean activity count per epoch during the day for controls was 122. For each PD patient the appropriate sensitivity for the nap analysis was calculated according to the following equation:

$$\frac{\text{Mean activity count per epoch}}{122} \times 10$$

Thus for patients with low overall activity counts the threshold was set at a lower level and therefore fewer periods of low activity were identified as sleep. For patients with high activity levels (primarily due to dyskinesias) the threshold was raised. This adjustment would lead to a more conservative estimate of sleep for those patients who appeared to be spending a lot time asleep during the day because of prolonged periods of low activity. Therefore those patients whose inactivity *was* caused by sleep might have their daytime sleep underestimated, but because according to interview data PD patients had greater levels of daytime sleepiness this imposed a greater level of stringency on group comparisons; being more conservative about PD patient sleep episodes would mean that a significant difference was all the more robust.

	PD	Control	χ^2	t
Mean no. naps per day[a]	2.60	0.70	30.920***	
Mean time napped per day (mins)	90.20	20.46		6.803***
Mean time all naps (mins)	32.15	21.59		3.393***

Table 8.7 Group comparisons between controls and PD patients on daytime actigraphic indices [a] Median values given, and χ^2 calculated for Kruskal-Wallis non-parametric test. *** $p < 0.001$

Daytime napping variables (number of naps per day, mean length per nap and total time napped per day) were all significantly greater in Parkinson's patients compared to controls

(see table 8.7). ANCOVA controlling for age showed greater total time slept per day for PD patients ($F = 19.974$, $p < 0.001$), although age also exerted a significant effect ($F = 6.564$, $p = .012$). Therefore daytime sleepiness appears to be particularly problematic for PD patients, and to a degree beyond the effect of old age alone.

8.1.7 Circadian rhythm

Non-parametric circadian rhythm analysis produced six key variables for controls and PD patients; interdaily stability (IS), intradaily variablility (IV), activity levels for the least active 5 hours (L5) and the most active 10 hours (M10), amplitude of activity (AMP) and relative amplitude (RA) (these variables are described in detail in appendix D). The use of rest-activity rhythms to represent circadian rhythm again presents a problem of confounding by the presence of motor symptoms in one group only. However the variables IS, IV and RA provide some degree of control as they consider within-subject variability, deriving values by examining variability within and across days for each individual or by providing a ratio or relative value for activity. For this reason comparisons between IV, IS and RA are expected to be most meaningful (raw measures of amplitude i.e. AMP, L5 and M10 are confounded by motor symptoms).

	PD	Control	t
Interdaily stability (IS)	0.56	0.63	-2.131*
Intradaily variability (IV)	1.18	0.79	6.603***
Least active 5 hours (L5)	879.68	901.07	-0.118
Most active 5 hours (M10)	9763.31	18907.29	-4.822***
Amplitude (Amp)	8883.63	18400.10	-5.285***
Relative amplitude (RA)	0.80	0.90	-4.334***

Table 8.8 Group comparisons of non-parametric rest-activity rhythm between PD patients and controls. * $p < 0.05$; *** $p < 0.001$

Significant differences were obtained for five of the variables including IV, IS and RA (table 8.8). Intradaily variability may be expected to be greater for PD patients because of fluctuations in response to medication, but IS should be less susceptible to medication related fluctuations if daily timings for medication are adhered to. The finding of significantly lower stability in circadian rhythm for PD patients is independent of age using ANCOVA ($F = 3.955$, $p = 0.050$). Relative amplitude gives a ratio measure of amplitude between L5 (the individuals 'night') and M10 (the individuals 'day') relative to overall amplitude which is reduced in PD patients compared to controls, and this effect is also independent of age ($F = 9.085$, $p = 003$). This suggests that PD patients have a relatively more active or disturbed night compared to day, or, as confirmed in previous sections, a more inactive or somnolent daytime.

8.1.8 Summary

i) Group comparisons between PD patients and controls found that the PD group displayed greater levels of sleeptalking and motor activity during sleep during both the previous 3 months and the diary period, but that there were no differences on 'altered dream events' type symptoms, possibly because of very low frequencies.

ii) Increased levels of daytime sleepiness were found using all three methods of data collection; via subjective and objective means and controlling for overall activity levels using the actigraphic technique. This effect is independent of age and is apparent in terms of actual time spent sleeping, number of naps and 'sleepiness' as measured by the ESS, a subjective clinical scale. Nocturnal sleep however was not consistently different, although PD patients reported more nocturnal awakenings in their diary records.

iii) Greater levels of variability in rest-activity rhythm, within and across days suggest a greater level of circadian rhythm disruption in PD patients compared to healthy older

adults. However, caution is needed when comparisons are made without a necessary covariate for motor status.

8.2. Validity and reliability of data collection – which methods are reliable ?

The following section addresses issues of validity and reliability for three methods of collecting data on sleep, interview, diary and actigraphy. Compliance rates for the diary and actigraphy are considered first. Internal consistency of answers on both interview and diary measures is addressed by examining correlations between variables and whether they are significant and in the expected direction. Consistency or agreement between the three methods is considered using two different approaches; firstly correlating equivalent variables using means, and day by day correlations for diary and actigraphic variables, and secondly by comparing values for equivalent variables. Where significant differences are obtained for two methods a discrepancy will be calculated for each subject, and this discrepancy correlated with cognitive status and motor status to assess the impact on subjective and objective methods.

8.2.1 Compliance rates for sleep data collection

8.2.1.1 Compliance rates for diaries

Diaries were completed to a standard that was considered reliable and coherent for 44 patients, 56.4% of the sample. Several diaries were completed by the CG on behalf of the patient, and where the patient was not able to give answers i.e. for awakenings that were not recalled, nocturnal vocalisations and motor activity and for daytime napping CG reports were used. Some patients who were living alone and found writing to be problematic were not asked to complete diaries, and for the purposes of actigraphic parameter setting typical self-reported bedtimes were used along with the movement record itself. Other

patients found the diaries time consuming and gave up or filled them in illegibly or infrequently. It appeared that the daytime napping section and the section for recording times the watches were removed were filled out less reliably than nocturnal records. All control subjects completed the diaries to a satisfactory standard and overall, entries were more comprehensive than for the PD group.

8.2.1.2 Compliance for actigraphic variables

Actigraphic data was obtained for 67 PD patients, 85.9% of the sample. Two patients were not given the watches because of concerns that they may remove them and lose them, one patient refused to wear one, and three took them off after a short period or wore them too infrequently for data to be meaningful. The data collected for five other patients failed to download correctly or were lost due to battery failure. As described in the methods section, diary entries were used in conjunction with activity count, experimenter's judgement and interview data in order to set times for bed time and in effect sleep onset, and for time risen. Therefore even in the absence of a complete diary record, actigraphic data could still be interpreted.

8.2.2 Internal consistency with the three methodologies

8.2.2.1 Associations amongst self-report variables - were they consistent ?

Data collected from interviews with elderly and possibly cognitively impaired patients may compromise the veracity of responses, and also the consistency between responses to different questions, i.e. the internal consistency of the overall sleep patterns. In order to asses the consistency of self-report, the variables were correlated with one another (full correlation tables for self-report and diary measures are shown in Table E.1, Appendix E).

Correlations between self-reported sleep variables showed good internal validity across the whole PD sample with total time asleep correlating negatively with total time awake in the night ($r = -0.681$, $p < 0.001$) number of times woken ($r = -0.312$, $p = 0.007$), and nocturnal sleep latency ($r = -0.725$, $p < 0.001$). Time awake during the night correlated positively with number of times woken ($r = 0.334$, $p < 0.001$) and nocturnal sleep latency ($r = 0.788$, $p < 0.001$). Furthermore, overall subjective rating of sleep quality on a five point scale from very good to very poor correlated positively with total time asleep ($r = 0.432$, $p < 0.001$), and negatively with total time awake ($r = 0.594$, $p < 0.001$), number of times woken ($r = -0.405$, $p < 0.001$) and nocturnal sleep latency ($r = 0.725$, $p < 0.001$).

Daytime sleepiness measures of number of naps taken, total time spent napping during the day, difficulty resisting sleep during the day and the degree of subjective nuisance caused by daytime sleepiness were all highly correlated with one another at $p < 0.01$ or less. In addition total score from the ESS was correlated with all daytime napping variables.

This pattern of results suggests that the ability to give consistent reports of average sleep quality is maintained in this patient population. However, interviews suggested that patients may underestimate degree of daytime napping in comparison to their CGs and in such cases the report of the CG was usually taken.

8.2.2.2 Associations amongst diary variables

For diary variables, a similar pattern of associations was observed; mean time spent awake at night correlated with number of awakenings ($r = 0.365$, $p = .011$) and negatively

with time spent asleep, subjective sleep quality and feeling refreshed on waking ($r = -0.452$, $p = .001$; $r = -0.460$, $p = 0.01$; $r = -0.426$, $p = .003$). For daytime sleep, time spent napping per day, number. of naps per day and mean time per nap were all significantly correlated (all at $r > 0.427$, $p < 0.002$). (See Table E.2, Appendix E.)

8.2.2.3 Associations amongst actigraphic variables

Actigraphic values were internally consistent as the software calculates parameters based on objective activity patterns, and parameters are to some extent dependant upon one another.

Therefore subjective reports for sleep patterns for the previous three months and during the diary period appear to be internally consistent, suggesting that PD patients are able to give internally reliable reports.

8.2.3 Agreement between sleep methodologies

A second issue is whether there is external validity of variables when compared to equivalent variables obtained using different methodologies.

8.2.3.1 Diary variables versus self-report variables

As mentioned above (section 8.2.1) compliance was rather poor for the diaries, and it was clear that many patients (and CG) found them difficult to complete. It was therefore important to assess the level of agreement between diary reports and interview reports for the same individual. Correlations between similar variables were performed to investigate this (see table 8.9)

		Self-report interview variables						
		Sleep latency	Total time asleep	Total time awake in night	Number of awakenings	Number of times out of bed	Nocturnal sleep latency	Self-report sleep quality
Diary variables	How long awake last night ?	0.328*	-0.388**	0.526***	0.406**	0.096	0.288	-0.339*
	How long sleep last night ?	-0.178	0.658***	-0.374**	-0.174	0.054	-0.253	0.183
	No. of awakenings ?	0.214	-0.151	0.014	0.564***	0.410**	0.001	-0.175
	No. times out of bed ?	0.107	0.050	-0.083	0.379**	0.618***	-0.239	0.006
	Sleep quality ?	-0.197	0.054	-0.080	-0.248	-0.114	-0.126	0.482**
	Refreshed ?	-0.155	0.083	-0.158	-0.011	0.140	-0.246	0.347***

Table 8.9 Correlations between interview variables and diary variables * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Total time slept and total time awake were highly correlated for interview self-report and for diary measures. The number of awakenings and the number of times out of bed were also highly correlated. Self-reported sleep quality at interview was correlated with mean sleep quality and feeling refreshed for diary.

However, there is the possibility that a substantial number of entries were retrospectively recorded, and agreement may be artificially inflated by subjects faking entries in accordance with their typical subjective pattern, i.e. the values they gave during their self-report interview. However, it is likely that the presence of the actiwatch may have increased motivation to give a reliable account as entries could be verified by looking at activity levels. Indeed, it may be that the recorded week was unusual or more disrupted as subjects were made more aware of their sleeping pattern and so more prone to disturbance thus reducing the strength of association.

For napping variables, equivalent values correlated significantly, although modestly (see table 8.10)

		Self-report interview variables			
		Number of unplanned naps	Total time asleep during the day	Able to resist sleep in day ?	Functional impairment caused by sleepiness
Actigraphic variables	Mean time spent napping per day	0.358*	0.349*	-0.255	0.215
	No. of daytime naps per day	0.335*	0.178	-0.227	0.087
	Mean nap time over all days	0.204	0.314*	-0.350*	0.208

Table 8.10 Correlations between interview variables and actigraphic variables * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

8.2.3.2 Diary variables versus actigraphic variables

For actigraphy, the presence of motor symptoms may have affected the data obtained and made accurate recording difficult. Analysing the concordance of diary entries with actigraphy is one means of assessing the validity of actigraphic measurements in a movement disordered population, but with the proviso that diaries were, in the majority of cases, used as a guide for setting time in bed parameters and for verifying apparent napping episodes. For this reason agreement rates may be inflated. The advantage over using diary variables as compared to interview (even though compliance was lower) was that they were derived for exactly the same time period, so if the week concerned was 'out of the ordinary' then this should be apparent in both records.

Mean values for the days recorded for diaries and for actigraphy were correlated; but these revealed low agreement rates. Sleep and wake times were not significantly correlated and the only significant associations were that the number of sleep and wake bouts (actigraphy) were negatively correlated with time spent awake (diary) ($r = -0.333$, $p =$

.033; r = -0.336, p = .032), and that the number of minutes immobile correlated negatively with subjective sleep quality (r = -0.323, p = .035).

However, the agreement improved to significant levels for some variables when correlated for concordant days. Total time spent asleep correlated with both assumed sleep (r vales ranged from 0.438 to 0.647, significant at p = .002 or less) and actual sleep (values ranged from r = 0.442 to 0.590, at p = .002 or less) and minutes immobile (values ranged from r = 0.316 to r = 0.534, at p = .032 or less) for days 1-5, and for 3 nights number of immobile phases. Time spent awake correlated with sleep efficiency for one night only, and with no other variables.

The number of times woken and the number of times out of bed were the diary measures most consistently correlated with actigraphic variables. Table 8.11 shows the number of days for which actigraphic and diary variables were significantly correlated at p < 0.05.

		Actigraphic variables				
		Actual sleep (%)	Actual wake time	Actual wake (%)	Sleep bouts	Wake bouts
Diary	No. of wakenings ?	4	4	4	3	3
	No. times out of bed ?	2	3	2	2	2

Table 8.11 Number of days (of 6) for which diary and actigraphic variables were significantly correlated (p < 0.05)

Therefore, agreement was greatest on a day by day basis, rather than overall as would be logically expected. The failure of time spent awake (diary) to correlate consistently with any actigraphic variables suggests that actigraphy is poor at detecting nocturnal wake, in particular wake after sleep onset (WASO) when the participant is lying awake but still.

However, those patients with some degree of cognitive impairment may be poor at estimating length of time spent awake, especially the following morning. Subjective *number* of wakenings rather than *duration* of time awake was more consistently associated with actigraphic WASO measures, and so actigraphy appears to underestimate the length of wake bouts for PD patients. Off periods during the night may well go undetected, and the inability to turn in many PD patients may mean that many awakenings are not associated with the usual levels of motor activity.

To assess whether WASO detection was better in a population without motor disturbances, diary and actigraphic variables for controls were correlated. Agreement for control subjects was better with mean values, subjective feeling of being refreshed was correlated with a number of actigraphic indices in the expected direction and time spent awake also correlated with a number of actigraphic indices, again in the expected direction (see table 8.12).

	Immob time (%)	Moving minutes	Moving time (%)	1 Minute immob (%)	Fragmn index
Diary: How long awake last night ?	-0.396*	0.409*	0.396*	0.379*	0.404*

Table 8.12 Correlation between diary report of nocturnal wake and actigraphic variables for controls only * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Therefore, for healthy patients without disability WASO may be more easily identified. When looking at day by day agreement time slept for diary and actigraphic variables were consistently correlated (values ranged from $r = 0.563$ to $r = 0.838$; $p = .002$ or less) and WASO was consistently correlated with a number of variables in the expected direction. Subjective ratings of feeling refreshed and sleep quality were also correlated with several

actigraphic variables, most consistently with sleep efficiency (values ranged from r = 0.534 to r =0 .737, p = .003 or less for subjective sleep quality).

Mean daytime actigraphic and mean diary variables were correlated as shown in table 8.13. Agreement was poor for mean values, little better on a day by day basis, and only the number of naps was consistently correlated for the two methods (for three days out of six, r > 0.333, p < 0.05). As noted earlier, compliance for diaries was particularly poor on the daytime napping sections and it is likely that some sections left blank indicating no daytime napping were actually overlooked or ignored so that diary records underestimated levels of daytime napping.

		Actigraphic variables		
		Mean No. actigraphic naps per day	Mean time actigraphic naps per day	Mean time per actigraphic nap
Diary variables	Mean time spent napping per day	0.204	0.298	0.359*
	Mean nap time over all days	0.058	0.121	0.225
	No. of daytime naps per day	0.227	0.253	0.231

Table 8.13 Relationship between daytime diary and actigraphic variables. * p < 0.05

8.2.3.3 *Actigraphy versus interview variables*

On correlating mean actigraphic values with self-reported values and with mean diary values a similar pattern to that with diary variables was observed. Although addressing the preceding 3 months rather than the monitored period, data was more complete for interview than diary records, especially for those living alone and with poorer cognition. Assumed and actual sleep time and self-reported total time asleep were correlated (r =

.364, p = .003; r = .426, p < .001), although self-reported and diary values were use to set values for bed time and rising time and so correlations will be raised. Actual wake time and percentage wake time however were not correlated, and so again actigraphy seems to be poorer at accurately identifying WASO. Self-reported sleep latency however was more closely related to actigraphic sleep latency, although still not at a significant level (r = .223, p = .074). As with diary measures, self-reported number of awakenings and number of times out of bed were most consistently correlated with actigraphic variables and in the expected direction (see table 8.14 for values).

		Number of awakenings	Number of times out of bed
Actigraphic variables	Actual sleep (%) MEAN	-0.430***	-0.313*
	Actual wake time MEAN	0.462***	0.406**
	Actual wake (%) MEAN	0.430***	0.313*
	Sleep bouts MEAN	0.343**	0.299*
	Wake bouts MEAN	0.342**	0.295*
	Mean wake bout time MEAN	0.361**	0.355**
	Immobile time (%) MEAN	-0.316**	-0.191
	Moving mins MEAN	0.372**	0.280*
	Moving time (%) MEAN	0.316**	0.191
	No. immobile phases MEAN	0.262*	0.352**
	1 Minute immobility MEAN	0.328**	0.397**
	1 Min immobility (%) MEAN	0.355**	0.299*
	Total activity score MEAN	0.333**	0.334**
	Mean activity score MEAN	0.279*	0.257*
	Fragmentation index MEAN	0.352**	0.261*

Table 8.14 Correlation of interview variables with actigraphic variables * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

For daytime sleep variables, there was better agreement between actigraphy and interview data, with the number of naps (r = 0.296, p < 0.05), and the time spent napping (r = 0.300,

$p < 0.05$) recorded by the two methods significantly correlated. This supports the idea that naps were underreported in diary records, and so interview data may give a more reliable report.

8.2.2.4 Relationship between actigraphy and QUE factor scores

The relationship between actigraphic variables and nocturnal UEs is worth exploring, particularly to see how the presence of REM behaviour disorder may affect activity patterns at night. Unexpectedly however, the sleep activity factor of the QUE was not correlated with any of the nocturnal actigraphic indices, suggesting that incidences of RBD were not quantified by actigraphy. However, when looking at diary measures of no. of nights with reported movement during sleep (either by P or CG) no. nights correlated with total activity score ($r = -0.293$, $p = 0.049$). But, when disease duration was covaried by means of a partial correlation the association was no longer significant. The number of nights with activity reported was also correlated *negatively* with actual wake time and mean wake bout time ($r = -0.329$, $p = 0.026$; $r = -0.365$, $p = .013$). Therefore individuals with more RBD had *less* recorded wake time (or movement after assumed sleep onset) and *shorter* wake bouts. The relationship between RBD and nocturnal activity patterns is unclear, but motor activity during sleep occurs predominantly in the lower limbs, and is therefore not detected by wrist monitors.

The altered dream events factor score only correlated with assumed sleep ($r = 0.272$, $p = .030$), and so appeared to exert no real effect on night time activity patterns. According to diaries, the number of occurrences of unpleasant dreams or night terrors was very low and so correlation was not attempted. However, the degree of confusion or disorientation on

waking over the monitored period correlated negatively with sleep efficiency ($r = -0.296$, $p = .046$).

Agreement was good between napping variables, with daytime sleep factor significantly correlated with the number of naps per day ($r = 0.418$, $p = .001$) and the time spent napping ($r = 0.365$, $p < 0.01$). The SA and ADE factors were not correlated with any of the daytime napping indices.

The daytime sleep factor score also correlated, albeit modestly, with some nocturnal variables, namely actual sleep time, mean sleep bout time, immobile minutes and 1 min immobility percentage (all at $p < 0.05$), with the effect that greater daytime somnolence was related to more activity or 'wake' during the night.

Summary

i) Internal consistency within self-report interview responses and diary records appears satisfactory amongst Parkinson's Disease patients. Correlations between the three methods suggest firstly that actigraphy is poor at detecting the duration of wake periods during the night in Parkinson's patients, as agreement is better for controls. However, the number of awakenings and risings may be more accurately reflected by actigraphy.

ii) Secondly, it is likely that diary records were not completed fully for PD patients when it came to daytime napping, and that actigraphic or combined patient and caregiver estimates may be more accurate.

iii) Thirdly motor activity during sleep is not quantified in any meaningful way by actigraphy, and is confounded by periods of movement during wakefulness. It may well be

that a far shorter epoch of 1or 2 seconds is necessary to usefully distinguish between different types of activity, as is used for actigraphic identification of PLMS.

Reasons for discrepancies between the three methods are explored in the following section.

8.2.4 Discrepancies - are absolute values correct ?

Agreement may appear to be good using correlations alone, but if one means of assessment consistently under or overestimates a variable, then correlations will be high, but mean values may be significantly different. Because no gold-standard objective measure is available for this study (such as polysomnography) it is not possible to calculate sensitivity and specificity values for actigraphy as diaries cannot be relied upon as being completely accurate, especially in relation to timings. Table 8.15 shows values for five key variables for the three different methodologies.

	Diary	Actigraphy	Interview
Total time awake in night (mins)	76.82	36.38	76.19
Total time asleep (mins)	387.65	399.63	379.40
Total time asleep during the day (mins)	33.29	90.20	82.46
Number of unplanned naps	0.94	2.60	1.84
Mean time per nap (mins)	27.82	32.15	38.94

Table 8.15 Mean values for sleep variables estimated by three methods (in minutes). Shading indicates significant difference from the other two methods, on matched-pairs t-test ($p < 0.05$).

From the pattern shown in table 8.15 it appears that actigraphy underestimates nocturnal wake as compared to both interview ($t = 3.626$, $p = .001$) and diary reports ($t = 3.707$, $p = .001$), and that diaries underreport levels of daytime napping. Actigraphy is of some use in determining daytime napping periods, despite problems of 'masking' by motor symptoms, as values are consistent with interview.

8.2.4.1 Daytime napping discrepancy - is poor cognition responsible for inaccurate diaries?

Comparisons of mean values for diaries and of equivalent interview sleep parameters showed that there were no significant differences in reported time awake and asleep at night, but that diary significantly underestimated time spent napping in the day and number of daytime naps relative to interview self-reports ($t = -3.944$, $p < 0.001$; $t = -4.575$, $p < 0.001$). Discrepancies however, were not significantly correlated with MMSE and so lower cognition had no observable effect on accurate diary keeping, although it is also clear that many of those who were most impaired did not manage to complete a diary at all.

Caregiver diary records of naps for the patient were considered to have been completed reliably for more than one day for only 13 patients. Comparisons showed that total time napping and no of naps were significantly underestimated by CGs compared to actigraphic and interview estimates ($t = -3.409$, $p = .004$; $t = -2.555$, $p = .023$). Therefore diaries are not likely to be a reliable guide for conducting actigraphic nap analysis.

8.2.4.2 Actigraphic discrepancies - are motor artifacts confounding rest-activity patterns?

Discrepancies between actigraphic variables and equivalent diary or interview variables are likely to be associated with various motor symptoms which may exert effects in either direction - dyskinesias inflating levels of activity and bradykinesia, poverty of movement and general disability reducing it. Of particular interest is whether the presence of tremor, dyskinesia or off periods has an effect on activity levels. Of additional interest is whether the 'additional' or discrepant motor score of actigraphy records compared to patient/ CG reports may be attributable directly to motor artefacts.

Simple correlations between motor scores and actigraphic variables showed an association between the dyskinesia factor and sleep latency ($r = 0.282$, $p = 0.026$) and associations between tremor and a number of actigraphic indices (see table 8.16). The relationship between tremor and actigraphic indices is puzzling as tremor is actually associated with less activity at night, longer periods of immobililty and less fragmentation. It may be that tremor-dominant PD is associated with less impaired sleep, compared to other motor subtypes, but in any case the argument that the presence of tremor may inflate nocturnal activity levels is not supported. Though dyskinesia is associated with longer sleep latency it may actually demarcate the boundary between wake and sleep more clearly rather than confounding it, and it is possible that for those patients without dyskinesia and with poverty of movement, sleep latency is underestimated. The off/freezing factor was not related to any of the raw actigraphic variables.

	Sleep bouts	Wake bouts	Mean sleep bout time	No. immobile phases	Mean length immobility	1 Minute immobility	1 Min immobility (%)
Tremor factor - UPD	-0.267*	-0.263**	0.280*	-0.361**	0.274*	-0.332**	-0.275*

Table 8.16 Relationship of tremor with nocturnal actigraphic variables * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Daytime napping variables were not examined as raw values were affected by the transformation applied to the threshold value.

Discrepancies between the five key actigraphy and diary variables were calculated for mean values, and correlated with motor variables, revealing a different set of associations. Discrepancy for nocturnal wake duration between diary and actigraphy was correlated negatively with the off/freezing factor ($r = -0.346$, $p = 0.031$), whereby greater levels of offs or freezing were associated with greater *under*estimation of wake periods by actigraphy.

Therefore symptoms leading to absence of movement may confound estimates of nocturnal wake. There was no effect for dyskinesia or tremor.

Diary versus actigraphy discrepancies on daytime napping variables correlated with dyskinesias (r = -.441, p = .003 for total time napped). However, on examining the scatter plot (figure 8.1) it appears that those with high dyskinesia scores were more likely to have least discrepancy, and so those with the greatest discrepancies are those without dyskinesias. Again, motor symptoms promoting an absence or poverty of movement, such as bradykinesia or 'offs' are likely to have led to *under*estimation of activity and *under*identification of wake periods. However, mean actigraphic estimates were closer to interview estimates than diaries

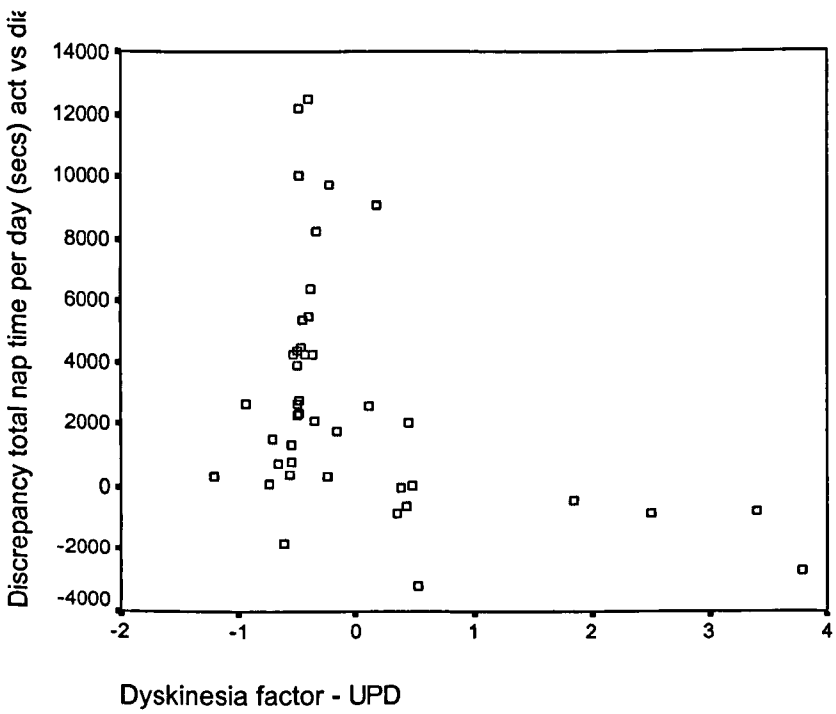


Figure 8.1 Scatterplot showing association of discrepancy scores for total daily nap time between actigraphy and diary with dyskinesias factor scores

Summary

Actigraphy has been shown to significantly underestimate duration of nocturnal wake periods compared to interview and diary records, and this discrepancy is associated with off periods. Poor compliance in keeping records of naps was evident in the PD group, and in this case actigraphy may have given a more reliable estimate of nap duration. This improvement in distinguishing wake and sleep periods during the day as compared to the night was achieved by varying the threshold for sleep detection for each individual. As such a feature was not available in the nocturnal sleep analysis software, it was not possible to take overall activity levels into account, which may well have addressed the problem of detecting nocturnal wake periods. It must be emphasised however, that none of the three methods could be validated against a gold-standard measure and so concepts of agreement and reliability remain relative rather than absolute.

8.3 Relationship between sleep variables and clinical variables in Parkinson's Disease

Nocturnal and daytime sleep variables were correlated with clinical variables to identify predictors of poor sleep patterns in PD patients, and relevant covariates for later comparisons between groups.

8.3.1 Interview variables

Sleep latency was associated with higher scores on the UPD motor scale ($r = 0.256$, $p = .029$), but there was no association between severity and time asleep, awake or number of time woken. Number of risings (in most cases to visit the toilet) correlated with longer disease duration ($r = 0.284$, $p = .015$) and also with older age ($r = 0.263$, $p = .024$).

For daytime sleep variables, the number of naps and time spent napping were correlated with greater motor severity ($r = 0.237$, $p = .048$; $r = 0.330$, $p = .005$) and with poorer cognition ($r = -0.395$, $p = .001$; $r = -0.478$, $p < 0.001$). They were also specifically correlated with scores on the face/speech factor and with dexterity, suggesting a possible role of disability; that reduced communication with CGs and inability to keep occupied with tasks requiring dexterity may lead to increased napping through lack of stimulation (full correlation tables are shown in Table E.3, Appendix E).

For control patients neither age nor cognitive status (MMSE) was correlated with any of the self-reported sleep variables.

8.3.2 Diary variables

For nocturnal variables, motor severity was not associated with any variables, although fluctuations scale total score was correlated with number of awakenings ($r = 0.334$, $p = 0.018$). Number of awakenings and risings were also correlated with disease duration ($r = 0.353$, $p = 0.011$; $r = 0.347$, $p = 0.014$). Age was not associated with any nocturnal variables. The off/freezing factor was specifically associated with wake and sleep duration and number of awakenings ($r = 0.0482$, $p = 0.001$; $r = -0.305$, $p = 0.039$; $r = 0.312$, $p = 0.035$), whereby greater off/freezing scores were associated with poorer sleep and more awakenings. For daytime variables, age, MMSE and motor severity were associated with time spent napping ($r = 0.418$, $p = 0.003$; $r = -0.341$, $p = 0.017$; $r = 0.310$, $p = 0.028$), and MMSE was associated with number of daytime naps ($r = -0.288$, $p = 0.045$).

For control patients age was correlated positively with feeling of being refreshed on waking ($r = 0.578$, $p = 0.001$), but MMSE was not correlated with any variables.

8.3.3 Actigraphic variables

Age was correlated with mean score in wake period only (r = -.261, p = .033). Global cognitive status was correlated with minutes moving only (r = -.242, p = .05). Disease and medication duration were correlated with a number or indices as shown in table 8.17, with an effect of greater activity levels at night for longer duration.

	Mean wake bout time	Total activity score	Mean activity score	Mean score in active
Disease duration	0.300*	0.376**	0.375**	0.348**
Medication duration	0.274*	0.363**	0.359**	0.345**

Table 8.17 Relationship between disease and medication duration and actigraphic indices
* $p < 0.05$; ** $p < 0.01$

Disease severity as measured by the overall UPDRS motor scale score was correlated positively with sleep latency (r = 0.275, p = 0.024), and mean score in wake period (r = 0.444, p < 0.001). The relationship with motor scale factor scores has been described in section 4.2.4.2, where tremor had the strongest relationship with actigraphic measures, and was associated with *improved* sleep quality. Dyskinesia was correlated with sleep latency but for these two factors a confounding of activity levels by the motor symptoms themselves cannot be ruled out. In addition, the dexterity factor was correlated with mean wake bout time (r = 0.293; p = .021), so higher or more impaired scores on dexterity were associated with longer bouts of wake during the night, and the remaining ambulatory, face/speech and off/freezing were not correlated with any actigraphic variables.

For napping actigraphic variables, age was correlated with both time spent napping and the number of naps (r = 0.262, p = 0.036; r = 0.299, p = 0.017), the dexterity factor was associated with the number of naps (r = 0.280, p = 0.032) and dyskinesias with less time napping (r = -0.259, p = 0.048), though this may well be due to motor artefacts.

For control patients, neither age nor MMSE were correlated with any actigraphic variables.

8.3.4 Circadian rhythm variables

The six circadian rhythm variables showed associations with several of the clinical and disease-related variables, most notably age, fluctuations score and dyskinesia factor score (see table 8.18).

	Interdaily stability	Intradaily variability	Activity L5	Activity M10	Amplitude	Relative amplitude
Age at time of test	-0.029	0.411**	0.094	-0.318*	-0.338**	-0.199
Disease duration	0.186	0.135	0.370**	0.150	0.113	-0.254
Medication duration	0.197	0.132	0.350**	0.154	0.119	-0.238
MMSE total score	0.217	-0.063	-0.058	0.188	0.200	0.323*
Total for motor scale	-0.082	0.226	0.130	-0.172	-0.193	-0.259*
Total fluctuations score	0.337**	-0.278*	0.018	0.410**	0.419**	0.175
Ambulatory factor	0.115	-0.065	0.257	0.048	0.020	-0.149
Dexterity factor	-0.106	0.276*	0.022	-0.254	-0.263*	-0.229
Dyskinesia factor	0.323*	-0.361**	-0.059	0.420**	0.438**	0.276*
Face factor	-0.227	0.193	-0.046	-0.105	-0.103	-0.097
Tremor factor	-0.150	0.191	-0.027	-0.095	-0.095	-0.047
Off/freezing factor	0.167	-0.079	-0.051	0.034	0.040	-0.040

Table 8.18 Correlation between circadian variables and clinical variables * $p < 0.05$; ** $p < 0.01$

As might be expected, older age was related to a reduction in amplitude and also with an increase in IV in accordance with previous findings. Disease duration was positively correlated with activity during the least active 5 hours or 'night', which ties in with its association with a greater number of awakenings and risings according to interview and diary. The fluctuations score and dyskinesia factor scores were, as expected, associated with greater amplitude and relative amplitude, but unexpectedly were associated with greater interdaily stability and reduced variability. This may be because they acted as a constant addition to actual activity patterns, thus masking changes in activity levels across

and within days. For this reason they should be used as a key covariate in later group comparisons. Poorer cognition and greater motor severity were significantly associated with reduced relative amplitude, which ties in their association with increased daytime sleep, which would effectively flatten relative amplitude.

Summary

i) Daytime napping, whether quantified by time or number of naps, was consistently associated with older age, poorer cognition and greater motor severity for PD patients. Accordingly, relative amplitude was associated with lower MMSE scores and greater motor severity. Of the clinical variables, disease and medication duration were associated most consistently with nocturnal variables, in particular number of awakenings and risings, and activity during the least active 5 hours. MMSE, age and overall motor severity were not correlated with night time sleep in any consistent way, although the off/freezing factor was associated with poorer sleep for diary data.

ii) Circadian rhythm analysis showed that dyskinesias and fluctuations confounded measures of variability and stability to some degree by masking underlying changes in activity, and need to be covaried in group comparisons. These were, however, taken into account during the nap analysis by varying threshold and so were not associated with napping variables.

iii) Control patients showed no consistent associations between sleep and age or cognition.

8.4. Group comparisons on sleep variables – how do hallucinators differ ?

8.4.1 Sleep characteristics for PD patients

Reported sleep problems for Parkinson's patients included problems turning at night, cramps, other pain at night and off periods. No significant differences were observed between groups using chi-square comparisons (Table 8.20). Neither were differences observed on likelihood of napping during the daytime, taking a siesta or experiencing 'sleep benefit', the transitory improvement of motor symptoms on waking. However there was a non-significant trend for greater numbers of the UPE group to experience 'cramps' or dystonia during the night ($\chi^2 = 5.616$, $p = .060$).

		Non-hall	UPE	Hall
Shares a bed with carer	Yes	10	5	13
Separate beds, same room	Yes	1	1	2
Separate rooms	Yes	6	1	8
Use of major tranquilisers or hypnotics	No	27	13	31
	Yes	1	1	4
Problems turning at night	No	9	2	10
	Yes	11	8	17
Cramps at night/ early morning	No	15	4	18
	Yes	4	7	9
Nocturnal off periods	No	17	8	22
	Yes	1	2	4
Nocturnal pain	No	13	4	15
	Yes	6	6	11
Sleep benefit	No	12	7	13
	Yes	6	2	5
Drowsiness in the day	No	5	3	1
	Yes	23	11	32
Planned siesta ?	No	19	11	25
	Yes	7	2	8

Table 8.20 Frequencies of nocturnal problems reported by PD patients

8.4.2 Group comparisons for interview sleep variables

The three PD groups and the control group were compared for interview data using ANOVA for those variables with normal distribution, and Kruskal-Wallis test for non-parametric data. No differences were found on any of the nocturnal variables, but all daytime napping variables showed significant differences between groups (see Table E.7, Appendix E) For total time spent napping ($F = 12.262$, $p < 0.001$) Bonferroni's post-hoc test revealed differences between the hallucinating group and controls and non-hallucinators, but not the UPE group. The number of naps during the day was higher for hallucinators compared to all other groups using Kruskal-Wallis comparisons ($\chi^2 = 35.121$, $p < 0.001$). For the ESS however differences were only apparent between the control group and the hallucinators and UPE group ($F = 6.526$, $p < 0.001$).

As control patients did not have data for motor status, ANCOVA comparing groups was performed for the three PD groups only. Covarying motor severity using ANCOVA revealed that there was still a significant effect for group for time spent napping and number of naps ($F = 3.537$, $p = 0.035$; $F = 5.553$, $p = 0.006$). Therefore, increased daytime napping in hallucinating patients was independent of increased disease severity. However, when MMSE score was also covaried, only the number of naps was still significantly different ($F = 4.031$, $p = 0.023$). Therefore there may be a contributory effect of poor cognitive abilities on daytime alertness.

8.4.3 Group comparisons for diary variables

Of nocturnal variables, only the number of awakenings and risings showed significant differences between groups ($\chi^2 = 10.792$, $p = 0.013$; $F = 10.153$, $p = 0.017$) but it was the UPE group that showed the highest number of awakenings. For number of risings, the

UPE and hallucinations group differed from the controls but not the non-hallucinators. Therefore there was no significant increase in number of awakenings or risings for the hallucinating group.

All daytime sleep variables showed significant differences between groups. For time spent napping Bonferroni's post-hoc test revealed differences between the control group and the hallucinations and UPE groups only ($F = 5.211$, $p < 0.01$). For number of naps ($F = 3.058$, $p = 0.033$) there were no differences according to post-hoc tests. Therefore there were no apparent differences according to diary data for hallucinating compared to non-hallucinating PD patients. This finding is at odds with the interview data, but it may well be that diaries were completed accurately for fewer hallucinating patients, as these patients were more likely to be cognitively impaired and to have less recall of napping episodes, so they may well have been underestimated. (Full tables for group comparisons are shown in Table E.8, Appendix E).

8.4.4 Group comparisons for actigraphic variables

Because of the nature of actigraphic assessment, and the fact that motor symptoms and reduced mobility might directly affect amplitude and frequency of nocturnal movement, it was decided that examination of differences between hallucinating and non-hallucinating patients would be more meaningful amongst PD patients alone. Including control patients in a four group comparison would introduce extra variance that might obscure a significant difference between the more homogeneous and therefore more comparable PD groups, particularly as a severity covariate was not available for controls. Moreover, on examining the data for some variables, it was clear controls scored more similarly to hallucinating patients than non-hallucinating patients because of the effect of motor symptoms. For example, actigraphy is likely to underestimate the level of wake after sleep onset for PD

patients because of reduced amplitude and frequency of movement and particularly difficulty turning, and so relatively increased wake in hallucinating patients might match controls in terms of raw activity count, but could actually reflect a greater amount of true wake.

	Non hall	UPE	Hall	ANOVA
	Mean (SD)	Mean (SD)	Mean (SD)	F
Mean sleep bout time (mins)	26.17 (± 15.62)	30.53 (± 18.48)	19.60 (± 9.13)	3.136*
Mean wake bout time (mins)	1.26 (± 0.43)	2.15 (± 1.07)	1.63 (± 0.66)	7.396**
Immobile time (%)	90.88 (± 4.81)	85.50 (± 9.78)	81.75 (± 13.69)	5.330**
Moving mins	39.74 (± 22.46)	65.47 (± 48.04)	79.80 (± 59.44)	5.190**
Moving time (%)	9.12 (± 4.81)	14.50 (± 9.78)	18.25 (± 13.69)	5.330**
Total activity score	3801 (± 2873)	8706 (± 9362)	6103 (± 4014)	4.082*
Mean activity score	4.32 (± 2.98)	10.06 (± 11.80)	7.13 (± 4.44)	3.975*
Fragmentation index	33.96 (± 15.65)	46.73 (± 22.62)	50.56 (± 25.88)	4.129*

Table 8.21 Group comparisons for actigraphic variables (significant differences shown only).

Table 8.21 shows group comparisons for the three PD groups for those variables with significant differences only (for full table see Table E.9, Appendix E). Post-hoc tests revealed that for mean sleep and wake bout time, differences lay between non-hallucinators and the UPE group. Similarly, for total activity and mean activity score differences were apparent between non-hallucinators and UPE only. However, for percentage immobile time, and minutes and percentage time moving differences lay between hallucinators and non-hallucinators with the effect that hallucinators spent less of the night immobile, and more moving. For the fragmentation index, differences lay between hallucinators and non-hallucinators with hallucinators showing the more fragmented pattern. As none of these three variables was associated with any motor variables, the differences appear to be due to hallucination status rather than motor artefacts. However, for the sake of caution, comparisons were repeated using ANCOVA

and covarying motor scale total score, and the effect for group was still significant on all four variables. Therefore hallucinators have a poorer sleep pattern according to nocturnal actigraphic monitoring.

	Non-hall Mean (SD)	UPE Mean (SD)	Hall Mean (SD)	F	X^2
Mean no. naps per day[a]	2.50	2.00	2.60	-	1.338
Mean time napped per day (mins)	96.53 (± 74.93)	69.98 (± 62.71)	93.54 (± 79.61)	0.545	-
Mean time per nap (mins)	34.95 (± 14.79)	29.09 (± 11.85)	31.18 (± 12.33)	0.918	-

Table 8.22 Group comparisons for actigraphic nap variables (PD groups only). Values in parenthesis represent SD All values non-significant

Differences between PD groups on daytime napping variables were not apparent using simple ANOVA and chi-square comparisons. Covariates of actigraphic napping included age and motor factor scores, but even covarying these using ANCOVA did not reveal a significant difference. Therefore, actigraphic estimates of napping, although similar to interview estimates did not detect differences amongst the three groups in degree of daytime napping.

8.4.5 Circadian rhythm variables

Table 8.23 shows the results of group comparisons using ANOVA for circadian rhythm variables.

	Non-hall	UPE	Hall	ANOVA
	Mean (SD)	Mean (SD)	Mean (SD)	F
Interdaily stability	0.60 (± 0.11)	0.64 (± 0.12)	0.50 (± 0.13)	6.911**
Intradaily variability	1.06 (± 0.38)	1.17 (± 0.39)	1.28 (± 0.32)	2.353
Least active 5 hours	589.30 (± 475.89)	1407.55 (± 1723.94)	910.82 (± 560.58)	3.437*
Most active 10 hours	9776.22 (± 5928.74)	10517.27 (± 8049.68)	9456.50 (± 9063.45)	0.072
Amplitude	9186.91 (± 5653.94)	9109.73 (± 7757.31)	8545.68 (± 8897.83)	0.050
Relative amplitude	0.87 (± 0.10)	0.77 (± 0.21)	0.75 (± 0.14)	4.301*

Table 8.23 Group comparisons for circadian rhythm variables (PD groups only). * $p < 0.05$; ** $p < 0.01$

Significant differences were obtained for three variables; interdaily stability, activity during least active 5 hours, and relative amplitude, with hallucinators showing reduced amplitude and lower IS. However, it was the UPE group who showed greatest levels of activity during L5. As the circadian rhythm variables had several clinical and disease-related concomitants (see section 8.3.4), analysis of covariance was used to control for these variables. ANCOVA comparing IS and controlling for the dyskinesia factor, showed that a significant effect for group remained ($F = 4.403$, $p = 0.017$) as well as an effect for dyskinesias ($F = 6.934$, $p = 0.011$). Relative amplitude maintained an effect for group also, independently of disease duration and dyskinesia factor ($F = 3.310$, $p = 0.045$), though effects for the covariates were stronger ($F = 7.854$, $p = 0.007$ for dyskinesias; $F = 4.822$, $p = 0.033$ for DD). Therefore, hallucinators show significantly lower stability across days and lower relative amplitude, independently of disease-related variables. Lower RA may arise from a flattening of daytime activity due to sleep episodes, as may lower IS if sleep episodes occur in a relatively random pattern. IS controls for general activity level and amplitude for each individual by looking for variability across days, but still may be

vulnerable to the effect of motor fluctuations if they vary in terms of timing and magnitude from day to day.

Summary

Three methods of data collection gave different results in group comparisons for similar variables:

Interview data found markedly higher levels of daytime sleepiness in hallucinating patients compared to other groups independently of motor severity, although low cognitive score confounded the effect for group on time spent napping.

Diary data did not reveal any significant differences for the hallucinating group compared to the non-hallucinators, only an increased number of awakenings for the UPE group.

Actigraphic data revealed significantly more time spent moving, less spent immobile, and a higher fragmentation index for hallucinators, which were independent of motor severity. However, on daytime variables no effect for increased sleep levels in hallucinators was found.

For circadian rhythm variables, interdaily stability and relative amplitude were found to be lower in hallucinators independently of disease status.

8.5 Predicting hallucinations - how do sleep variables improve the model ?

The final section in this chapter extends the models of hallucinations built in the previous chapter, and examines whether sleep variables improve predictive power of the existing model.

8.5.1.1 QUE sleep factor scores - relationship with hallucinations scores

As discussed in chapter 6, the sleep activity and altered dream events factor scores were correlated with the VH factor summed score, although 'altered dream events' factor was correlated with disease severity. Partial correlations revealed that only the 'sleep activity' factor correlated significantly with factor and summed scores independently of severity,

8.5.1.2 Interview, diary and actigraphic variables

Full correlation tables between factor and summed scores and interview, diary and actigraphic variables are shown in Appendix E (Tables E.10 to E.13).

	Interview		Actigraphy	
	Total time asleep during the day	Epworth Sleepiness Scale total	Mean wake bout time MEAN	Circadian analysis - relative amplitude
Summed score factor	0.363**	0.237	0.216	-0.237
VH factor score	0.287*	0.248*	0.288*	-0.248

Table 8.24 Correlations between sleep variables and hallucinations scores * $p < 0.05$; ** $p < 0.01$;

Of the variables derived from interview, time spent napping per day and ESS score were significantly correlated with summed and factor scores (see table 8.24). Covarying cognitive status and motor severity by means of partial correlation reduced the association between time spent napping and hallucination scores, but the association with ESS remained largely significant (see table 8.25).

	Summed score factor	VH factor score
Time spent napping	0.287*	0.211
Epworth Sleepiness Scale	0.240	0.267*

Table 8.25 Partial correlations between interview variables and hallucinations scores controlling for MMSE score and motor severity score. * $p < 0.05$

Covarying cognitive status and motor severity by means of partial correlation reduced the association between time spent napping and hallucination scores, but the association with ESS remained largely significant. No diary variables were associated with hallucinations score.

Of actigraphic variables, only the mean wake bout time was correlated with hallucinations, whereby current hallucinators have relatively longer wake bouts during the night. This variable was also correlated with dexterity factor and so partial correlations were performed to remove the motor influence of this variable, and the association remained significant ($r = 0.258$, $p = 0.045$; $r = 0.265$, $p = 0.039$).

Of circadian rhythm variables, relative amplitude was correlated with hallucinations scores, and interdaily stability was at a close to significant level ($p < 0.065$ for all scores), and these association remained significant after dyskinesias and duration were controlled for (see table 8.26), but were no longer significant when MMSE was added as a covariate. Therefore changes in circadian rhythm may well be related with the changes associated with dementing processes once motor artefacts have been taken into account.

	Interdaily stability	Relative amplitude
Summed score factor	-0.276*	-0.301*
VH factor score	-0.254	-0.268*

Table 8.26 Partial correlations of hallucinations scores and circadian rhythm variables controlling for disease duration and dyskinesia factor score. * $p < 0.05$

8.5.2 Multiple regression - predicting current hallucinations scores

As described in section 7.4.1, disease severity (motor scale score) and global cognition (MMSE score) were entered into a multiple regression as a single step to predict VH factor score, and VH factor summed score. The following section examines whether the existing predictive model, the 'medical model', can be improved by adding sleep variables. Daytime sleeping variables (time spent napping, and ESS score), QUE 'sleep activity' factor scores, circadian rhythm variables (IS and RA) and actigraphic variable mean wake bout time were correlated with hallucinations score independently of disease variables.

In a series of regressions to predict VH factor summed score, time spent napping, ESS score, SA factor score and SA factor summed score added to the model producing a significant change in R^2, and had significant β weights. Circadian variables IS and RA did not add significantly to the model largely because they shared much variance with MMSE score.

The best model predicting VH factor summed score was obtained entering disease severity and MMSE as the first step, time spent napping as the second, and 'sleep activity' factor summed score as the third. The overall model was significant at $p = 0.002$ ($R = 0.479$, $R^2 = 0.230$), and all steps added significantly to the explained variance and gave significant β weights. For the VH factor score, ESS score, SA factor score, SA summed score and mean wake bout time added to the variance explained by the medical model. The best model was obtained by adding ESS score as the second step, and SA factor summed score as the third ($R = 0.446$, $R^2 = 0.199$, $p = 0.012$).

Therefore, to predict current hallucinations score, adding daytime sleep variables (time spent napping or ESS score) and 'sleep activity' scores, significantly improves the medical model.

CHAPTER 9

NEUROPSYCHOLOGICAL PERFORMANCE AND HALLUCINATIONS

9.0 Strategy of analysis

The following chapter examines the performance of the three PD groups and controls across a range of cognitive tests, and also their qualitative performance in terms of errors made. As detailed in Chapter 4 the pattern of neuropsychiatric symptoms experienced by an individual may be reflected in their qualitative performance on neuropsychological tests; depression and negative symptoms will be reflected in performance deficits and fewer incorrect responses, or errors of commission, and positive symptoms such as hallucinations will be reflected in more frequent incorrect, inappropriate or confabulatory responses, i.e. errors of commission.

The analyses proceeded as follows:

1. Group comparisons between the PD group as a whole and the controls using T-tests will be used to confirm the presence or absence of specific neuropsychological deficits *prior* to between group comparisons between hallucinators and non-hallucinators. If differences are still apparent after controlling for age, global cognition, premorbid IQ and depression using ANCOVA, then these deficits appear to be part of the neuropsychological profile specific to PD, rather than an ageing effect.
2. The relationship between neuropsychological performance and clinical variables including age, global cognition, disease severity, depression and anxiety will be examined within the PD group as a whole using correlational analyses. This will assess the impact of disease severity

on neuropsychological performance and identify relevant covariates for further group comparisons.

3. ANOVAs will be used to compare the three PD groups and controls on six tests completed by all participants, and between the three PD groups on the remaining three tests (see Chapter 5). Where differences between hallucinators and non-hallucinators are found, ANCOVA between the three PD groups will be used to determine whether these are independent of other factors such as global cognition and disease severity.

4. The qualitative performance of participants will be described in terms of median scores for the different types of errors and subtests. Relationships between different error scores will be examined, to determine whether a composite score of errors is valid. Consideration of median raw scores, and mean scores for percentage and composite scores will determine which test statistic should be used for between group comparisons.

5. Group comparisons using the Kruskal-Wallis non-parametric test for independent group comparisons, and chi-square will be made between the three PD groups, and where possible controls for raw error scores. ANOVA will be used for group comparisons on percentage error scores and composite error scores. Where differences between hallucinators and non-hallucinators are found, ANCOVA between the three PD groups will be used to determine whether these are independent of other factors such as global cognition and disease severity.

6. The relationship between neuropsychological performance, including error scores, and the QUE factor score and summed hallucinations score will be examined using both correlations, and partial correlations, controlling for relevant covariates such as global cognition and disease severity, to identify those variables which are appropriate for a regression model.

7. A final set of linear regressions will add further steps to the model derived in previous chapters to predict QUE factor and summed scores. Neuropsychological predictors of hallucinations in PD which add significantly to the model *beyond* global cognition, disease severity, sleep-related variables and will thus be identified, and a final model presented.

9.1 Are cognitive deficits in PD due to ageing effects ?

Those cognitive deficits found in PD patients but not healthy controls may simply be the result of normal ageing processes that are not specific neuropsychological effects of PD itself. In order to establish the presence or absence of deficits in the PD group across a range of neuropsychological tests, *prior* to comparisons of hallucinators and non-hallucinators, performance of the control group was compared to that of the PD group using T-tests.

9.1.1 Group comparisons of global cognitive measures

As described in the methods section controls completed six of the nine cognitive tests, and did not complete verbal fluency, trailmaking or block design tests, for which speech and motor impairment would be a confounding factor. Section 7.2 described significantly lower MMSE, current IQ and premorbid IQ scores in PD patients, and higher depression scores. MMSE score was signifcantly lower in PD patients independently of both age and premorbid IQ.

	Means (SD)		
	PD (N=78)	Controls (N=31)	t
MMSE total score	26.34 (± 3.10)	28.87 (± 1.02)	-6.322***
Mill Hill Vocab total score	15.04 (± 3.29)	16.90 (± 2.74)	-2.746**
Full NART equivalent score	28.19 (± 11.17)	33.55 (± 11.30)	-2.230**

Table 9.1 Group comparisons between controls and PD patients on global cognitive measures using t-tests *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

9.1.2 Group comparisons of logical memory measures

PD patients scored significantly lower on all logical memory measures; immediate and delayed recall of both detail and theme, learning slope and recognition (see table 9.2).

	Means (SD)		
	PD (N=78)	Controls (N=31)	t
Logical memory Total Recall 1+2	14.21 (± 6.97)	22.84 (± 5.00)	-7.175***
Logical memory Total Recall 1+2+2	24.05 (± 11.30)	37.10 (± 7.90)	-6.786***
Logical memory Learning slope	3.28 (± 2.46)	4.48 (± 2.57)	-2.276*
Logical memory Total Recall II	12.80 (± 8.53)	23.16 (± 6.37)	-6.848***
Logical memory Total Recog	22.36 (± 3.56)	25.61 (± 2.99)	-4.421***
Logical memory Total Theme 1+2+2	12.99 (± 4.31)	17.23 (± 3.32)	-5.471***
Logical memory Total Theme II	7.27 (± 4.01)	11.48 (± 2.16)	-6.952***

Table 9.2 Group comparisons between controls and PD patients on Logical Memory using t-tests. *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

ANCOVA examined difference between PD patients and controls on memory logical measures independently of age, current IQ and premorbid IQ, and depression score. Differences remained for recall immediate and delayed recall measures ($F = 12.292$, $p = 0.001$; $F = 8.236$, $p = 0.005$; $F = 7.736$, $p < 0.007$), with significant effects also for age, premorbid and current IQ, and for depression also on delayed recall. However, no difference was evident for learning slope, and no covariates showed a significant effect. For immediate and delayed thematic recall, differences remained ($F = 4.700$, $p = 0.033$; $F = 5.706$, $p = 0.019$) with an effect also for current IQ and for depression on the delayed condition. For recognition, there was no significant effect, with an effect for current IQ and a strong effect for depression score ($F = 10.822$, $p = 0.002$) suggesting that motivation may exert a large effect on performance in recognition tests. Therefore PD patients displayed deficits in immediate and delayed recall of

detail and theme, as compared to healthy older adults, but differences in recognition were largely explained by increased levels of depression in the PD group.

9.1.3 Group comparisons for VOSP battery

Differences between PD patients and controls were evident for all but one subtest on the VOSP battery, including the 'screening test', suggesting that lower-level visual deficits may play a role on poor performance on the battery.

	Means (SD)		
	PD (N=78)	Controls (N=31)	t
VOSP Shape detection total	19.09 (± 1.57)	19.94 (± 0.25)	-4.510***
VOSP Incomplete letters total	17.69 (± 2.79)	19.06 (± 0.85)	-3.838***
VOSP Silhouettes total	17.25 (± 5.25)	20.35 (± 3.95)	-2.957**
VOSP Object decision total	15.04 (± 3.30)	18.26 (± 1.63)	-6.637***
VOSP Progressive silhouettes total	10.25 (± 3.00)	9.42 (± 3.33)	1.247
VOSP Grand total	59.90 (± 11.43)	68.45 (± 7.49)	-3.813***

Table 9.3 Group comparisons between controls and PD patients on VOSP battery using t-tests *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

ANCOVA controlling for age, current and premorbid IQ, and depressions scores left only object decision showing a significant effect for group ($F = 7.442$, $p = 0.008$). The overall total score across five tests was also non-significant, and age and current IQ showed significant effects on the total score ($F = 12.768$, $p = 0.001$; $F = 13.789$, $p < 0.001$) as well as on the silhouettes, object decision and progressive silhouettes subtests. Therefore differences in age and IQ explain poorer performance on the VOSP battery for PD patients, although there is still an effect for group on the object decision test.

9.1.4 Group comparisons for overlapping figures task

PD patients were slower to name eight object correctly on the overlapping figures test for both figures and named fewer objects correctly on both tests and overall (see table 9.4).

	Means (SD)		
	PD (N=78)	Controls (N=31)	t
Overlapping figure A time to 8 (in secs)	46.52 (± 36.53)	21.69 (± 8.96)	4.630***
Overlapping figure A total objects named	10.27 (± 2.49)	13.29 (± 1.07)	-8.638***
Overlapping figure B time to 8 (in secs)	46.60 (± 30.10)	23.41 (± 11.01)	4.798***
Overlapping figure B total objects named	10.81 (± 2.86)	13.35 (± 1.33)	-6.198***
Total figures named OFigs A + B	21.08 (± 5.02)	26.65 (± 2.24)	-7.812***

Table 9.4 Group comparisons between controls and PD patients on overlapping figures using t-tests *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

ANCOVA covaried reading speed for the timed measures as well as age, current and premorbid IQ, and depression score. For the timed measures, neither figure alone showed a significant effect for group, but a total time score (Figure A + Figure B) did show a significant effect for group ($F = 4.079$, $p = 0.048$). Significant effects were also apparent for reading speed and age ($F = 8.310$, $p = 0.006$; $F = 5.186$, $p = 0.026$). For total number of objects named an effect for group was observed ($F = 7.486$, $p = 0.008$), and significant effects for age and current IQ were also apparent. PD patients are therefore less able to correctly identify objects amongst an array of overlapping objects, and are slower to name 8 items correctly, although slower reading or vocalisation speed in the PD group accounted for much of the variance in the ANCOVA model.

9.1.5 Group comparisons for divided and undivided attention test

As expected, mean reaction-time (RT) times for both the divided and undivided condition were higher for the PD group, and standard deviations for RT were also greater showing more variation in response time as would be expected in a group with problems initiating movement. The coefficient of variation measure which considers variability taking overall response time into account, was greater in PD patients for the undivided but not the divided task (see Table 9.5).

	Means (SD)		
	PD (N=78)	Controls (N=31)	t
Standard deviation RT test undivided	286.22 (± 174.07)	124.79 (± 50.70)	6.752***
Mean RT test undivided	1353.25 (± 365.89)	944.84 (± 223.73)	6.617***
Coefficient of variation RT test undivided	0.21 (± 0.10)	0.14 (± 0.06)	3.976***
Standard deviation RT test divided	280.49 (± 171.84)	169.41 (± 120.75)	3.549**
Mean RT test divided	1367.31 (± 400.02)	961.58 (± 251.20)	5.830***
Coefficient of variation RT test divided	0.20 (± 0.11)	0.18 (± 0.12)	0.952

Table 9.5 Group comparisons between controls and PD patients on attention test using t-tests *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

As no motor assessment was made of control subjects, motor status could not be covaried. ANCOVA compared measures covarying age, current and premorbid IQ and depression scores, and for the divided condition measures reading speed also, as the secondary task involved repeated articulation a series of numbers. For mean RT for both undivided and divided conditions, there was still an effect for group ($F = 13.169$, $p = 0.001$; $F = 4.928$, $p = 0.030$) with an effect for reading speed for the divided condition ($F = 7.433$, $p = 0.008$).

However, when mean RT for the undivided condition was also covaried, there was no significant effect for group on the divided condition ($F = 0.681$, $p = 0.412$). Therefore baseline differences in choice reaction time explained a large amount of variance in a model for reaction-time in the divided attention condition ($F = 184.170$, $p < 0.001$). For standard deviation measures effects for group were still apparent ($F = 14.990$, $p < 0.001$; $F = 4.144$, $p = 0.046$), and for coefficient of variation for the undivided task a group effect remained ($F = 10.405$, $p = 0.002$). Therefore the PD group displayed more variability in reaction-time (RT) controlling for both mean RT and other variables, although the effect of motor status is unknown.

9.2 What is the relationship of cognitive performance to clinical variables?

9.2.1 Correlation of all main cognitive variables - effect of global IQ ?

It is clear that MMSE and premorbid and current IQ are highly correlated with the majority of cognitive variables. Age, motor scale score, reading speed and depression scores are also associated with many cognitive variables. Therefore much variance shared by cognitive variables may be due to global cognition, age, disease and clinical variables. To examine the relationship between different cognitive tests more thoroughly partial correlations were performed covarying age, MMSE score, current and premorbid IQ, motor scale score, reading speed and depression score. Results are shown in Table 9.6.

	Logical memory Total Recall	Logical memory Total Delayed Recall	Logical memory Total Recog	VOSP Grand total	Total overlapping figures named	Verbal fluency grand total	Block design total correct	Block design total points	Trailmaking A time (in secs)	Trailmaking B time (in secs)	Mean RT test undivided	Mean RT test divided
Logical memory Total Recall	1.000	0.840***	0.611***	0.135	0.287*	0.305*	0.364*	0.292	-0.341*	-0.123	-0.176	-0.120
Logical memory Total Del Rec	0.840***	1.000	0.606***	0.182	0.256	0.252	0.335*	0.118	-0.223	-0.096	-0.156	-0.126
Logical memory Total Recog	0.611***	0.606***	1.000	0.465***	0.457***	0.304*	0.662***	0.517***	-0.234	-0.224	-0.117	-0.090
VOSP Grand total	0.135	0.182	0.465***	1.000	0.585***	0.195	0.535***	0.372*	-0.025	-0.086	-0.083	0.067
Total overlapping figures named	0.287*	0.256	0.457***	0.585***	1.000	0.301*	0.606***	0.487***	-0.058	0.029	-0.277	-0.111
Verbal fluency grand total	0.305*	0.252	0.304*	0.195	0.301*	1.000	0.253	0.477**	-0.228	-0.307	-0.162	-0.146
Block design total correct	0.364*	0.335*	0.662***	0.535***	0.606***	0.253	1.000	0.753***	-0.282	-0.325	-0.216	-0.063
Block design total points	0.292	0.118	0.517***	0.372*	0.487***	0.477**	0.753***	1.000	-0.373*	-0.418*	-0.314*	-0.225
Trailmaking A time (in secs)	-0.341*	-0.223	-0.234	-0.025	-0.058	-0.228	-0.282	-0.373*	1.000	0.179	0.299	0.221
Trailmaking B time (in secs)	-0.123	-0.096	-0.224	-0.086	0.029	-0.307	-0.325	-0.418*	0.179	1.000	0.324	0.447*
Mean RT test undivided	-0.176	-0.156	-0.117	-0.083	-0.277	-0.162	-0.216	-0.314*	0.299	0.324	1.000	0.850***
Mean RT test divided	-0.120	-0.126	-0.090	0.067	-0.111	-0.146	-0.063	-0.225	0.221	0.447*	0.850***	1.000

Table 9.6 Partial correlations between major cognitive variables, covarying age, MMSE score, current and premorbid IQ, motor scale score, reading speed and depression score. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

9.2.2 Correlation between cognitive and clinical variables

A strong relationship was found between global cognitive measures and disease severity, whereby cognitive abilities declined as disease severity increased. Table 9.7 shows the relationship between the main cognitive variables and measures of age, disease and medication duration, motor scale score, fluctuations score and depression and anxiety measures.

	Age at time of test	Disease duration	Total for motor scale UPDRS	Total fluctuation score UPDRS	Geriatric Depression Scale total	State Anxiety Inventory total
MMSE total score	-0.334**	-0.036	-0.472***	-0.024	-0.346**	-0.222
Mill Hill Vocab total score	0.116	-0.062	-0.300*	-0.133	-0.276*	-0.146
Full NART equivalent score	0.014	0.035	-0.208	-0.083	-0.184	-0.021
Logical memory Total Recall	-0.275*	-0.107	-0.270*	0.047	-0.318*	-0.101
Logical memory Total Recall II	-0.257*	-0.116	-0.297*	0.047	-0.367**	-0.124
Logical memory Total Recog	-0.237	0.069	-0.185	0.108	-0.421***	-0.245
VOSP Grand total	-0.244*	0.072	-0.442***	0.112	-0.317*	-0.18
Total overlapping figures named	-0.302**	0.01	-0.329**	0.053	-0.403***	-0.277*
Verbal fluency letter total	-0.277*	0.142	-0.213	0.117	-0.310*	-0.192
Block design total correct	-0.322*	-0.005	-0.481***	0.09	-0.372**	-0.231
Block design total points	-0.491***	0.01	-0.534***	0.148	-0.331*	-0.157
Trailmaking A time (in secs)	0.262	-0.006	0.436***	0.011	0.163	0.08
Trailmaking B time (in secs)	0.345*	0.065	0.173	0.023	0.039	-0.146
Mean RT test undivided	0.322*	0.161	0.425***	0.073	0.279*	0.176
Mean RT test divided	0.245	0.112	0.383**	0.12	0.320*	0.284

Table 9.7 Correlations between major cognitive variables, age, disease-related variables and psychological measures. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

It is clear that age, motor scale score and depression score are correlated with several of the cognitive scores. Disease duration and fluctuations score are not. Therefore severity of disease as conceptualised by motor impairment is predictive of poor performance on global cognitive measures and on specific cognitive abilities such as recall and visual processing

which have little demand on motor abilities, and also verbal fluency, the trailmaking test, construction and reaction time which do depend upon to some extent on motor ability. Duration of disease and degree of complications of therapy however are not associated with cognitive performance.

However, this effect of disease severity is *not* independent of age, current and premorbid IQ, and when these factors are covaried motor scale score is associated with only VOSP total score, and also with trailmaking and block design tasks which are both dependent to some degree upon motor abilities. Therefore the decline of specific cognitive abilities as the disease progresses is strongly mediated by a global cognitive decline. Although Parkinson's Disease patients in the current study showed specific cognitive deficits when compared to healthy older adults, and independently of current and premorbid IQ, disease severity itself is a less potent predictor of specific cognitive deficits on the above tests than global cognitive measures.

The consistent association of depression with cognitive scores suggests that motivation may play an important part in performance and persistence on cognitive tasks. However, it may also be that those individuals with PD who are depressed or apathetic display a poorer prognosis in terms of cognitive decline over time. A partial correlation covarying age, current and premorbid IQ found that the association between depression and specific cognitive scores was largely lost, and that depression was no longer associated with disease severity. Therefore depression is related primarily to cognitive decline, although the direction of causality is not possible to determine, as all cognitive measures may be confounded by depression.

The following sections (9.2.2.1 – 9.2.2.6) consider associations between clinical variables and specific cognitive abilities.

9.2.2.1 Relationship between logical memory and clinical measures

Table F.3, Appendix F shows full correlations between logical memory measures and clinical measures. Immediate and delayed recall, and recall one week later of both story detail and gist are closely associated with global cognition and disease severity, and also with depression. Covarying global cognition and age reduced the associations with disease severity and depression to non-significant levels. The learning slope measure (i.e. increase in recall from first to second reading of story one) was associated with MMSE only. Recognition showed a different pattern of association, and was significantly correlated with depression after global cognition was covaried ($r = -0.314$, $p = 0.019$). Therefore tasks giving a choice of response i.e. yes/no may be more susceptible to confounding by poor motivation, than those requiring an open response.

9.2.2.2 Relationship between visual measures and clinical measures

Subtests of the VOSP battery and overall score showed a strong relationship to age global cognition, disease severity and depression. Covarying age and global cognition reduced the associations with depression to a non-significant level, but left the incomplete letters subtest and the VOSP overall score significantly correlated with disease severity. It may be that visual deficits associated with disease severity via central and retinal dopaminergic levels contribute to the impairment on the incomplete letters subtest which requires visual closure. Subtests

requiring high level visual processing such as object recognition may be less affected by central dopaminergic function.

For the overlapping figures test, timed measures were associated with global cognition, reading speed and the overall measure with depression, but not disease severity. Measures concerning number of objects correctly identified were correlated with age, global cognition, disease severity, reading speed and depression. Covarying age and cognition, number of objects named was still significantly associated with depression, suggesting motivation may have affected task persistence. Disease severity however, was not still associated with overlapping figures measures, and therefore tests requiring componential visual processing may be affected more by global cognitive status than by visual dopaminergic systems.

9.2.2.3 Relationship between executive measures and clinical measures

Verbal fluency measures and overall scores were consistently associated with age, global cognition, disease severity, reading speed and depression. However, associations with depression and disease severity were lost altogether when global cognition was covaried. A strong association with global IQ is expected for verbal fluency as current IQ is a vocabulary measure, and premorbid IQ also taps knowledge of words.

Only 63.5% of PD patients were able to complete the trailmaking B task, and subjects were not pressed to continue for the full 5 minutes if they felt unable. Thus for part B a score for number of correct responses completed was calculated. Total time taken to complete part B was therefore a misleading variable and so a time per correct response was calculated for

both sections. Finally, to calculate the extra time devoted to the executive demand of part B, beyond the 'baseline' time for part A, time per correct response was used rather than overall time.

Time taken to complete the trailmaking A test, and time per correct response were correlated with MMSE, motor scale score and specifically with the dexterity factor and the face/speech factor for total time taken. After covarying MMSE score the associations with motor scores were lost, which is unexpected as motor speed is paramount in this task, although there is also a need to conduct a visual search, and keep track of which numbers have been completed. On the trailmaking B task, time per correct response were associated with age, MMSE score, and time per correct response was associated with motor scale score and the face/speech factor. Again though, associations with depression and motor scores were not apparent when age and MMSE score were covaried. Depression and motor scale score were also correlated with number of responses completed for task B, but not after global cognition was covaried. The difference measure or 'executive component' was correlated with age, MMSE and motor scale score, but again motor and depression associations were lost after MMSE was partialled out.

Executive measures therefore displayed a strong association with global cognition, which was responsible for association with motor severity even for the trailmaking task, for which motor speed was an important component. For the verbal fluency task, vocabulary skills may have added to the variance shared between IQ measures and verbal fluency scores. The visual search and attentional components of the trailmaking task may have slowed PD patients more

than motor disability, as motor severity was not associated even with the 'baseline' non-executive task A.

9.2.2.4 Relationship between construction and clinical measures

Both total number of correct responses and number of points scored, which was weighted toward speed of completion, were correlated with age, global cognition, motor scale score, depression and also specifically with the dexterity and face/speech factors. Covarying age and global cognition still left significant associations with motor scale score and the dexterity and face/speech factors for the total points score. This may reflect the fact that points gave weighting towards tasks completed quickly.

9.2.2.5 Relationship between attention task and clinical measures

Mean response times for both divided and undivided attention were correlated with global cognition, motor scale score, depression, and specifically with the dexterity factor. For the undivided attention test, measures of variability in response time (SD and COV) were correlated with disease and medication duration as well as global cognition and motor scale score for SD. For the divided attention task, SD was correlated with global cognition, motor scale score, and the ambulatory factor, but COV was not correlated with any other variables. Covarying age and global cognition, mean RTs were still correlated with the motor scale score, but no other associations for SD and COV remained.

Thus measures of variability appear to be independent of motor status. Global cognition predicts variability for the undivided task, but COV for the divided attention task is not

correlated with any other variables (apart from mean RT scores). Mean RT itself is confounded by motor ability. It is clear however, that the undivided and the divided tasks had different patterns of association.

9.2.2.6 Summary

Global cognition as measured by current IQ, premorbid IQ and MMSE were strongly associated with memory, visual, construction, attention and particularly executive tasks. Therefore specific cognitive deficits are reflected in overall non-specific cognitive measures. Furthermore cognition was largely responsible for the association between disease severity and specific cognitive variables. However, disease severity was independently associated with the incomplete letters subtest of the VOSP, and with points scored on block design and with mean RT on the attention task. Disease-related variables were not however associated with the trailmaking test although motor speed is an important part of the test. In prediction of hallucination score or hallucinating group membership it will be important to covary global cognition in order to assess the 'added-value' of using specific cognitive deficits to identify those vulnerable to hallucinations.

9.3 Comparisons between groups - do hallucinators score differently?

The three PD groups and the control group were compared using one-way ANOVA, though comparisons between PD groups only were made for verbal fluency, trailmaking and block design as controls did not complete these tests. For comparisons controlling for relevant covariates only PD groups were used as motor variables were not available for controls

9.3.1 Group comparisons on global cognition measures

Section 7.3.1 described significantly lower MMSE scores in hallucinating patients as compared to non-hallucinators and controls (see table 9.8 for values). Amongst PD patients this effect was independent of age. Current IQ however, was lower in hallucinators compared to controls, but not to other PD patients.

	Means (SD)				
	Control	Non-hall	UPE	Hall	F
MMSE total score	28.87 (± 1.02)	27.93 (± 1.90)	26.57 (± 2.65)	25.03 (± 3.45)	14.891***
Mill Hill Vocab total score	16.90 (± 2.74)	16.00 (± 2.00)	14.92 (± 2.91)	14.29 (± 4.09)	4.019*
Full NART equivalent score	33.55 (± 11.30)	29.70 (± 12.07)	24.62 (± 8.85)	28.36 (± 11.21)	2.261

Table 9.8 Group comparisons between controls and 3 PD groups on global cognition using ANOVA. *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

9.3.2 Group comparisons of logical memory measures

Immediate recall was significantly poorer in all PD groups as compared to controls, but Bonferroni post-hoc tests revealed there was no difference amongst the PD groups (see table 9.9 for values). For delayed recall however, controls scored significantly better than all PD groups, but hallucinators also scored more poorly than non-hallucinators. For recall delayed for one week (which controls did not complete) hallucinators scored significantly more poorly

than non-hallucinators. No effect was observed for learning slope. For immediate and delayed recall of theme or story gist controls performed significantly better than PD patients, and for delayed recall of theme hallucinators also performed more poorly than non-hallucinators. For recall of theme one week later, hallucinators performed significantly more poorly than non-hallucinators. For recognition the only differences observed were between hallucinators and controls.

Therefore immediate recall of both story detail and theme, for learning slope and for recognition there was no effect of hallucinating status. For delayed recall of 30 minutes and one week hallucinators performed significantly worse than non-hallucinators. Scores for the UPE group fell between hallucinators and non-hallucinators.

	Means (SD)				
	Control	Non-hall	UPE	Hall	ANOVA
Logical memory Total Recall 1+2	22.84 (± 5.00)	16.29 (± 7.36)	14.64 (± 6.07)	12.32 (± 6.65)	15.580***
Logical memory Total Recall 1+2+2	37.10 (± 7.90)	27.82 (± 11.52)	24.14 (± 10.26)	20.91 (± 10.87)	14.346***
Logical memory Total Recall II	23.16 (± 6.37)	16.42 (± 8.07)	13.29 (± 8.90)	9.82 (± 7.79)	17.139***
Logical memory Visit 2 story recall		5.43 (± 5.14)	3.07 (± 2.87)	2.11 (± 3.56)	
Logical memory Learning slope	4.48 (± 2.57)	3.68 (± 2.36)	3.64 (± 2.90)	2.79 (± 2.33)	2.504
Logical memory Total Theme 1+2+2	17.23 (± 3.32)	13.96 (± 3.96)	13.93 (± 4.63)	11.79 (± 4.27)	10.147***
Logical memory Total Theme II	11.48 (± 2.16)	8.69 (± 3.32)	7.71 (± 4.46)	6.00 (± 4.00)	13.949***
Logical memory Visit 2 theme recall		5.00 (± 2.05)	3.70 (± 2.06)	2.44 (±) 2.81	
Logical memory Total Recog	25.61 (± 2.99)	23.29 (± 3.38)	23.00 (± 3.02)	21.39 (± 3.73)	8.362***

Table 9.9 Group comparisons between controls and 3 PD groups on Logical Memory using ANOVA. *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

ANCOVA comparisons for the 3 PD groups only controlled for age, current and premorbid IQ, motor scale score and depression. No significant effect remained for group for delayed and one week recall of either story detail or theme. Therefore poorer delayed recall in hallucinators appears to be secondary to factors such as current IQ, age and depression which all exerted significant effects on at least one of the models.

9.3.3 Group comparisons of visual measures

Significant effects were observed for comparisons of all VOSP subtests, other than the progressive silhouettes test, with hallucinators scoring significantly lower than both the control group and the non-hallucinating group, and lower than the UPE group for the shape detection test also. For all subtests other than the shape detection test, controls and non-hallucinators did not differ according to Bonferroni post-hoc tests.

	Means (SD)				
	Control	Non-hall	UPE	Hall	F
VOSP Shape detection total	19.94 (± 0.25)	19.67 (± 0.62)	19.64 (± 0.74)	18.41 (± 2.03)	9.731***
VOSP Incomplete letters total	19.06 (± 0.85)	18.93 (± 1.41)	18.14 (± 1.61)	16.53 (± 3.49)	8.745***
VOSP Silhouettes total	20.35 (± 3.95)	19.22 (± 4.48)	17.00 (± 4.67)	15.79 (± 5.67)	5.672**
VOSP Object decision total	18.26 (± 1.63)	16.48 (± 2.47)	15.57 (± 3.59)	13.59 (± 3.26)	15.954***
VOSP Progressive silhouettes total	9.42 (± 3.33)	9.19 (± 2.70)	10.86 (± 1.92)	10.84 (± 3.42)	2.156
VOSP Grand total	68.45 (± 7.49)	65.58 (± 8.49)	59.86 (± 8.61)	55.00 (± 12.73)	11.069***

Table 9.10 Group comparisons between controls and 3 PD groups on VOSP battery using ANOVA. *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

Covarying age, current and premorbid IQ, motor scale score and depression using PD patients only, left a significant effect for group on the shape detection screening test ($F = 4.087$, $p = 0.023$) and the object decision subtests only ($F = 5.063$, $p = 0.010$). The total score for 5 tests was also non-significant ($F = 2.761$, $p = 0.073$) with ANCOVA comparisons. Significant main effects were also observed for age and current IQ on the silhouettes subtest and the overall score, and for motor scale score on the incomplete letters test, again suggesting that this visual closure task may be dependent upon dopaminergically mediated visual systems. Therefore hallucinators may possess a greater degree of low-level visual deficits as picked up by the shape detection test which is conceived of as a 'screening test'. They also have less ability to discriminate between real and pseudo-objects, independently of global cognitive status.

One-way comparisons between the four groups on the overlapping figures test found significant effects for group membership for all timed variables and for all variables concerning number of objects correctly identified (see table 9.11 for values). For the total time score hallucinators were significantly slower than all other groups, and controls, non-hallucinators and the UPE group formed a homogenous subset. For total number of objects named hallucinators scored significantly fewer than controls and non-hallucinators, and controls higher than all PD groups.

	Means (SD)				
	Control	Non-hall	UPE	Hall	ANOVA
Overlapping figure A time to 8 correct (in secs)	21.69 (± 8.96)	35.64 (± 22.23)	43.60 (± 52.48)	59.95 (± 37.41)	6.570**
Overlapping figure A total objects named	13.29 (± 1.07)	11.26 (± 2.07)	10.77 (± 2.31)	9.27 (± 2.55)	20.749*** *
Overlapping figure B time to 8 correct (in secs)	23.41 (± 11.01)	37.90 (± 24.03)	34.11 (± 8.81)	63.00 (± 36.45)	10.695***
Overlapping figure B total objects named	13.35 (± 1.33)	12.52 (± 1.83)	10.77 (± 2.83)	9.42 (± 2.86)	18.956***
Total figures named OFigs A + B	26.65 (± 2.24)	23.78 (± 3.50)	21.54 (± 4.96)	18.70 (± 5.03)	22.421***
Total time for figures A + B	44.81 (± 17.49)	65.32 (± 26.74)	61.44 (± 17.82)	99.53 (± 47.75)	11.268***

Table 9.11 Group comparisons between controls and 3 PD groups on overlapping figures using ANOVA. *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

Covarying age, current and premorbid IQ, motor scale score, depression and for timed measures reading speed, the effect for group was lost for the timed measure, but maintained for total number of objects correctly named ($F = 5.143$, $p = 0.010$). Therefore, hallucinators were able to identify fewer objects correctly, though they were not slower once reading speed was covaried.

Of the visual measures then, hallucinators were more impaired on a visual screening test, ability to discriminate between real and pseudo-objects and ability to identify objects amongst an array of overlapping objects, independently of decreases in global cognition, and increases in disease severity and depression.

9.3.4 Group comparisons on executive measures

Only PD patients completed executive tests verbal fluency and trailmaking. Significant effects were observed for all conditions of the verbal fluency (VF) task; single letter and category fluency, three alternating fluency conditions and total score for appropriate words produced

(see table 9.12 for values). For all measures hallucinators scored significantly lower than non-hallucinators, and the UPE group was not significantly different from either controls or hallucinators, except for the alternating letter/category condition, where they scored more poorly than controls.

	Means (SD)			
	Non-hall	UPE	Hall	F
Verbal fluency letter total	12.56 (± 4.39)	11.00 (± 5.11)	9.42 (± 4.23)	3.667*
Verbal fluency category total	12.56 (± 4.36)	12.21 (± 4.28)	9.42 (± 4.70)	4.126*
Verbal fluency alternating letter total	9.67 (± 3.81)	8.71 (± 4.48)	6.58 (± 4.71)	3.901*
Verbal fluency alternating category total	11.19 (± 4.14)	8.57 (± 3.67)	7.81 (± 4.59)	4.766*
Verbal fluency alternating let/cat total	9.07 (± 3.89)	5.50 (± 3.39)	5.59 (± 3.45)	8.033**
Verbal fluency grand total	54.48 (± 15.91)	46.71 (± 15.86)	38.22 (± 16.11)	7.602**

Table 9.12 Group comparisons between 3 PD groups on verbal fluency using ANOVA
*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

For verbal fluency, ANCOVA comparisons controlled for reading speed as well as age, current and premorbid IQ, motor scale score and depression. No effects for group were observed using ANCOVA, and age was the only covariate which consistently exerted an effect. Therefore the number of appropriate words produced in a VF task, appeared to be more affected by age than by membership of group, and even reading speed did not exert a significant effect.

The trailmaking test showed a significant effect for group on time to complete Part A only, and the effect was too weak to produce differences between groups on the Bonferroni post-hoc

test (although hallucinators were the slowest group). No other measure showed a significant effect despite taking into account the fact that Part B was not always completed.

	Means (SD)			
	Non-hall	UPE	Hall	F
Trailmaking A time (in secs)	77.06 (± 42.95)	72.33 (± 26.77)	114.96 (± 60.24)	3.968*
Trailmaking B time (in secs)	182.22 (± 89.62)	190.56 (± 135.30)	260.39 (± 135.14)	2.437
Trailmaking A complete / 25	25.00 (± 0.00)	25.00 (± 0.00)	24.29 (± 3.47)	0.552
Trailmaking B complete / 25	21.39 (± 7.06)	19.22 (± 9.12)	17.91 (± 9.25)	0.847
Time per correct response for Trailmaking A	3.08 (± 1.72)	2.89 (± 1.07)	5.24 (± 4.36)	3.026
Time per correct response for Trailmaking B	11.64 (± 10.79)	13.39 (± 10.25)	23.42 (± 21.16)	2.923
Trailmaking B - A time per correct response	8.56 (± 9.36)	10.49 (± 9.65)	18.94 (19.56)	2.646

Table 9.13 Group comparisons between 3 PD groups on trailmaking test using ANOVA
*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

ANCOVA comparisons covarying age, current and premorbid IQ, motor scale score, depression and the dexterity factor found that the effect for time to complete Part A vanished. In fact the only covariate which exerted a significant effect in any of the ANCOVA models was age in time to complete Part B. The trailmaking test is a complex task involving motor speed, attention, an executive component of 'set-shifting' as well as a visual search. It is therefore perhaps not surprising that no clear effect was found for any other covariate or for group, as different task components may have different patterns of association.

To summarise results for executive tasks, there were no differences for hallucinators compared to non-hallucinators on any measures of verbal fluency or on the trailmaking test once relevant covariates were entered into the model.

9.3.5 Group comparisons on construction measures

Significant effects were observed on both number of items correct on the block design test and total number of points scored, where hallucinators score more poorly than non-hallucinators.

	Means (SD)			
	Non-hall	UPE	Hall	F
Block design total correct	10.85 (± 2.25)	9.83 (± 3.13)	7.80 (± 3.07)	6.837*
Block design total points	28.15 (± 9.57)	26.50 (± 14.07)	17.84 (± 11.46)	5.179*

Table 9.14 Group comparisons between 3 PD groups on Block Design using ANOVA
*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

Covarying age, current and premorbid IQ, motor scale score, depression and the dexterity factor meant that effects for group were lost, and that age accounted for the largest amount of variance ($F = 5.849$, p 0.021; $F = 17.246$, $p < 0.001$). The block design test requires dexterity and speed, but age seems to exert a stronger effect, and group differences are not independent of age.

9.3.6 Group comparisons on measures of attention

One-way ANOVA showed effects for mean RT for both undivided and divided attention, standard deviation of RT for both and COV for the undivided attention test only (see table 9.15 for values). For the undivided attention task mean RT was slower for all PD groups compared to controls, and for the hallucinators compared to the non-hallucinators. As for measures of

variability, for coefficient of variation which effectively controls for differences in RT, group differences were apparent between controls and hallucinators only. For the divided attention task, mean RT was significantly greater in hallucinators than both non-hallucinators and controls, but there was no effect for COV.

	Means (SD)				
	Control	Non-hall	UPE	Hall	F
Standard deviation RT test undivided	124.79 (± 50.70)	214.55 (± 136.88)	279.58 (± 188.43)	355.03 (± 177.85)	14.138***
Mean RT test undivided	944.84 (± 223.73)	1183.62 (± 253.29)	1267.54 (± 149.72)	1538.89 (± 420.51)	19.301***
Coefficient of variation RT test undivided	0.14 (± 0.06)	0.18 (± 0.11)	0.21 (± 0.13)	0.23 (± 0.09)	5.108**
Standard deviation RT test divided	169.41 (± 120.75)	214.99 (± 110.38)	222.95 (± 135.17)	376.71 (± 199.21)	9.661***
Mean RT test divided	961.58 (± 251.20)	1207.63 (± 219.92)	1244.47 (± 159.10)	1588.95 (± 508.76)	16.294***
Coefficient of variation RT test divided	0.18 (± 0.12)	0.18 (± 0.10)	0.18 (± 0.11)	0.23 (± 0.11)	1.408

Table 9.15 Group comparisons between controls and 3 PD groups on attention task using ANOVA; *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

Covariation of age, current and premorbid IQ, motor scale score, depression and dexterity factor meant that group effects for all measures were lost. Therefore both reaction time and variability in reaction time are not significantly greater in hallucinators after relevant covariates are controlled for. There were no consistent effects of any single covariate on attention task measures.

9.3.7 Summary

Group differences between hallucinators and non-hallucinators on specific neuropsychological measures were in many cases explained by the effect of covariates such as age, current and premorbid IQ, disease severity and depression. The effect for poorer performance on delayed recall, verbal fluency, block design and attention in hallucinators was lost after ANCOVA was performed to control for covariates. Specific visual measures however, showed an effect even after controlling for potential confounders; hallucinators were less able to detect a degraded stimulus against background noise in the shape detection test, were less able to distinguish between silhouettes of real and pseudo-objects, and were less able to identify objects in an array of overlapping figures. Thus when considering the overall *correct* neuropsychological performance of hallucinators compared to non-hallucinators, the strongest evidence was for specific visual deficits, as is reflected in the current literature. Deficits in other areas were more strongly influenced by age, disease severity, premorbid IQ and depression, and were *not* independent of the global cognitive decline shown by hallucinators.

9.4 Do cognitive errors give more information than correct performance alone?

Performance on specific cognitive tasks varied according to group membership, although many differences were lost once global cognitive variables and age were covaried. This suggests that hallucinators perform poorly on cognitive tasks simply because they are more impaired on global measures of IQ. ANCOVA comparisons of scores obtained identified some specific deficits independent of global cognition, but examination of the frequency and types of errors made by PD patients may be more revealing than considering correct scores alone. Hallucinations are conceptualised as part of a range of 'positive' psychotic phenomena, in contrast to 'negative' symptoms such as withdrawal or apathy. Failure or poor performance on cognitive tests can be seen as either an absence of response or failure to respond correctly, but may also result from increased levels of incorrect, out of context or even bizarre responses. The role of depression or apathy in contributing to poor cognitive performance is clear from the above results. Hallucinators however are not more depressed than non-hallucinators, and their cognitive performance may differ qualitatively from non-hallucinators in terms of types of errors made. The type and frequency of errors are examined.

9.4.1 Scores on components of MMSE examination

Correct responses	Median (Range)	%age correct
MMSE orientation score / 10	9 (5 - 10)	
MMSE repetition / 3	3 (1 - 3)	
MMSE serial task / 5	5 (0 - 5)	
MMSE recall / 3	2 (0 - 3)	
MMSE object naming / 2	2 (1 - 2)	
MMSE Phrase repetition[b]	86.8 %	86.8 %
MMSE Three stage task / 3	3 (0 - 3)	
MMSE 'Close your eyes'[b]	96.1 %	96.1 %
MMSE sentence[b]	94.7 %	94.7 %
MMSE pentagons[b]	69.7 %	69.7 %

Table 9.16 Correct responses for sections of the MMSE test for all PD patients

Points were lost most often on the orientation section, specifically the date item, the recall section of the MMSE, and on the pentagon copying item.

Table F.1, Appendix F, shows correlations between MMSE subscale scores and clinical variables. MMSE orientation score is negatively associated with age and with motor scale score (see table 9.16 for values), recall score is negatively correlated with motor scale score and three stage task was associated with motor scale score and dexterity and tremor factor scores. As the three stage task involved completing a series of physical actions presence of tremor and impairments in dexterity may have interfered with the task. Group comparisons between those who passed and failed the pentagon copying item showed that those who failed were older, had lower current and premorbid IQ scores, greater motor scale scores and higher anxiety and depression scores. (For other one-point tasks frequency of failure was too low to make valid comparisons). Therefore the subtasks of which the MMSE was comprised were most consistently associated with motor scale score, whereby increased disease severity led to poorer performance.

9.4.2 Error scores on logical memory

Incorrectly recalled detail on the logical memory task was divided into three types of error; recall inaccuracies, novel intrusions and cross-trial errors. Raw scores for 'new' and total number of these errors (including repeated errors) across the five recall trials are shown below. Also given are percentages of these errors, which takes into account total output (both correct and incorrect) which may be affected by memory, speech difficulties or apathy. Medians are low for raw error scores, and for this reason non-parametric comparisons will be used in later analysis.

		Median (Range)	Mean (SD)
Raw scores	Recall inaccuracies new to trial 5[a]	0.5 (0 - 6)	
	Novel intrusion new to trial 5[a]	1 (0 - 11)	
	Cross-trial errors new to triall 5[a]	0 (0 - 3)	
	Recall inaccuracies total to trial 5[a]	0.5 (0 - 6)	
	Novel intrusion total to trial 5[a]	1 (0 - 14)	
	Cross-trial errors total to trial 5[a]	0 (0 - 3)	
Percentage scores	Percentage new recall inaccuracies (5 trials)		2.748 (± 3.921)
	Percentage new novel intrusions (5 trials)		4.240 (± 7.921)
	Percentage new cross-trial errors (5 trials)		0.548 (± 2.369)
	Percentage total recall inaccuracies (5 trials)		3.239 (± 4.828)
	Percentage total novel intrusions (5 trials)		4.690 (± 8.677)
	Percentage total cross-trial errors (5 trials)		0.548 (± 2.369)
	Percentage all-types of confabulations LM		8.480 (± 10.28)

Table 9.17 Descriptives for Logical Memory errors

Table F.2, Appendix F, shows correlations between error scores and correct scores for the logical memory test. Examining the relationship between error scores and correct scores showed that percentage confabulations was strongly negatively correlated with all correct measures (all at $p < 0.001$, except for learning slope and one-week recall at $p < 0.050$). Therefore production of erroneous material cannot be seen as reflecting increased levels of total output, or as facilitating recall by 'filling in the gaps' in order to aid accurate recall. As for

specific types of error, novel intrusions were negatively correlated with delayed recall both of detail and gist (30 mins) and with recognition. Cross-trial intrusions were also negatively correlated with delayed recall. Recall inaccuracies were not however correlated with any correct measures. Therefore cross-trial intrusions and novel intrusions are related to a decline in delayed recall and in recognition.

Table F.3, Appendix F, shows correlations between errors on logical memory and clinical variables. Novel intrusions were correlated negatively with MMSE and positively with anxiety score, suggesting that perceived need to provide an answer of some kind may increase erroneous recall (see Table F.3 for values). Cross-trial intrusions were correlated negatively with MMSE score, and positively with disease duration and medication duration. Recall inaccuracies were correlated with disease severity. Clearly then different types of errors are associated with different clinical variables, and furthermore there was no correlation between the different types of errors.

Performance on the recognition test within logical memory can be broken down into measures concerning whether errors were essentially 'misses' or failure to recognise part of the original story, or 'false positives' where red-herring items are incorrectly recognised as part of the original story. 'False positives' are therefore conceptually similar to confabulations, and are correlated with novel intrusions ($r = 0.310$, $p = 0.015$). Table 9.18 shows frequency of each type of error, and also the ratio of false alarms to correct negatives.

	Median (Range)	Mean (SD)
Hits LM recognition	16 (9 - 18)	15.492 (± 1.795)
Correct negatives LM recognition	8 (0 - 12)	7.082 (± 2.842)
False alarms LM recognition	4 (0 - 12)	4.869 (± 2.831)
Misses LM recognition	2 (0 - 9)	2.557 (± 1.840)
False alarms: correct negative ratio LM	0.5 (0 - 5)	1.000 (± 1.023)

Table 9.18 Descriptives for Logical Memory recognition errors

Table F.2, Appendix F, gives full values of correlations between recognition measures and correct LM scores. Number of false alarms and the false alarms: correct negatives ratio were both highly negatively correlated with all correct logical memory scores (all at $p < 0.001$). Misses were also negatively correlated with correct scores other than one week recall and learning slope. Patterns of association are therefore fairly non-specific.

Full correlations between recognition measures and clinical variables are shown in Appendix F, Table F.3. False alarms, and the ratio measure are associated negatively with global measures MMSE, current IQ and premorbid IQ, and depression, and also for the ratio measure anxiety. Therefore presence of false positives on recognition is related to poorer memory scores all round, poor global cognition, depression *and* the presence of novel intrusions.

9.4.3. Error scores on verbal fluency

The verbal fluency task also produced inappropriate verbal responses that were outside the range demanded by cues, or were due to interference from previous cues. Frequencies for

repetition of words, perseveration of a probe in the alternating conditions, and intrusion of a response that was inappropriate to the current probe or probes are shown in table 9.19. Intrusions were of two types; those relevant to previous probes which represented 'cross-trial' interference, and those 'novel intrusions' which were no related to any probes, but which tended to result from a phonological or semantic 'drift' during the task, or some idiosyncratic association. Percentage values in terms of total output are also given to control for speed of articulation and general poverty of response.

		Median (Range)	Mean (SD)
Raw scores	Verbal fluency repetition total[a]	1 (0 - 8)	
	Verbal fluency perseveration total[a]	1 (0 - 9)	
	Verbal fluency intrusion total[a]	1 (0 - 15)	
	Cross-trial intrusions verbal fluency[a]	0 (0 - 9)	
	Novel intrusions verbal fluency[a]	1 (0 - 12)	
Percentage scores	VF repetition percentage		2.85 (± 3.20)
	VF perseveration percentage		3.62 (± 5.57)
	VF intrusions percentage		5.58 (± 7.05)
	VF novel intrusion percentage		2.88 (± 4.38)
	VF cross-trial intrusion percentage		2.71 (± 4.71)

Table 9.19 Descriptives for verbal fluency errors

Table F.4, Appendix F, shows the relationship between VF error scores and correct scores for each condition, giving full correlation values. For raw scores only number of perseverations

was negatively correlated with total number of words produced. Therefore repetitions and intrusions were not clearly related to poorer production of correct words, and therefore may not be mediated by the same mechanisms as overall word production and perseveration which are typically taken to be measures of frontal function. The three types of error were not correlated with one another.

Associations of VF error scores with clinical measures are given in full in Table F.5, Appendix F. Percentage measures of perseveration were positively correlated with age, and motor scale score, and negatively with MMSE. Percentage repetition was correlated with anxiety score. Intrusions of either type however were not correlated with any clinical measures.

Although the logical memory and verbal fluency tasks tap different systems, the errors produced by each may have some similarities, and it is clear that there are qualitative differences between types of errors within each task. Table 9.20 shows the relationship between percentage measures of errors on the logical memory task and on verbal fluency.

	Percent new recall inaccuracies	Percent new novel intrusions	Percent new cross-trial errors	Percent total recall inaccuracies	Percent total novel intrusions	Percent total cross-trial errors
Percentage repetition verbal fluency	-0.015	-0.060	0.041	-0.045	-0.064	0.041
Percentage perseveration verbal fluency	0.097	0.147	0.682***	0.081	0.123	0.682***
Percentage intrusions verbal fluency	0.117	0.345**	0.035	0.058	0.395***	0.035
Percentage novel intrusion verbal fluency	0.314**	0.245*	0.031	0.224	0.273*	0.031
Percentage cross-trial verbal fluency	-0.118	0.287*	0.023	-0.122	0.335*	0.023

Table 9.20 Correlations between errors on logical memory and verbal fluency. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Repetition on verbal fluency is not associated with any type of error on logical memory. Perseveration or failure to shift-set on verbal fluency is highly associated with cross-trial errors on logical memory (see table for values), which can also be seen as a failure to shift from set of previously appropriate responses. Novel intrusions on verbal fluency correlate with both novel intrusions and recall inaccuracies on logical memory and tendancy to produce irrelevant or idiosyncratic responses on both tasks are associated. However, cross-trial intrusions on verbal fluency did not correlated with cross-trial intrusions on logical memory, but instead with novel intrusions on logical memory. This last finding is puzzling as cross-trial errors on both tests represent a kind of perseveration of response over time. Clearly though, error scores on the separate tests have some similarities, and the pattern of association remains after age, current and premorbid IQ and motor scale score are covaried.

As mentioned previously, raw error scores have low medians, and percentage measures are rather skewed so a composite score was derived, adding the number of novel intrusions on logical memory to the total number of intrusions (of either type). A percentage measure for this was also calculated, and descriptive statistics are shown below in table 9.21.

Derived measures	Median (Range)	Mean (SD)
Confabulations LM + intrusions VF	4 (0-18)	5.24 (± 4.91)
Novel intrusions LM + total intrusions VF	2 (0-16)	3.86 (± 4.29)
%age confab + %age novel intrusions		9.98 (± 12.77)

Table 9.21 Descriptives for composite error scores

9.4.5 Error scores on VOSP battery

For subtests of the VOSP battery error scores will be related inversely related to correct scores, as there a limited number of responses made. Error scores shown below (table 9.22) are excluding 'passes' and concern incorrect identifications of the stimulus concerned. For object decision, 'incorrect' responses were where participants identified a pseudo-object as a real object and named it, and 'misidentifications' were where the participant chose the real object but identified as something else.

	Median (Range)	Mean (SD)
VOSP Shape detection false positives	0 (0 - 5)	0.253 (± 0.840)
VOSP Shape detection false negatives	0 (0 - 7)	0.640 (± 1.215)
VOSP Shape detection confabulations	0 (0 - 6)	0.253 (± 0.887)
VOSP Incomplete letters incorrect	1 (0 - 7)	1.627 (± 1.784)
VOSP Silhouettes incorrect	9 (1 - 19)	8.827 (± 4.108)
VOSP Object decision incorrect	3 (0 - 9)	3.658 (± 2.382)
VOSP Object decision misidentifications	2 (0 - 7)	1.836 (± 1.572)

Table 9.22 Descriptives for VOSP battery errors

Table F.6, Appendix F, shows associations between error scores and total scores for the VOSP. Because of the necessary inverse relationship between the two sets of scores, each error score was highly correlated with the correct score for that subtest, and error scores across the battery were also correlated with most correct scores. Strong associations amongst error scores (see Table F.6, Appendix F) also suggested that tendency to make visual errors

was consistent across subtests. Only shape detection false negatives and confabulations were not correlated with all other scores.

Table F.7, Appendix F, shows the association between VOSP error scores and clinical variables. MMSE score was consistently associated with VOSP error scores, whereby poorer cognitive status led to more error scores. Motor scale score however was associated with incorrect responses on the incomplete letters and object decision subtests only, whereas all correct scores were correlated with motor scale scores. Older age was associated with presence of confabulations on the shape detection test.

9.4.6 Error scores on the overlapping figures test

Errors made on the overlapping figures test are shown in Table 9.23, which fell into three categories, repetition of previously named objects, anomia or inability to name an object that was otherwise described correctly, and misidentifications. Misidentifications usually resulted either from selecting a portion of an object and 'identifying' that feature, or by merging features of two or more objects. To control for overall level of response, and because some patients identified the same object or its features more than once, a percentage measure was calculated for misidentifications in relation to all responses correct or incorrect.

	Median (Range)	Mean (SD)
Overlapping figures: repetition total	0 (0 - 8)	
Overlapping figures: anomia total	0 (0 - 4)	
Total misidentifications OFigs A + B	2 (0 - 14)	
Percentage misidentifications OFigs		12.080 (± 11.124)

Table 9.23 Descriptives for overlapping figures errors

Table F.9, Appendix F, shows correlations between correct and error scores on the overlapping figures test. Misidentifications were strongly positively correlated with all timed measures and negatively with non-timed measures, and repetitions showed a similar pattern. Anomia was associated with longer time taken overall. No associations existed between the three types of errors.

Associations of errors on the overlapping figures tests with clinical variables are shown in Table F.9, Appendix F. Number of misidentifications and percentage misidentifications were correlated with both age and MMSE score, but neither repetitions nor anomia were correlated with any clinical measure. As with correct identifications no error scores were associated with any of the disease-related variables.

Table 9.24 shows the association between error scores on the VOSP and on the overlapping figures test, covarying age, current and premorbid IQ and motor scale score to minimise spurious associations.

	VOSP Shape detection false positives	VOSP Shape detection false negatives	VOSP Shape detection confabulations	VOSP Incomplete letters incorrect	VOSP Silhouettes incorrect	VOSP Object decision incorrect	VOSP Object decision misidentification s
Total misidentifications OFigs A + B	0.484***	0.061	0.118	0.416***	0.589***	0.459***	0.398***
Percentage misidentifications OFigs	0.579***	0.039	0.179	0.376**	0.601***	0.470***	0.421***
Overlapping figures repetition total	-0.021	0.011	-0.079	0.247*	0.184	0.123	0.214
Overlapping figures anomia total	0.074	0.117	0.312*	0.217	0.068	0.096	0.005

Table 9.24 Correlations between errors on the VOSP battery and the overlapping figures test.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

It is clear that misidentifications on the overlapping figures test are associated with errors on all VOSP tests other than false negatives or confabulations on the shape detection test. Anomia is associated with confabulations on shape detection, and repetition with errors on the incomplete letters test. Therefore visual errors on visual closure tasks, recognition of silhouettes tasks and componential processing appear to be closely related in a Parkinson's Disease population.

It was therefore desirable to derive a composite score for visual errors or misperceptions, and this was done by adding raw scores for incorrect identifications on incomplete letters, silhouettes, object decision and the overlapping figures test. For object decision incorrect identifications (of a pseudo-object) were included in the total as well as clear misidentifications of real objects, where the error was not simply due to anomia. (A percentage score was also calculated to take into account the possibility of low verbal response on the overlapping figures measure.) Descriptives for derived measures of visual misidentification are given below in Table 9.25 for PD patients.

Derived measures	Median (Range)	Mean (SD)
Visual misidentifcations	17 (1-51)	18.54 (± 9.55)
% age visual misidentifications		19.51 (± 10.13)

Table 9.25 Descriptives for composite error scores

9.4.6 Errors on the trailmaking task

Errors on the trailmaking task for both parts are shown as raw scores and as percentage scores as a proportion of the total number of correct responses completed, in table 9.26

	Median (Range)	Mean (SD)
Trailmaking A errors	0 (0 - 5)	
Trailmaking B errors	2 (0 - 5)	
Trailmaking A (percentage errors)	3.37 (± 7.04)	3.37 (± 7.04)
Trailmaking A (percentage errors)	11.81 (± 12.59)	11.81 (± 12.59)

Table 9.26 Descriptives for trailmaking errors

Table F.10, Appendix F, shows the relationship between error scores and correct scores on the trailmaking test. Raw error scores were positively correlated with time taken to complete respective parts. For both parts of the test, percentage errors were correlated positively with time per correct answer for both tests, and negatively with proportion of the test completed for both.

The relationship with clinical variables is shown in Table F.11, Appendix F. Error scores on part A are correlated with global cognitive measures MMSE and current IQ and with motor scale score, depression, anxiety, and with dexterity scores. However, error scores on part B were correlated with MMSE and the face/speech factor only. As discussed earlier, this may reflect the complexity of trailmaking B.

The trailmaking B task involves executive abilities of shifting-set, and attentional, visual and motor components. Percentage errors on part B correlated with percentage perseveration on the verbal fluency task ($r = 0.444$, $p = 0.003$) and with false positives and confabulations on the screening test of the VOSP ($r = 0.463$, p 0.002; $r = 0.617$, $p < 0.001$). Therefore deficits or errors on both executive and visual tasks may be involved in trailmaking part B.

9.4.7 Relationship of error scores of all types

Verbal errors on both logical memory and verbal fluency have been shown to be related as have visual errors on the VOSP and overlapping figures test. Table F.12, Appendix F, shows the relationship between all error scores, covarying age, current and premorbid IQ, and motor scale score.

Correlations between the composite measures and clinical variables were as follows. Percentage verbal intrusions were correlated with MMSE score ($r = -0.379$, $p < 0.001$), anxiety score ($r = 0.341$, $p = 0.012$) and ambulatory factor score ($r = 0.306$, $p = 0.013$). Percentage visual misidentifications were correlated with age ($r = 0.252$, $p = 0.034$) MMSE score ($r = -0.544$, $p < 0.001$) motor scale score ($r = 0.351$, $p = 0.003$) and dexterity factor score ($r = 0.319$, $p = 0.010$). Therefore composite error scores share similar predictors to correct cognitive scores, namely age, global cognition and motor scale score. There is however no association with depression, the presence of which is a key predictor of poor performance on cognitive tests. Table 9.27 below, shows the relationship between the derived composite measures of verbal and visual errors.

	Visual misidentifcations	% age visual misidentifications
Novel intrusions LM + intrusions VF	0.412***	0.400***
%age novel intrusions LM + intrusions VF	0.501***	0.499***

Table 9.27 Partial correlations between composite visual and verbal error scores, covarying age, current and premorbid IQ and motor scale score.

It is clear that the two measures are highly correlated independently of age, global cognition and disease severity. Therefore individuals more likely to make intrusions on verbal tasks are

also more likely to make erroneous perceptions on visual tests. The following section investigates the relationship between cognitive error scores and hallucinations.

9.5 Group comparisons - do hallucinators make more errors ?

9.5.1 Group comparisons on MMSE subscores

Table 9.28 shows group comparisons for component scores of the MMSE. Significant differences were observed for orientation score, serial task, recall, three stage task, visual instruction and pentagon copying between the four groups.

	Means (SD)				
	Controls	Non-hall	UPE	Hall	Test statistic
MMSE orientation score[a]	10 (8 - 10)	9 (7 - 10)	10 (8 - 10)	9 (5 - 10)	9.172*
MMSE repetition[a]	3 (3 - 3)	3 (3 - 3)	3 (3 - 3)	3 (1 - 3)	2.057
MMSE serial[a]	5 (2 - 5)	5 (2 - 5)	4.5 (2 - 5)	5 (0 - 5)	13.393**
MMSE recall[a]	3 (2 - 3)	2 (0 - 3)	2 (0 - 3)	2 (0 - 3)	21.220***
MMSE object naming[a]	2 (2 - 2)	2 (1 - 2)	2 (2 - 2)	2 (1 - 2)	1.524
MMSE Phrase repetition[b]	96.8%	92.6%	85.7%	82.9%	3.945
MMSE Three stage task[a]	3 (2 - 3)	3 (2 - 3)	3 (1 - 3)	2 (0 - 3)	24.211***
MMSE 'Close your eyes'[b]	100%	100%	85.7%	97.1%	8.446*
MMSE sentence[b]	100%	100%	85.7%	94.3%	6.960
MMSE pentagons[b]	100%	92.6%	57.1%	57.1%	24.914***

Table 9.28 Group comparisons between controls and 3 PD groups on MMSE subtests

[a] Median and range for non-parametric variables, Kruskal-Wallis comparisons
[b] Percentage correct for dichotomous variables, chi-square comparisons
*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

Post-hoc tests revealed that differences lay between hallucinators and both non-hallucinators and controls on the recall subtest, reflecting impairments on logical memory in this group, and on the three stage task, suggesting problems with carrying out a sequence of verbal

instructions. Hallucinators and the UPE group showed greater impairment on the pentagon copying item, which may reflect both visual perceptual and constructional difficulties.

9.5.2 Group comparisons of errors on the logical memory test

Table 9.29 shows group comparisons on errors for the logical memory test. It is clear that the percentage values are more revealing than the raw scores, as controls gave the greatest number of recall inaccuracies according to raw scores. However, when total output was taken into account, it was novel intrusions which displayed significant differences, with hallucinators making a greater proportion than controls and non-hallucinators according to Bonferroni's post-hoc test. Therefore recall inaccuracies may aid recall by providing approximations which facilitate flow of recall.

	Means (SD)				
	Controls	Non-hall	UPE	Hall	Test statistic
Recall inaccuracies new [a]	1 (0 - 3)	0 (0 – 4)	0 (0 – 3)	1 (0 – 6)	10.527*
Novel intrusion new [a]	0 (0 - 4)	0 (0 – 2)	0.5 (0 – 4)	1 (0 – 11)	6.138
Cross-trial errors new [a]	0 (0 - 1)	0 (0 – 0)	0 (0 – 0)	0 (0 – 3)	7.409
Recall inaccuracies total [a]	2 (0 - 5)	0 (0 – 5)	0 (0 – 4)	1 (0 – 6)	9.543*
Novel intrusion total [a]	0 (0 - 6)	0 (0 – 3)	1 (0 – 4)	1 (0 – 14)	6.718
Cross-trial errors total [a]	0 (0 - 1)	0 (0 – 0)	0 (0 – 0)	0 (0 – 3)	7.409
Percentage new recall inaccuracies	2.03 (± 1.59)	1.71 (± 3.47)	1.81 (± 2.83)	3.93 (± 4.36)	3.021*
Percentage new novel intrusions	1.14 (± 1.60)	1.08 (± 1.53)	4.96 (± 9.88)	6.36 (± 9.26)	5.011**
Percentage new cross-trial errors	0.21 (± 0.67)	0.00 (± 0.00)	0.00 (± 0.00)	1.19 (± 3.41)	2.433
Percentage total recall inaccuracies	2.74 (± 2.37)	2.01 (± 3.80)	2.34 (± 3.24)	4.55 (± 5.76)	2.202
Percentage total novel intrusions	1.41 (± 2.14)	1.22 (± 1.73)	5.27 (± 9.83)	7.11 (± 10.51)	4.948**
Percentage total cross-trial errors	0.21 (± 0.67)	0.00 (± 0.00)	0.00 (± 0.00)	1.19 (± 3.41)	2.433

Table 9.29 Group comparisons between controls and 3 PD groups on Logical Memory errors

[a] Median and range for non-parametric variables, Kruskal-Wallis comparisons
*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

ANCOVA comparisons were carried out using the three PD groups only, to prevent undue influence of both high global cognitive scores and low error scores for the control group, and to allow covariation on disease severity. Covarying age, current and premorbid IQ and motor scale score left a non-significant effect for group on percentage novel intrusions ($F = 3.011$, $p = 0.057$), although it was close to significant, and group accounted for more variance than any of the other covariates. It is clear that novel intrusions are raised in the hallucinators and UPE groups, though not to a significant level, but this may be due to skewing and low incidence. A test which provoked greater levels of intrusion in all subjects may have revealed clearer differences.

Table 9.30 shows group comparisons on recognition measures, with differences in correct negatives and false alarms, and in the false alarms: correct negatives ratio. For numbers of correct negatives and false alarms the difference lay between controls and all PD groups only, but for the false alarms: correct negatives ratio differences were apparent between hallucinators and both controls and non-hallucinators Therefore hallucinators show a greater bias toward false positives on recognition at 30 minutes.

	Means (SD)				
	Controls	Non-hall	UPE	Hall	Test statistic
Hits LM recognition	15.80 (± 1.63)	15.67 (± 1.74)	15.75 (± 1.60)	15.25 (± 1.94)	0.542
Correct negatives LM recognition	9.83 (± 1.60)	7.86 (± 2.85)	7.08 (± 2.97)	6.50 (± 2.74)	9.421***
False alarms LM recognition	2.03 (± 1.56)	4.10 (± 2.88)	4.83 (± 2.86)	5.46 (± 2.74)	10.090***
Misses LM recognition	2.33 (± 1.63)	2.38 (± 1.75)	2.33 (± 1.67)	2.79 (± 2.01)	0.390
False alarms: correct negative ratio LM	0.24 (± 0.23)	0.57 (± 0.49)	1.04 (± 1.01)	1.29 (± 1.22)	8.737***

Table 9.30 Group comparisons between controls and 3 PD groups on Logical Memory recognition errors

[a] Median and range for non-parametric variables, Kruskal-Wallis comparisons
*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

ANCOVA covarying age, current and premorbid IQ, and motor scale score reduced group differences to non-significant levels. Significant effects were found for both age and current IQ on correct negatives ($F = 4.925$, $p = 0.031$; $F = 5.483$, $p = 0.024$) and false alarms ($F = 5.594$, $p = 0.022$; $F = 5.036$, $p = 0.030$). Therefore the bias towards making false alarms in hallucinators is explained largely by age and current IQ.

9.5.3 Group comparisons of errors on the verbal fluency task

Group comparisons for the verbal fluency task are shown in Table 9.31. Both raw scores and percentage scores corrected for total output showed significant differences amongst the groups. For percentage measures hallucinators display significantly more perseverations, intrusions of both types, cross-trial intrusions and novel intrusions, as compared to non-hallucinators.

	Means (SD)			
	Non-hall	UPE	Hall	Test statistic
Verbal fluency repetition total	1 (0 - 8)	1 (0 - 3)	1 (0 - 5)	0.577
Verbal fluency perseveration total	0 (0 - 7)	1 (0 - 7)	1 (0 - 9)	5.657
Verbal fluency intrusion total	0 (0 - 6)	1 (0 - 15)	4 (0 - 14)	15.684***
Cross-trial intrusions verbal fluency	0 (0 - 5)	0.5 (0 - 5)	1 (0 - 9)	13.658**
Novel intrusions verbal fluency	0 (0 - 4)	0.5 (0 - 10)	1 (0 - 12)	6.783*
Percentage repetition verbal fluency	3.06 (± 3.92)	2.05 (± 1.98)	3.02 (± 2.98)	0.538
Percentage perseveration verbal fluency	1.66 (± 2.68)	3.22 (± 3.50)	5.49 (± 7.40)	3.721*
Percentage intrusions verbal fluency	1.71 (± 2.80)	5.20 (± 5.77)	9.02 (± 8.34)	9.845***
Percentage novel intrusion verbal fluency	1.11 (± 1.95)	2.94 (± 3.79)	4.33 (± 5.53)	4.310*
Percentage cross-trial verbal fluency	0.59 (± 2.14)	2.26 (± 2.68)	4.68 (± 6.05)	6.459**

Table 9.31 Group comparisons between controls and 3 PD groups on verbal fluency errors

[a] Median and range for non-parametric variables, Kruskal-Wallis comparisons
*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

ANCOVA group comparisons, covarying age, current and premorbid IQ and motor scale score left significant effects for group for percentage total intrusions ($F = 7.020$, $p = 0.002$) and percentage cross-trial intrusions ($F = 4.535$, $p = 0.015$), with a near significant effect for percentage novel intrusions ($F = 3.079$, $p = 0.053$). No significant effects were observed for any other covariates, and therefore intrusions of both types appear to be a robust predictor of hallucinations.

9.5.4 Group comparisons of composite verbal intrusion scores

Group comparisons for the composite measures derived from the logical memory and verbal fluency tasks are shown in table 9.32. (Scores were unavailable for controls as they did not complete the verbal fluency task.) It was hoped that composite scores would provide score with a greater range and therefore a more stable means of comparing low frequency errors such as intrusions. Both raw and percentage scores taking into account total output showed significant differences with hallucinators scoring significantly higher than non-hallucinators on Bonferroni's post-hoc test. Scores for the UPE group fell between those for the other two groups.

	Means (SD)				
	Controls	Non-hall	UPE	Hall	Test statistic
Percentage confabulations LM	4.36 (± 3.06)	3.22 (± 4.39)	7.61 (± 11.57)	12.86 (± 11.15)	8.919***
Confabulations LM + intrusions VF		1 (0 – 11)	3.5 (1 -16)	6 (0 -18)	18.197***
Novel intrusions LM + intrusions VF		1 (0 – 7)	2.5 (0-15)	4 (0 -16)	13.828**
%age confab + %age novel intrusions		3.11 (± 3.63)	10.47 (± 12.42)	15.13 (± 15.08)	7.373**

Table 9.32 Group comparisons between controls and 3 PD groups on composite verbal errors

*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

ANCOVA covarying age, current and premorbid IQ and motor scale score maintained significant effects for both raw ($F = 6.816$, $p = 0.002$) and percentage measures ($F = 6.358$, $p = 0.003$). Significant effects were not observed for any other covariates. Therefore the

composite scores for verbal intrusions have proved to be robust indicators of experiencing hallucinations.

9.5.5 Group comparisons of errors on the VOSP battery

Table 9.33 show group comparisons for errors on the VOSP battery for the four groups. Significant effects were obtained for all measures and post-hoc tests (though not appropriate in a nonparametric comparison) indicated that differences were observed between hallucinators and non-hallucinators as well as hallucinators and controls on all three shape detection error scores, and on incomplete letters incorrect. Hallucinators gave more incorrect answer than any other group on the object decision task. However, incorrect answers on the silhouettes test and *misidentifications* on the object decision task showed differences between hallucinators and controls only.

	Means (SD)				
	Controls	Non-hall	UPE	Hall	Test statistic
VOSP Shape detection false positives	0 (0 - 1)	0 (0 - 1)	0 (0 - 0)	0 (0 - 5)	14.198**
VOSP Shape detection false negatives	0 (0 - 1)	0 (0 - 2)	0 (0 - 2)	0 (0 - 7)	16.221**
VOSP Shape detection confabulations	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 6)	20.587***
VOSP Incomplete letters incorrect	1 (0 - 3)	1 (0 - 5)	1 (0 - 4)	1 (0 - 7)	10.261*
VOSP Silhouettes incorrect	7 (2 - 13)	8 (1 - 14)	8 (4 - 18)	9 (1 - 19)	9.839*
VOSP Object decision incorrect	1 (0 - 5)	2 (0 - 7)	2.5 (0 - 8)	5 (1 - 9)	30.107***
VOSP Object decision misidentifications	1 (0 - 3)	1 (0 - 5)	2 (0 - 6)	2 (0 - 7)	15.611**

Table 9.33 Group comparisons between controls and 3 PD groups on VOSP battery errors using Kruskal-Wallis comparisons

*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

ANCOVA comparisons on VOSP error scores, covarying age, current and premorbid IQ and motor scale score left a significant effect for group on object decision incorrect answers only (F = 5.780, p = 0.005), and a near significant effect for shape detection false negatives (F = 3.099, p = 0.053). No significant effects were observed for any of the covariates.

9.5.6 Group comparisons of errors on the overlapping figures test

Table 9.34 shows group comparisons of errors for the overlapping figures task. Significant differences were observed on number and percentage of misidentifications, and number of repetitions, for which hallucinators scored significantly higher than either hallucinators or controls.

	Means (SD)				
	Controls	Non-hall	UPE	Hall	Test statistic
OF: Total misidentifications[a]	1 (0 - 4)	1 (0 – 5)	3 (1 – 6)	3 (0 – 14)	26.466***
OF: Percentage misidentifications	3.87 (± 3.81)	6.73 (± 6.34)	12.74 (± 5.78)	16.20 (± 13.83)	11.678***
Overlapping figures: repetition total[a]	0 (0 - 1)	0 (0 – 2)	0 (0 – 8)	1 (0 – 5)	18.342***
Overlapping figures: anomia total[a]	0 (0 - 2)	0 (0 – 4)	0 (0 – 1)	0 (0 – 4)	5.639

Table 9.34 Group comparisons between controls and 3 PD groups on VOSP battery errors

[a] Median and range for non-parametric variables, Kruskal-Wallis comparisons
*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

ANCOVA comparisons between the three PD group covarying age, current and premorbid IQ and motor scale score left significant effects for group on both raw score (F = 4.399, p = 0.016) and percentage score (F = 3.951, p = 0.024) for misidentifications.

9.5.7 Group comparisons on composite scores of visual misperception

Table 9.35 shows the composite scores derived for visual misperception from the VOSP subtests and overlapping figures test. Significant differences were observed for both measures, with hallucinators scoring more highly than both controls and non-hallucinators.

	Means (SD)				
	Controls	Non-hall	UPE	Hall	Test statistic
Total visual misidentification	11 (2 - 24)	14 (1 - 26)	17 (9 - 31)	21 (4 - 51)	24.794***
%age total visual misidentification	11.79 (± 5.73)	14.45 (± 7.22)	19.55 (± 6.95)	23.91 (± 11.50)	12.230***

Table 9.35 Group comparisons between controls and 3 PD groups on VOSP battery errors

*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

ANCOVA comparisons between the three PD groups covarying age, current and premorbid IQ and motor scale score revealed significant effects for group on both raw ($F = 3.977$, $p = 0.024$) and percentage scores ($F = 4.092$, $p = 0.022$). No other covariates showed significant effects and therefore the composite score for visual misidentifications appears to give a stable measure showing differences for hallucinators compared to non-hallucinators, independently of covariates.

9.5.8 Group comparisons of errors on the trailmaking test.

Lastly, errors on the trailmaking test are compared below for the three PD groups, in Table 9.36. No significant differences were observed, and neither did ANCOVA comparisons reveal any effect for group after covarying motor scores, and age and global cognitive measures. The

trailmaking test therefore does not appear useful in distinguishing hallucinating patients from non-hallucinators.

	Means (SD)				
	Controls	Non-hall	UPE	Hall	Test statistic
Trailmaking A errors[a]	(-)	0 (0 - 3)	0 (0 - 5)	0 (0 - 5)	5.026
Trailmaking B errors[a]	(-)	1.5 (0 - 3)	2 (0 - 5)	2 (0 - 5)	2.748
Trailmaking A percentage errors	(-)	1.02 (± 2.72)	2.28 (± 5.54)	5.55 (± 9.05)	2.379
Trailmaking B percentage errors	(-)	6.84 (± 7.85)	12.09 (± 8.92)	15.58 (± 15.54)	2.597

Table 9.36 Group comparisons for error scores on cognitive variables (Mean, standard deviation and ANOVA)

[a] Median and range for non-parametric variables, Kruskal-Wallis comparisons
*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

9.5.9 Summary

Group comparisons between PD hallucinators and non-hallucinators have revealed the value of examining qualitative performance on neuropsychological test, and specifically the types of errors made. Hallucinators were more likely to display deficits on the intersecting pentagons item of the MMSE, reflecting findings of specific difficulties with this item in patients with PDD and DLB. Low raw scores on many of the error scores made ANCOVA comparisons controlling for covariates difficult, though comparisons of percentage scores were more stable, although after controlling for covariates several of the differences were lost. The most robust findings were a greater number of novel and cross-trial intrusions on the verbal fluency task, more incorrect identifications on the object decision test and misidentifications on the

overlapping figures test, which were independent of covariates. ANCOVA comparisons for the composite confabulations and intrusions scores, and for the composite visual misidentification scores showed significantly higher scores for hallucinators. Therefore hallucinators show a tendency toward certain types of cognitive error or bias, across a range of neuropsychological tests.

9.6 Relationship of cognitive scores to QUE factor scores

9.6.1 Correlation with correct cognitive scores

Table F.14, Appendix F, shows the shows the relationship between correct cognitive scores and hallucinations summed and factor scores and the three sleep factors derived from the QUE. Those variables which were significantly correlated with one or more of these variables are shown in the table 9.37 below.

	QUE visual hallucinations summed score	QUE visual hallucinations factor score	QUE sleep activity factor	QUE daytime sleepiness factor	QUE altered dreams factor
MMSE total score	-0.267*	-0.266*	-0.025	-0.139	-0.341**
Mill Hill Vocab total score	-0.160	-0.132	0.079	0.125	-0.213
Full NART equivalent score	-0.171	-0.196	0.146	0.143	-0.066
Logical memory Total Recall 1+2	-0.080	-0.113	0.000	-0.125	-0.238*
Logical memory Total Recall 1+2+2	-0.093	-0.134	0.036	-0.099	-0.236*
Logical memory Total Recall II	-0.177	-0.205	-0.078	-0.063	-0.197
Logical memory Visit 2 story recall	-0.171	-0.180	-0.041	-0.044	-0.112
Logical memory Learning slope	-0.150	-0.162	0.038	-0.017	-0.001
Logical memory Total Theme 1+2+2	0.008	-0.035	-0.003	-0.126	-0.168
Logical memory Total Theme II	-0.148	-0.199	-0.121	-0.071	-0.174
Logical memory Visit 2 theme recall	-0.148	-0.165	-0.098	-0.010	-0.137
Logical memory Total Recog	-0.218	-0.247*	0.106	-0.298*	-0.115
VOSP Shape detection total	-0.342**	-0.364**	0.053	-0.034	-0.224
VOSP Incomplete letters total	-0.329**	-0.284*	0.073	-0.007	-0.189
VOSP Silhouettes total	-0.164	-0.231	-0.032	-0.038	-0.257*
VOSP Object decision total	-0.151	-0.143	0.054	0.121	-0.283*
VOSP Progressive silhouettes total	0.130	0.152	-0.002	0.083	0.271*
VOSP Grand total	-0.247*	-0.262*	0.034	0.005	-0.315**
Overlapping figure A time to 8 (in secs)	0.008	-0.071	0.032	-0.158	0.406**
Overlapping figure A total objects named	-0.085	-0.086	0.219	-0.069	-0.253*
Overlapping figure B time to 8 (in secs)	0.241	0.154	-0.045	0.297*	0.192
Overlapping figure B total objects named	-0.369**	-0.380***	0.107	0.020	-0.380***
Total figures named OFigs A + B	-0.253*	-0.260*	0.170	-0.023	-0.340**
Verbal fluency letter total	-0.082	-0.049	0.062	0.046	-0.316**
Verbal fluency category total	-0.146	-0.130	0.048	-0.226	-0.215
Verbal fluency alternating letter total	-0.228	-0.211	-0.042	-0.144	-0.237*
Verbal fluency alternating category total	-0.357**	-0.346**	-0.075	-0.161	-0.311**
Verbal fluency alternating let/cat total	-0.219	-0.222	-0.144	-0.006	-0.327**
Verbal fluency grand total	-0.234*	-0.221	-0.023	-0.130	-0.319**
Block design total correct	-0.389**	-0.361*	0.074	-0.281	-0.171
Block design total points	-0.350*	-0.293*	0.153	-0.377**	-0.161

Table 9.37 Correlations between QUE factor and summed scores and cognitive variables.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

	QUE visual hallucinations summed score	QUE visual hallucinations factor score	QUE sleep activity factor	QUE daytime sleepiness factor	QUE altered dreams factor
Trailmaking A time (in secs)	0.367**	0.332*	0.089	0.111	0.197
Trailmaking B time (in secs)	0.370**	0.352*	0.086	-0.010	-0.117
Trailmaking A complete / 25	-0.17	-0.086	-0.121	-0.116	0.166
Trailmaking B complete / 25	-0.149	-0.138	0.028	0.031	-0.250
Time per correct response A	0.342*	0.265	0.133	0.144	0.011
Time per correct response B	0.243	0.250	0.0250	0.014	0.128
Standard deviation RT test undivided	0.308*	0.278*	0.117	0.155	0.239
Mean RT test undivided	0.450***	0.494***	-0.021	0.226	0.362**
Coefficient of variation RT test undivided	0.116	0.052	0.193	0.044	0.119
Standard deviation RT test divided	0.466***	0.453***	-0.129	0.021	0.245
Mean RT test divided	0.516***	0.555***	-0.156	0.124	0.285*
Coefficient of variation RT test divided	0.227	0.167	-0.071	-0.075	0.098

Table 9.37 Correlations between QUE factor and summed scores and cognitive variables (cont). * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

To investigate the value of those variables associated with hallucinations scores in adding to the existing model, partial correlations were conducted covarying those variables already used in the model. For the hallucinations factor score these were MMSE, motor scale score, time spent napping and sleep activity summed score. For the hallucinations summed score covariates were MMSE, motor scale score, ESS and sleep activity summed score. For verbal fluency variables reading time was also covaried, and for the trailmaking, block design and attention task dexterity factor score was also covaried.

9.6.2 Relationship with correct factor scores, controlling for covariates

Tables 9.38 and 9.39 show those variables which were still significantly associated with hallucinations factor or summed scores, after covariates were partialled out.

	QUE visual hallucinations summed score
VOSP Shape detection total	-0.272*
VOSP Incomplete letters total	-0.242*
Overlapping fig B total objects named	-0.366**
Total figures named OFigs A + B	-0.263*
Verbal fluency alternating category total	-0.201
Block design total correct	-0.377*
Block design total points	-0.320*
Trailmaking B time (in secs)	0.315*
Mean RT test undivided	0.375**
Standard deviation RT test divided	0.401**
Mean RT test divided	0.481**

Table 9.38 Partial correlation between hallucinations summed score and correct cognitive scores, covarying MMSE, motor scale score, time spent napping and sleep activity summed score.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

	QUE visual hallucinations factor score
VOSP Shape detection total	-0.288*
VOSP Incomplete letters total	-0.194
Overlapping figure B total objects named	-0.276*
Total figures named OFigs A + B	-0.112
Verbal fluency alternating category total	-0.262*
Block design total correct	-0.362*
Block design total points	-0.259
Trailmaking B time (in secs)	0.309*
Mean RT test undivided	0.406**
Standard deviation RT test divided	0.407**
Mean RT test divided	0.532***

Table 9.39 Partial correlation between hallucinations summed score and correct cognitive scores, covarying MMSE, motor scale score, Epworth Sleepiness Scale and sleep activity summed score.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Tables 9.38 and 9.39 show that no logical memory variables were associated with hallucinations scores, independently of the variables belonging to the existing models. Poorer scores on visual tests, including shape detection, incomplete letters and the overlapping figures test were associated with higher hallucinations scores, though more consistently for the summed score. Of verbal fluency scores, only the alternating category score was associated with hallucinations scores and for the factor score only. Poorer scores on block design as measured by total correct or points weighted for speed were associated with greater hallucinations scores, though more consistently for the summed score. Time to complete trailmaking B was also associated with hallucinations scores, though this was not corrected for number of responses complete and so this seemed to be an arbitrary association. Slower response times on the attention task on both divided and undivided conditions was also associated with higher hallucinations score as was standard deviation for RT on the undivided task.

9.6.3 Correlation with cognitive error scores

Table 9.37 shows the relationship between cognitive error scores and hallucinations summed and factor scores and the three sleep factors derived from the QUE.

	QUE visual hallucinations summed score	QUE visual hallucinations factor score	QUE sleep activity factor	QUE daytime sleepiness factor	QUE altered dreams factor
MMSE orientation score	-0.236*	-0.262*	0.009	-0.225	-0.241*
MMSE repetition	0.082	0.097	-0.111	-0.105	-0.012
MMSE serial	-0.052	-0.002	-0.023	-0.098	-0.052
MMSE recall	-0.08	-0.14	-0.017	-0.06	-0.132
MMSE object naming	-0.053	-0.067	-0.031	-0.119	-0.073
MMSE Three stage task	-0.460***	-0.440***	-0.061	0.027	-0.405***
Hits LM recognition	-0.126	-0.188	0.093	-0.088	-0.018
Correct negatives LM recognition	-0.038	-0.015	0.152	-0.284*	-0.117
False alarms LM recognition	0.056	0.032	-0.162	0.305*	0.111
Misses LM recognition	0.092	0.152	-0.076	0.056	0.029
False alarms: correct negative ratio LM	0.142	0.148	-0.12	0.268*	0.072
Recall inaccuracies new to trial 5	0.186	0.128	0.143	-0.03	0.078
Novel intrusion new to trial 5	0.226	0.155	-0.134	0.192	0.053
Cross-trial errors new to trial 5	0.097	0.049	0.305**	0.181	0.082
Recall inaccuracies total to trial 5	0.102	0.054	0.104	-0.049	0.03
Novel intrusion total to trial 5	0.287*	0.219	-0.126	0.186	0.047
Cross-trial errors total to trial 5	0.097	0.049	0.305**	0.181	0.082
Percentage new recall inaccuracies	0.158	0.151	0.174	0.016	0.111
Percentage new novel intrusions	0.174	0.168	-0.120	0.195	0.102
Percentage new cross-trial errors	0.048	0.013	0.320**	0.165	0.207
Percentage total recall inaccuracies	0.090	0.082	0.130	-0.010	0.084
Percentage total novel intrusions	0.244*	0.218	-0.139	0.187	0.075
Percentage total cross-trial errors	0.048	0.013	0.320**	0.165	0.207
Novel intrusions LM + intrusions VF	0.417***	0.390***	-0.058	0.148	0.148
%age confab + %age novel intrusions	0.416***	0.380***	-0.104	0.203	0.203
VOSP Shape detection false positives	0.386***	0.383***	-0.107	0.176	0.071
VOSP Shape detection false negatives	0.226	0.257*	0.018	-0.078	0.219
VOSP Shape detection confabulations	0.23	0.247*	0.132	0.073	-0.004
VOSP Incomplete letters incorrect	0.293*	0.239*	0.013	0.115	0.006
VOSP Silhouettes incorrect	0.274*	0.309**	0.116	0.278*	0.188
VOSP Object decision incorrect	0.341**	0.323**	0.071	-0.013	0.211
VOSP Object decision misidentifications	0.213	0.22	-0.027	0.124	0.131

Table 9.37 Correlations between QUE factor and summed scores and cognitive error scores.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

	QUE visual hallucinations summed score	QUE visual hallucinations factor score	QUE sleep activity factor	QUE daytime sleepiness factor	QUE altered dreams factor
Total misidentifications OFigs A + B	0.329**	0.305**	0.043	0.194	0.309**
Percentage misidentifications OFigs	0.296*	0.283*	0.003	0.224	0.305*
Ofigs: repetition total	0.203	0.204	-0.058	0.012	0.047
Ofigs: anomia total	0.025	0.092	0.233	-0.132	-0.085
Verbal fluency repetition total	0.064	0.117	-0.053	-0.038	-0.01
Verbal fluency perseveration total	0.256*	0.293*	0.057	0.155	0.311**
Verbal fluency intrusion total	0.390***	0.390***	0.035	0.077	-0.135
Cross-trial intrusions verbal fluency	0.256*	0.265*	-0.117	0.183	-0.159
Novel intrusions verbal fluency	0.365**	0.360**	0.155	-0.056	-0.05
Percentage repetition verbal fluency	0.115	0.177	0.01	-0.023	0.032
Percentage perseveration verbal fluency	0.225	0.264*	0.147	0.108	0.445***
Percentage intrusions verbal fluency	0.428***	0.395***	0.029	0.159	-0.079
Percentage novel intrusion verbal fluency	0.406***	0.364**	0.208	0.021	-0.024
Percentage cross-trial verbal fluency	0.260*	0.251*	-0.151	0.219	-0.096
Trailmaking A errors	0.353*	0.308*	-0.038	-0.078	0.256
Trailmaking B errors	0.283*	0.288*	0.085	-0.225	0.19
Trailmaking A time per error	0.346*	0.277	0.029	-0.004	0.113
Trailmaking B time per error	0.219	0.22	-0.032	-0.134	0.302*

Table 9.37 Correlations between QUE factor and summed scores and cognitive error scores (cont). * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

9.6.4 Correlations with cognitive errors scores, controlling for covariates

Tables 9.41 and 9.42 show those variables which were still significantly associated with hallucinations factor or summed scores, after covariates were partialled out.

	QUE visual hallucinations summed score
VOSP Shape detection false positives	0.158
VOSP Object decision incorrect	0.245*
Total misidentifications OFigs A + B	0.284*
Percentage misidentifications OFigs	0.259*
Overlapping figures repetition total	0.254*
Visual misidentifcations percentage	0.332**
Verbal fluency intrusions total	0.338**
Novel intrusions verbal fluency	0.318**
Percentage intrusions verbal fluency	0.309*
Percentage novel intrusion verbal fluency	0.276*
Novel intrusions LM + intrusions VF	0.372**
%age novel intrusions LM + intrusions VF	0.344**
Trailmaking A errors	0.359*
Trailmaking B errors	0.282

Table 9.41 Partial correlations between hallucinations summed score and cognitive error scores, covarying MMSE, motor scale score, time spent napping and sleep activity summed score.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

	QUE visual hallucinations factor score
VOSP Shape detection false positives	0.329*
VOSP Object decision incorrect	0.192
Total misidentifications OFigs A + B	0.173
Percentage misidentifications OFigs	0.142
Overlapping figures repetition total	0.180
Visual misidentifcations percentage	0.282*
Verbal fluency intrusion total	0.376**
Novel intrusions verbal fluency	0.363**
Percentage intrusions verbal fluency	0.335**
Percentage novel intrusion verbal fluency	0.325*
Novel intrusions LM + intrusions VF	0.374**
%age novel intrusions LM + intrusions VF	0.346**
Trailmaking A errors	0.300
Trailmaking B errors	0.344*

Table 9.42 Partial correlations between hallucinations summed score and cognitive error scores, covarying MMSE, motor scale score, Epworth Sleepiness Scale and sleep activity summed score.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

9.7 Predicting hallucinations – how do neuropsychological variables improve the model

The final section in this chapter builds on the model developed throughout the results section, adding further steps using the neuropsychological measures described in this chapter. Following findings from previous studies, the next step in the model will consider visual perceptual variables, as there is a small but consistent body of work describing specific visual deficits in hallucinating PD patients (see Chapter 2, and Appendix A). Following steps will assess the predictive value of other neuropsychological factors such as executive function, memory, construction and attention, as there are few consistent findings in these areas.

9.7.1 Multiple regression – predicting current hallucinations scores

Step 4 – Visual variables

In a model predicting the QUE summed hallucinations score, previous steps in the regression were MMSE total score, total motor examination scale score (UPDRS), total time asleep during the day and a summed score for the sleep activity factor; together predicting 23.0% of the overall variance (R = 0.479). Those variables significantly correlated with the QUE summed score after controlling for covariates (see Table 9.41) were entered as a fourth step, and the best model was achieved with the composite score for visual errors (R = 0.556; R^2 = 0.309). The model predicting the QUE VH *factor* score included previous steps of MMSE score, motor examination score, Epworth Sleepiness Scale score and the sleep activity summed score. On adding visual variables as a fourth step, the best model was achieved again with the composite score for visual errors (R = 0.530; R^2 = 0.281). It is of note that the visual *error* scores were more predictive than any of the correct visual scores suggesting that visual *mis*perception

where an inaccurate identification has been made, rather a simple failure of perception, is key to the experience of visual hallucinations.

Further steps – Other cognitive variables

Further steps in the regression were added to obtain the best model for both the QUE summed and factor scores. In a similar fashion manner to the previous step, the composite verbal error score was a stronger predictor than correct scores for executive and memory tasks for both dependent variables. Mean RT for the divided attention task also added to the model as a final step for both outcome variables, highlighting the role of attention, although not *fluctuations* in attention as hypothesised. The final models are presented below, with both achieving over 56% explanation of variance, and p values of <.001.

Step		R	R^2
1	MMSE Motor examination scale	.299	.090
2	Total time asleep during the day	.391	.153
3	Sleep activity summed score	.479	.230
4	Composite visual errors score	.556	.309
5	Composite verbal errors score	.613	.375
6	Mean RT divided attention task	.750	.562

Table 9.43 Final linear regression model to predict QUE summed hallucinations score

Step		R	R^2
1	MMSE Motor examination scale	.271	.074
2	Epworth Sleepiness scale	.369	.136
3	Sleep activity summed score	.446	.199
4	Composite visual errors score	.530	.281
5	Composite verbal errors score	.585	.342
6	Mean RT divided attention task	.752	.566

Table 9.44 Final linear regression model to predict QUE summed hallucinations score

CHAPTER 10

DISCUSSION

10.1 Review of the results

The following section reviews results of the present study and compares them to previous findings, and discusses the theoretical limitations.

10.1.1 Hypothesis 1

The first hypotheses concerning the multi-dimensional nature of sleep-related symptoms and unusual perceptual experiences was supported both by the pilot study and the main study. Chapter 6 details the factor structure of the sleep symptoms for both studies, with similar results, yielding a 'sleep activity' factor, an 'altered dream phenomena' factor, and for the main study an 'excessive daytime sleepiness' factor. Chapter 6 also detail the factor structure for the unusual perceptual experiences and hallucinations items, each giving a similar factor representing the archetypal experience of (predominantly visual) hallucinations in PD. The similarity between the factors generated by the two analyses suggests that these are indeed robust associations between certain clusters of symptoms, and that these may reflect aetiological differences. These findings demonstrate the value of a factor analytic approach in examining the phenomenology of neuropsychiatric and psychotic symptoms, as has been demonstrated in the Alzheimer's literature (Lerner et al, 1994; Harwood et al, 1998; Ballard et al, 1995) and the schizophrenia literature (Andreasen et al, 1982). Frith (1992) and Bentall (1997) argue for the examination of single symptoms or a cluster of symptoms based on *empirical* associations, when developing a model of mechanisms to explain psychotic phenomenon. Grouping symptoms merely on the basis of phenomenological similarities may

assume homogeneity where none exists, and confuse what are in fact distinct mechanisms underlying them. Earlier studies using a single item to assess hallucinations, or including hallucinations with other 'psychotic' behaviours such as delusions may have in fact been seeking concomitants for more than one phenomenon.

10.1.2 Hypothesis 2

It was hypothesised that the distinct sleep factors would show *different* patterns of associations with clinical variables including disease severity and cognition, and also with hallucinations. For the pilot study, both sleep factors (sleep activity, and altered dream phenomena) were associated with the hallucinations factor score, and with disease severity, with symptoms increasing in frequency as the disease progressed. Further analysis however, revealed different patterns of association for the two factors. Sleep activity was primarily associated with disease severity and duration, and was no longer correlated with the hallucinations score once these severity variables were covaried. Altered dream phenomena, on the other hand, were associated with hallucinations even after severity and duration were covaried. These findings emphasise the importance of covarying disease severity which may act as a key confounding variable when examining associations amongst symptoms. They also reflect an earlier study by Pappert et al (1999) which found that 'altered dream phenomena' were empirically associated with hallucinations, whereas sleep fragmentation was not.

The main study also found that the distinct factors showed different patterns of association with hallucinations and other clinical variables. However, despite the fact that sleep factors derived from the pilot and main studies were conceptually similar, there was no consistency in their pattern of associations with other variables. For the main study it was 'sleep activity' that was associated with hallucinations independently of disease severity, whereas 'altered dream

phenomena' were not. It would therefore appear that although factor structure amongst sleep symptoms may be relatively stable across PD samples, the variables that they are associated with is not. Section 6.2.3 discusses the various methodological differences between the two studies and why these may have caused such a discrepancy between results. Empirical explanations include the addition of extra sleep items in the main study which led to a three factor solution with 'daytime sleep' as the third, and use of a different frequency scale to increase raw scores in the main study. Methodological explanations include (i) the use of different data collection methods (self-report questionnaire versus experimenter administered interview), (ii) the use of different types of sample (one attending a local support group and one recruited from an outpatient clinic) and (iii) the use of different measures of severity (self-report ADL scale versus motor examination). Although chapter 6 attempted to address these possibilities empirically by reanalysis, none of these explanations seemed to account for the discrepancy. It is most likely that the differences arose from small sample sizes, reducing the power of any analysis involving covariates, and that a larger sample is needed to achieve a stable and replicable result. Nonetheless, the hypothesis was supported in that the different factors did indeed show a distinct pattern of associations with clinical variables and hallucinations, although this was inconsistent across the two studies.

Previous studies and reviews have supported the notion that altered dream phenomena such as vivid dreams are associated with hallucinations (Moskowitz et al, 1978; Nauseida et al, 1982; Sharf et al,1978). However, in most cases these were based on anecdotal evidence, and one empirical study confirming this did not take disease severity into account statistically (Pappert et al, 1999). Two objective studies of the relationship between dream activity found that daytime hallucinations were likely to occur following napping episodes or sleep where REM activity was observed polysomnographically (Arnulf et al, 2000; Manni et al, 2002). In the

PD, narcolepsy and sleep deprivation literature the idea of 'REM breakthrough' where REM activity occurs on the boundaries of sleep and wake leading to abnormal percepts has received much attention. This idea has also been grounded in neurobiological theory, and Manford & Andermann (1999) provide an elegant model of disinhibition of visual afferent transmission to the cortex when changes in consciousness controlled by the reticular activating system occur. The current study assesses only subjective reports of vivid dreams, and lack of insight or recall of dreams may well mean that such an association with hallucinations is missed when using subjective data.

Associations between REM behavioural disorder and hallucinations are more difficult to explain theoretically. The finding that RBD is associated with disease severity is supported by the model of dopaminergic loss in the substantia nigra which has a reciprocal connection with the PPN, and which is in turn connected with the REM-atonia circuit (Pal et al, 1999; Gagnon et al, 2002). Moreover, RBD often precedes the onset of motor systems (Schenk et al, 1996), suggesting that dopamine loss in the nigrostriatal pathway may manifest in pathology of the motor system during sleep, before it is severe enough to impair waking movement to a clinical level. Investigations of RBD in Parkinson's Disease patients have found that medication related factors play a key role. Boeve et al (1999) found that patients with RBD who went on to develop cognitive impairment showed a pattern of neuropsychological deficits similar to that found in DLB. Therefore RBD, extra-pyramidal motor signs and hallucinations will co-occur in some patients. However, it is likely that RBD is a different outcome of the same pathological processes in the α-synucleinpoathies which contribute to the genesis of hallucinations, rather than being implicated as a mechanism itself. In the main study, the daytime sleepiness factor was *not* associated with the hallucinations score, which contradicts previous findings (Fenelon et al, 2000; Arnulf et al, 2000; Tandberg et al, 1999; Gjersted et al, 2002), and the theories

described above. Given other results, it is likely that the subjective nature of the data collected and the high frequency of daytime sleepiness led to a ceiling effect where the factor was non-discriminating in its associations. More objective measures of daytime sleep, or measures of its severity in terms of frequency and duration each day may reveal an association with hallucinations. The use of frequency over the last three months may have been too sensitive for daytime sleepiness in PD, as many patients napped every day. Daytime sleep was not associated with disease severity either, as has been found by Tandberg et al (1999), and confirmed longitudinally by Gjersted et al (2002), and therefore a ceiling effect may have left these associations undetected also.

Neither sleep activity nor altered dream phenomena were associated with age, suggesting that they result from the various pathophysiological effects of PD, rather than the normal ageing process. Daytime sleep on the other hand, was associated with age, whereby levels of daytime napping and drowsiness increased with age, as has been found in healthy populations.

To summarise, both 'sleep activity' and 'altered dream events' were associated with hallucinations, but their association with disease severity was inconsistent and where variance was shared with disease severity, some associations with hallucinations were lost.

10.1.3 Hypothesis 3

Following studies investigating motor phenotypes of PD and whether they have distinct correlates and prognoses (Burn et al, 2003; Levy et al, 2000, Jankovic et al, 1990), it was hypothesised that the UPDRS items used for the current study would show a multi-dimensional factor structure. Chapter 6 details the factor structure of the pooled UPDRS items, yielding a six factor solution. The strongest factor 'ambulatory items' has conceptual similarities with Jankovic et al's (1990) Postural-Instability-Gait Dominant (PIGD) subtype, which has been

found to represent a poorer prognosis in terms of disease progression and likelihood of cognitive impairment compared with a Tremor Dominant (TD) subtype. The ambulatory factor was correlated positively with the visual hallucinations summed score, and negatively with MMSE score, suggesting that patients with prominent 'ambulatory' or axial symptoms have a poorer prognosis in terms of cognitive decline and risk for hallucinations, although the present study could not assess this prospectively. Accordingly Fenelon et al (2000) and Graham et al (1997) found that axial signs were associated with hallucinations in PD patients, and Burn et al (2003) found that the axial symptom or PIGD subtype predominates in PDD and DLB patients, who show greater levels of neuropsychiatric symptoms including hallucinations (Aarsland et al, 2001). Considering motor symptoms as separate factors has thus allowed identification of one facet of disease severity that is more highly associated with hallucinations and cognitive decline than others. Implications of this include the hypothesis that hallucinations in PD and the wider α-synucleinopathies are mediated by changes in the cholinergic system (Perry & Perry, 1995 etc), as axial symptoms are likely to arise from pathology outside the basal ganglia, and are less responsive to dopamine replacement. Indeed the positive association between the 'offs/freezing' factor and hallucinations (see section 6.2.3.5) may reflect the fact that hallucinators are less responsive to the positive effect of DRT.

Of the motor factors, only the tremor factor was associated significantly with any of the sleep factors, and showed a positive correlation with the altered dream phenomena factor. If tremor dominant and PIGD subtypes are indeed associated with different outcomes, this finding is at odds with the idea that altered dream events and hallucinations should co-occur in the same individuals, but is consistent with the findings of the main study. The tremor factor was not associated with any other variables including global cognition.

To summarise, different facets of motor performance were associated with different clinical variables; the 'ambulatory' factor was correlated with age, cognitive decline and hallucinations; the 'offs/freezing' factor with hallucinations and disease and medication duration, and the 'dexterity' factor with cognitive decline. Tremor symptoms did not appear to show associations with adverse outcomes, other than altered dream phenomena. Thus disease severity itself is a multi-faceted concept, and the present study lends support to the hypothesis that different phenotypes of PD have differential outcomes, including likelihood of developing hallucinations.

10.1.4 Hypothesis 4

A sample of healthy older adults was used as a control group for statistical comparisons, to confirm the presence or absence of deficits or greater levels of symptomatology in PD patients compared to their healthy counterparts. A difference in global cognitive measures that was independent of other potential confounders such as age, premorbid IQ and depression was hypothesised, where the PD patients would score more poorly. (In the PD group, both increased depression and age, and lower premorbid IQ were associated with poorer performance on global cognitive tests.) The hypothesis was indeed confirmed using both the MMSE and a measure of current verbal IQ, and neither the slightly younger age of controls, nor their significantly lower levels of depression could explain this difference. As a whole then, the PD group showed significantly poorer global cognitive ability, although this only reached the MMSE cut-off for mild dementia in 13 (16.7%) PD patients. Differences in current IQ between hallucinators and non-hallucinators demonstrate the importance of covarying global cognitive status, when examining specific cognitive deficits in PD patients, which for the purposes of this study were assumed to be independent of a global cognitive decline.

10.1.5 Hypothesis 5

Following the robust associations between hallucinations and increased disease severity and greater cognitive decline in the literature (see tables A.1 and A.2 for details) it was hypothesised that the hallucinators in the present study would show the same pattern of results, independently of other covariates. This was indeed the case for disease severity with hallucinators showing significantly higher scores on the UPDRS motor examination scale as has been found by previous studies. However, hallucinators did not show longer disease duration. The fact that there were no differences on disease duration suggests that hallucinators may show a more *rapid* increase in severity over time as has been shown by Kraft et al (1999). Furthermore, Goetz et al (1999) showed that a group of patients initially treated for PD developed hallucinations relatively early in the disease, within 3 months of commencing levodopa treatment, and that several of these were later diagnosed as having symptoms consistent with dementia. It is therefore possible that a subgroup of 'PD' patients experience hallucinations early in the disease, whereas others develop them after a number of years, thus confounding associations with duration. Some studies have divided hallucinators into early onset groups (within 5 years disease onset) and later onset groups (more than 5 years after disease onset), finding that both early and late hallucinators showed greater levels of disease severity than non-hallucinators matched for disease duration. However, early hallucinators showed a more rapid onset of motor fluctuations (Graham et al, 1997), and late hallucinators showed more axial signs (Graham et al, 1997; Fenelon et al, 2000). These findings again suggest that two subtypes of PD patient exist, and reflect the two motor factors which were associated with hallucinations in the current study; the 'ambulatory' factor, and the 'offs/freezing' factor. Some studies have suggested that hallucinations are more likely to occur during 'on' periods, when plasma dopamine levels are at their peak (Sanchez-Ramos et al,

1996; Klein et al, 1997), though see Fernandez et al (1992) for exception. The present study showed no relationship between dyskinesias and hallucinations, and neither was there an effect for the fluctuations scale total score. One direct experimental investigation of this theory also found that PD patients with regular hallucinations were not more likely to experience them during infusion of levodopa (Goetz et al, 1998), arguing against a simplistic correlation between plasma levodopa and hallucinations. It is more likely, as detailed in Chapter 2 that a complex relationship between receptor sensitivity and hallucinations exists, following upregulation of a dwindling number of dopaminergic neurons, and that neurotransmitters other than dopamine are involved (Perry & Perry, 1995; Gomez-Tortosa et al, 1999; Perry et al, 2003). To summarise, disease severity as measured by the UPDRS motor examination scale, and also specific facets of severity 'ambulatory' or axial signs, and off periods and freezing were significantly associated with hallucinations, although disease duration was not.

Global cognitive ability, measured in the present study by the MMSE and current verbal IQ, was significantly poorer in hallucinators in the current study, as has been found by most other studies. In addition, hallucinators were more likely to have a MMSE score that fell within the criterion range for dementia. A strong relationship existed between disease severity and global cognition, indicating the importance of covarying severity when conducting group comparisons. MMSE score was still significantly poorer in hallucinators when disease severity, as well as age, depression and premorbid IQ were covaried. As mentioned above, there likely exist two or more subgroups of hallucinating patients; and 'early hallucinators' when defined as those developing hallucinations shortly after commencing levodopa are more likely to be diagnosed with a dementing condition five years later (Goetz et al, 1999). Studies of early and late hallucinators found that the late hallucinators displayed more axial signs, which has been established as a predictor of later cognitive decline (Jankovic et al, 1990). However, when

early hallucinators are defined as those developing hallucinations within 5 years of PD onset they are not more likely to show cognitive decline, whereas late hallucinators (> 5 years) are, compared to patients matched for disease duration. Given that DLB has emerged as a recognised diagnostic entity relatively recently, it is possible that some earlier studies included DLB patients and PDD patients in their PD sample. There is evidence that the risk of hallucinations as a side-effect of DRT may be heightened in DLB (Goetz et al, 1998; McKeith et al, 1996). Those patients in Goetz et al's (1998) study who developed hallucinations shortly after starting DRT were likely to be diagnosed with DLB or AD five years later, those who develop hallucinations within five years of PD onset and show more motor fluctuations (Graham et al, 1997) may develop hallucinations primarily as a result of medication side-effects, neuronal adaptation and upregulation, and finally those with late hallucinations (> 5 years) who show more axial signs suggesting PIGD subtype (Graham et al, 1997; Fenelon et al, 2000), display global cognitive deficits which may include *specific* cognitive deficits which heighten vulnerability to hallucinations and compromise reality monitoring abilities. To summarise, hallucinators display greater levels of global cognitive decline, though there is a complex relationship with disease duration and specific motor signs, which suggests there are subgroups of hallucinators, some displaying greater levels of cognitive impairment than others.

10.1.6 Hypothesis 6

The first two hypotheses addressed the phenomenology of subjective sleep symptoms and their associations with hallucinations and clinical variables in PD patients. It was also hypothesised that PD patients would show a greater level of sleep-related symptoms than a control group of healthy older adults; namely increased levels of daytime sleepiness, 'altered dream events' and 'sleep activity'. Group comparisons on summed scores for the three factor

indicated that PD patients experienced significantly more daytime sleepiness and sleep activity, but not greater levels of altered dream events. As items belonging to the altered dream events factor had the lowest medians for both groups, a trend for greater scores in the hallucinators may not have reached significance due to skewing. Although daytime sleepiness increases with age, it is clear that this is exaggerated in PD patients, and may be of a qualitatively different nature, sometimes occurring as 'sleep attacks' (Olanow, 2001) with rapid onset at inappropriate times such as when driving or during meals.

10.1.7 Hypothesis 7

Using a subjective questionnaire about sleep-related symptoms, PD patients were shown to have greater summed scores for the daytime sleepiness items. Further hypotheses were made about nocturnal and daytime sleep pattern measured both subjectively and objectively and circadian rhythm conceptualised as rest-activity rhythm.

Firstly, it was hypothesised that PD patients would show a more fragmented pattern for nocturnal sleep with a greater number of awakenings during the night. This was the case with self-reported number of awakenings with data from both interview and diary measures, as found by Van Hilten et al (1993), but was not reflected in actigraphic data, with a significantly greater number of 'wake' bouts for controls, and no differences on the 1 minute immobility score or the fragmentation index. Given the disparity between self-report and activity measures, it is possible that actigraphy is less able to detect WASO in patients with movement disorders, if WASO is marked by activity of low amplitude, or if PD patients are woken by periods of rigidity, with little movement. Accordingly, nightime awakenings were associated with longer disease duration, greater motor fluctuations, and more specifically the 'offs/freezing' factor. suggesting firstly that sleep maintenance declines as the disease

progresses (Van Hilten et al, 1994), and secondly 'off' periods lead to a more fragmented sleep, as PD patients experience difficulty turning, pulling up bed covers and uncomfortable rigidity (Van Hilten et al, 1993). No effects were found for overall duration of wake or sleep on any measures. Therefore, despite the fact that *duration* for wake and sleep are similar in controls and PD patients, sleep *maintenance* seems to be poorer in PD patients. Healthy older adults may experience sleep that is less broken, but characterised by early morning waking, reducing overall sleep duration. Secondly, it was hypothesised that increased scores on the daytime sleepiness items on the QUE would be reflected by greater number of daytime naps, and a greater overall duration of sleep during the day. These hypotheses were supported using interview data, diary data and actigraphy (controlling for overall activity level). In addition there was support for the idea of a more overwhelming pressure of sleep in PD patients, with higher scores on the Epworth Sleepiness Scale and lower self-reported ability to resist sleep in the day. Indeed several PD patients achieved scores of >10 on the ESS which is considered a pathological level of daytime sleepiness (Zeman et al, 2001), and many slept for more than 2 hours per day which Tandberg et al (1999) define as 'excessive daytime sleepiness'. Using the MSLT as a more objective measure of rapid onset sleepiness, Arnulf et al (2000) and Roth et al (2002) describe a rapid sleep onset in some PD patients, which is comparable to speed of sleep onset in narcolepsy. Daytime sleep was associated with age, motor severity, and cognitive decline in the present study, which is reflected in the literature (Tandberg et al, 1999; Gjersted et al, 2002). In themselves, reduced mental abilities, physical disability and old age are likely to reduce physical and mental engagement in the form of household chores and leisure activity, thus increasing the likelihood of dozing though boredom. However, group differences in daytime sleepiness were independent of age and global cognition. To summarise, PD patients show a greater degree of daytime sleepiness than healthy older

adults, independently of age and global cognition, and in some patients this can be considered 'excessive' daytime sleepiness, and may be similar to the rapid onset, overwhelming sleep experienced by narcolepsy patients.

An alternative explanation of both nighttime sleep fragmentation and daytime sleepiness is that they reflects loss of the normal monophasic circadian rhythm, and replacement with a polyphasic rhythm. A third hypothesis was that PD patients would display a loss of the typical circadian rhythm signal, with more frequent transitions from high to low activity, or sleep to wake, and loss of strength of the overall signal across a number of days. Indeed PD patients showed greater levels of intradaily variability in their activity rhythms and lower interdaily stability, both of which are measures that are independent of the overall reduced levels of activity in PD patients. However, motor fluctuations were a major confounding variable in assessing intradaily variability, as the alternation of off periods with dyskinesias will induce transitions in activity levels that mask 'core' circadian rhythm that might be indexed by changes in temperature or cortisol levels. Therefore a healthy non-disabled population may not provide a comparable group. Apart from fluctuations score and the dyskinesias factor, circadian rhythm variables were correlated with age in PD patients. It is well-documented that age can induce phase advance of circadian rhythm, and also so that normal ageing can lead to adoption of a polyphasic circadian rhythm (Vitellio et al, 1986; Weitzman et al, 1982). Group differences between PD patients and controls were however independent of age, suggesting that the disease process in PD may exaggerate the effect of ageing or affect key structures involved in maintaining circadian rhythm. Van Someren at al (1997) argue for the role of visual deficits leading to CR desynchrony as the retina is less able to detect the high luminance levels which signal the active daytime period. The role which visual dysfunction in PD may play in affecting efferent transmission to the SCN is unclear.

Interestingly, only relative amplitude was correlated with MMSE score, which is surprising as IV increases and IS decreases in dementing populations such as those with AD, although it is likely that there is an inverted 'U' relationship between CR disturbance and severity of cognitive decline. Whether loss of normal circadian rhythm is more associated with the 'cortical' type cognitive deficits and pathology found in AD warrants investigation. However, the extent to which motor fluctuations influenced these variables may have masked a more subtle association with cognition.

To summarise, PD patients showed poorer sleep maintenance with a greater number of awakenings, greater daytime sleepiness, and on a more global level greater disruption to rest-activity rhythm than healthy older adults. However, because of the presence of motor fluctuations as a confounding factor this latter finding must be interpreted with caution.

There is a body of literature arguing for neurochemical explanations of daytime sleepiness. As mentioned in Chapter 3, many arguments have been made for the neurochemical effects of DRT in producing sleepiness or sleep attacks, although different types of medication appear to be equally consistent in producing this effect (Pal et al, 2000). Given that medication dose is likely related to disease and medication duration it is perhaps surprising that these variables were not associated with daytime sleepiness.

Loss of cholinergic transmission in the brainstem as occurs in PD is likely to induce greater levels of somnolence, and possibly fluctuations in consciousness, akin to those in DLB (Perry & Perry, 1995). Indeed specific neuropsychological deficits in attention in PD may be associated with EDS. Investigation of the relative levels of sleepiness in TD and PIGD Parkinson's Disease may shed light on whether dopaminergic versus cholinergic function is implicated in excessive daytime sleepiness.

However, lower overall daytime activity level in PD patients suggests that sleepiness may arise from disability, with a lack of physical activity reducing the feedback to the SCN which normally maintains the amplitude of the daily rest-activity rhythm signal and synchronisation to the environment (Wright et al, 1972; Campbell, 1984).

10.1.8 Hypothesis 8

It has already been established that certain sleep-related phenomena, particularly 'sleep activity' symptoms are associated with hallucinations in PD, independently of disease severity. It was also hypothesised that sleep patterns measured both as subjective self-report variables, and objectively with actigraphy would differ between PD hallucinators and non-hallucinators. As it was possible to covary disease severity in these group comparisons, any differences in actigraphic variables would be more valid.

Firstly it was hypothesised that hallucinators would show greater levels of daytime sleepiness. Although the QUE factor 'daytime sleepiness' was not associated with hallucinations scores, this may have been due to a ceiling effect, with daily somnolence in many PD patients. Hallucinators showed increased levels of time spent napping as reported at interview during the day, independently of disease severity, and increased number of naps per day independently of both disease severity and global cognition. Actigraphic and diary data revealed no group differences between hallucinators and non-hallucinators, though it seems clear that diary methods underreported naps and actigraphic estimation of naps was difficult in patients with motor fluctuations. An association between daytime naps and hallucinations has been reported previously (Fenelon et al, 2000; Arnulf et al, 2000), and moreover napping is posited to play a key role in the genesis of hallucinations in PD, if REM episodes are present during naps, much like in narcoleptic hypnagogic hallucinations (Arnulf et al, 2000). The

present study supports the association between napping and hallucinations, though it was unable to use any gold-standard techniques such as MSLT or PSG for detecting REM episodes. Arnulf et al (2000) detected a number of sleep onset REM episodes (SOREMS) during their MSLT investigation suggesting that the pedunculopontine nucleus (PPN) which controls transitions to and from REM sleep, may be affected by the cholinergic loss that is characteristic of PD and especially PDD and DLB (Manford & Andermann, 1999). To summarise, the association between daytime sleepiness and hallucinations is supported by the present and previous studies, and there are strong theoretical grounds for implying a mechanism by which napping leads to hallucinations in PD.

One problem with this explanation, in the light of the results of the present study, is that hallucinators do not report more vivid dreams or other altered dream phenomena than non-hallucinators. Rather they report greater levels of 'sleep activity' which may be indicative of REM behavioural disorder. This association has also been reported by Comella et al (1993) and Onofrij et al (2003), and contrasts with earlier notions of a progression from altered dream phenomena to waking hallucinations. The distinction between altered dream phenomena and sleep activity may be artificial as vivid and violent dreams are often associated with aggressive motor activity during REM episodes. In a population with some degree of cognitive impairment, there may be less recall of vivid dreams leading to under-reporting,

but where a spouse is present the patient is likely to have been told that they have been moving around during sleep, particularly if the caregiver has been on the receiving end of aggressive movements. The PPN also innervates the REM-atonia circuit, and so disturbances in control of REM sleep, and the loss of REM-atonia which characterises RBD may both arise from changes in brainstem cholinergic function. The PPN has strong reciprocal connections with the substantia nigra, and so it is likely that both disease and medication factors contribute

to loss of REM-atonia, changes in dream activity and by extension hallucinations, via their effects on the PPN. In this way RBD and hallucinations, as well as altered dream phenomena may arise from pathological changes in the brainstem, which are correlated with disease severity and affected by dopaminergic medication. As mentioned earlier medication related factors are posited to play a role in the onset, maintenance and treatment of RBD symptoms. To summarise, the present study and previous studies support the theory that disturbance in the control of sleep-wake mechanisms and REM activity, which arise from the Reticular Activating System (RAS) in the brainstem, are responsible for both sleep-related phenomena such as altered dream phenomena and RBD and for hallucinations.

In the Alzheimer's literature there exists the idea that behavioural disturbances such as periods of confusion, agitation and aggression are linked to disruption in circadian rhythm. Volicer et al (2001) found that AD patients showing 'sundowning' behaviour displayed a phase delay of body temperature, and Bliwise et al, (1993) described a trend for greater levels of agitation during the winter season in institutionalised dementia patients. Additional support comes from a small number of studies using bright-light therapy to treat AD patients with hallucinations and delusions (Lyketsos et al, 1999). Whilst there is clear evidence that the superchiasmatic nucleus can be affected by Alzheimer's pathology (Van Someren, 2000), there is less direct evidence for the role of SCN-mediated circadian rhythm changes in the α-synucleinopathies, beyond reports of fragmented sleep, daytime sleepiness and phase advance of melatonin as a result of L-dopa treatment in PD (Fertl et al, 1993). Grace et al (2000) describe a greater frequency of both sleep disturbance and distressing behaviours at nighttime in DLB patients compared to AD patients. Given elevated levels of daytime sleepiness in PD patients with hallucinations (Fenelon et al, 2000; Arnulf et al, 2000), it was hypothesised that PD

hallucinators would should more disruption to circadian rhythm on a global level with greater levels of intradaily variability and lower levels of interdaily stability than non-hallucinators. The present study found that hallucinators showed greater levels of interdaily stability and reduced relative amplitude compared to non-hallucinators, indicating a weaker overall rest-activity rhythm across days, and a reduced ratio of daytime to nighttime activity. These effects were independent of disease-related variables. The results provide some support for the idea that PD hallucinators show a greater level of circadian rhythm disturbance than non-hallucinators. If PD or PDD pathology exerts an effect on the SCN, the resulting increase in daytime sleep, which appears be a mechanism through which hallucinations occur, may be mediated by the SCN rather than the RAS. Comparisons between hallucinators and non-hallucinators using more direct measures of SCN-mediated circadian rhythm such as core body temperature and melatonin would reveal whether the SCN plays a role in the changes in sleep architecture which are associated with hallucinations.

To summarise, increased levels of daytime sleepiness, reduced interdaily stability and relative amplitude are associated with hallucinations independently of disease severity. The relative contribution of disruption to the control of REM sleep, mediated by the RAS and global disruption of circadian rhythm, mediated by the SCN, to hallucinations is unknown. However, there is greater theoretical evidence and neurobiological evidence that the RAS is more greatly affected in PD.

10.1.9 Hypothesis 9

It was demonstrated that measures of global cognitive function were lower in PD patients as a group than for a control group of healthy older adults, independently of age, premorbid IQ and depression. Differences between the PD group and controls were also hypothesised for tests

of visual perception, executive function, recall, attention and construction, that were independent of age, premorbid IQ and depression. In addition, it was hypothesised that these differences would also be independent of global cognitive score, in other words, that they represented specific cognitive deficits that could not be explained by an overall decrease in global cognitive abilities.

Results from the logical memory tests revealed that both verbatim and gist recall for the immediate and delayed condition were significantly poorer for the PD group, and that these effects were independent of all covariates. Older adults have been demonstrated to show age-related decrements in verbatim recall, but not in the recall of story gist i.e. its semantic compenent (La Rue, 1992). Therefore the deficits found in recall in PD are not simply an extension of the ageing affect, and recall of both kinds of information is affected, suggesting a deficit in internally-cued retrieval underlies recall deficits (Brown & Marsden, 1990; Dubois & Pillon, 1997). There was no independent effect for recognition, which is supported by the existing literature and again fits the model of intact mnemonic function when external cues are supplied (Brown & Marsden, 1990; Downes et al, 1993).

Tests of visual perception showed that poorer performance on most of the subtests of the VOSP battery was explained by the effects of age and current IQ, with the exception of the object decision subtest. This suggests that PD patients do not demonstrate difficulty with aspects of visual closure and object recognition, that are independent of global cognitive decline. They do however show deficits on the object decision test which contains an executive component in that it requires the subject to make a decision about which of the stimuli presented represents a real object, and reject the distractors. A poor strategy on this task which was observed in some patients was to simply give an answer according to the approximate shape of the top-left stimulus and ignore the others. This suggests that some PD

patients may have problems in suppressing erroneous or automatic responses, so that they can complete a full appraisal of each stimulus. Alternatively, a specific deficit may exist in distinguishing real from unreal objects, when the real object is in a foreshortended form. However, Laatu et al (2004) found no deficit in PD patients on a similar test of real and unreal objects, although their stimuli consisted of line drawings that were easier to interpret than the silhouettes used in the VOSP, and their subjects were less cognitively impaired than some of the present sample. Laatu et al (2004) did find a deficit on a test requiring mental assembly of an object that had been broken down into constituent parts, which involves an executive component and some degree of strategy. Therefore, it may be the executive demands of the object decision subtest which PD patients find particularly difficult to complete, with a loss of ability to suppress the first mental association which comes to mind.

The overlapping figures test (Pillon et al, 1990) showed that PD patients were less able to correctly identify line drawings of objects from an array of overlapping objects, and were slower to reach the criterion score, independently of age, current and premorbid IQ and depression. This suggests that PD patients have a deficit in visual componential processing which is independent of other factors. Such a deficit has been demonstrated by Cousins et al (1999) also using the Pillon overlapping figures test. Again a degree of strategy is required to scan the array of figures in a logical sequence and to visually isolate each object and its components. On the attention task mean choice reaction time for the PD patients was longer than for controls in both the divided and undivided attention conditions, independently of other covariates. However, this difference is likely to reflect the motor slowness of PD patients, and accordingly when mean RT for the undivided attention task was covaried, the effect for group on divided attention disappeared. Therefore PD patients did not show a greater decrement in speed as a result of the extra attentional burden of a simultaneous task. They did however

show a greater degree of variation in reaction time within the undivided condition, although the contribution of motor slowing and hesitation could not be assessed.

To summarise, the PD patients in the present sample showed evidence of impairments in immediate and delayed recall of verbatim and gist information, deficits in object recognition when distracted by either competing 'pseudo-objects' or by an overlapping array of objects. These deficits may reflect an underlying problem with executive function, involving internal-cueing of retrieval, suppression of automatic responses before the task is complete, and generation of a strategy (Brown & Marsden, 19990; Dubois & Pillon, 1997).

10.1.10 Hypothesis 10

Following findings in the existing literature it was hypothesised that hallucinators would show specific cognition compared to non-hallucinators, and independently of deficits in global cognition, and other covariates; namely in visual perception, executive function, attention and construction (Mori et al, 2000; Barnes et al, 2003; Haeske-Dewick, 1995; Graham et al, 1997; Manford & Andermann, 1999; Ballard et al, 2002; McCormack et al, 2000).

For mnemonic function, an effect for poorer delayed recall was explained by the effects of age, current IQ and depression, with hallucinators showing no independent differences in either recall or recognition.

Of visual measures, only the shape detection screening test of the VOSP, and the object decision subtest of the VOSP, and the total number of objects named in the overlapping figures test were significantly poorer in hallucinating patients compared to non-hallucinators, and independently of covariates. This suggests that hallucinations are associated with specific deficits in the area of visual perception and cognition. The shape detection test was designed as a screening tool for the VOSP battery, to identify those patients whose vision was adequate

enough to be able to complete the full battery fairly (Warrington & James, 1991). As such, no firm conclusions can be drawn from the association of poorer performance on the test by hallucinators. Either hallucinators have poorer peripheral vision than non-hallucinators which contributes to hallucinations by reducing the accuracy and completeness of visual afferent information, or they have a specific deficit in figure-ground discrimination, which is the perceptual process that the screening task taps. Poor figure ground discrimination may contribute to visual hallucinations by confusing visual input, and merging objects with background scenery.

The finding of poorer performance on the object decision subtest in PD hallucinators replicates that of Barnes et al (2003). This test measures the ability to reject 'pseudo-objects' and select the real object shown in silhouette and foreshortened, suggesting that hallucinators may show a disinhibition of visual processes driven by an effort after meaning, that results in "overinterpretation" of available stimuli. If the process of object recognition results in overly rapid interpretation of a stimulus according to approximate shape, and with a lower criterion for acceptance, then either misperceptions in real life, or errors on the VOSP object decision subtest will be made, with selection of a meaningless stimulus as being meaningful. Erroneous interpretations would most likely be in line either with expectation, or with frequently stimulated visual 'templates' of familiar or personally meaningful stimuli. Similarly, problems with deconstructing an array of complex visual input into meaningful components, as demonstrated by poorer performance of hallucinators on the overlapping figures test, would increase the likelihood of erroneous visual perception. The following section will discuss the results of visual tests in terms of types of error made, which may shed more light on the mechanisms by which misperceptions and hallucinations occur.

Executive deficits in hallucinators were not observed on either the verbal fluency task or the trailmaking test, after current and premorbid IQ, age, depression and disease severity were covaried. This finding is inconsistent with previous studies, where verbal fluency performance was poorer in hallucinators compared to non-hallucinators (Haeske-Dewick, 1995) in late hallucinators compared to late non-hallucinators (Graham et al, 1997). However, these studies did not covary age, premorbid IQ or disease severity when comparing performance on verbal fluency, suggesting that it may be an artefact of differences between the two groups, particularly in global cognition and rate of articulation due to greater disease severity. Similarly, after controlling for age and other covariates no group effect was observed for block design, as a measure of construction. Although no previous studies have assessed construction in hallucinating patients with PD, DLB patients have been found to show a poorer performance on both pentagon copying and clock drawing than PD patients and AD patients, suggesting a possible association with hallucinations (Cormack et al, 2002). However, it may be the perceptual component of pentagon copying that DLB patients have problems with rather than the construction aspect.

10.1.11 Hypothesis 11

Following findings in the psychosis literature it was hypothesised that PD hallucinators would show a qualitatively distinct pattern of performance on neuropsychological tests characterised by a greater production of errors and intrusions of task-irrelevant material (Frith et al, 1992; Brebion et al, 1997; 1998; 1999; 2002; Bentall & Slade, 1985).

Hallucinators showed a trend for a greater percentage of novel intrusions on the logical memory test compared to non-hallucinators, that fell just outside of significance after covarying for age, disease severity, depression and anxiety, premorbid IQ and global cognition (p =

0.057). The effect for group was, however, stronger than for any of the covariates. There was no greater bias towards making false alarms (as measured by the false alarms to correct negatives ratio) for hallucinators after controlling for covariates. Similarly, on the verbal fluency test, hallucinators showed significantly greater percentage scores for total intrusions, cross-trial intrusions, and a near significant effect for novel intrusions, compared to non-hallucinators and after controlling for covariates. As raw scores for number of intrusions for both logical memory and verbal fluency were low, and stringent control of covariates was used, it is likely that tests which provoked a greater number of intrusions in all subjects may have increased the non-significant trend to significant levels, as data were skewed. For the composite raw and percentage scores for intrusions on verbal fluency and logical memory, hallucinators had significantly higher scores than non-hallucinators, independently of covariates.

For visual measures, hallucinators gave a greater number of incorrect identifications for 'pseudo-objects' on the object decision subtest, and made a greater number of misidentifications on the overlapping figures test using both raw and percentage scores, after covariates were controlled for. Accordingly a composite score for visual identification errors on the VOSP and the overlapping figures test was significantly higher in hallucinators than non-hallucinators for both raw and percentage scores, when covariates were controlled for. Hallucinators demonstrated a greater tendency towards intrusions of task-irrelevant material on a composite score for logical memory and verbal fluency, and a greater number of visual misperceptions as measured by a composite score for the VOSP battery and the overlapping figures test. These results are consistent with findings of a number of studies in schizophrenic populations, where positive symptoms such as hallucinations and delusions have been associated with an increased number of intrusions provoked by cognitive tasks (Brebion et al, 1997; 1999). However, unlike other studies (Bentall & Slade, 1985; Brebion et al, 1997; 1998;

1999) there was no significant relationship between bias towards making false alarms on recognition tests and hallucinations. This may be because stringent controls were imposed on analyses in the present study, including covariation of age, premorbid and current IQ, disease severity and depression. Other studies have also found that a failure to respond or to respond correctly have been linked to negative symptoms, and specifically depression (Frith, 1992; Brebion et al, 1997; 1998). In the present study depression was negatively correlated with correct performance on a number of cognitive tests. Results therefore suggest that a model of neuropsychological performance in schizophrenia can be successfully applied to hallucinating Parkinsons patients.

10.1.12 Hypothesis 12

A series of regressions was conducted to assess the relative validity of the medical model as compared to an expanded model incorporating sleep-related phenomena and neuropsychological performance. As the most robust findings of earlier studies were for a combined effect of global cognitive impairment and increased disease severity, the medical model which dominates early studies was conceptualised in the present study as being composed of MMSE score and UPDRS motor examination score. These are the measures which have been used most often by second generation concomitant studies. The "medical model" explained 9% of the variance in hallucination score whereas the extended model (using the medical model as its first step) explained 56.2% of the variance. These results demonstrate the power of alternative variables in predicting hallucination score, and the amount of variance explained is all the more impressive considering that medication was not included as a variable.

10.2 Limitations of the present study

Limitations of the present study are discussed, and means of improving study design presented.

10.2.1 Small sample size

The present sample consisted of 78 patients with Parkinson's disease with 29 non-hallucinators, 14 with minor unusual perceptual experiences and 35 with complex hallucinations. This sample size is comparable with other studies which have investigated sleep-related phenomena and neuropsychological performance in hallucinators and non-hallucinators with PD (Arnulf et al, 2000; Onofrj et al, 2002; Barnes et al, 2003). However, stringent controls were imposed during analysis to account for important covariates, thus increasing the chance of a Type II error. Nonetheless, the fact that significant group differences were still found suggests that these variables were both valid and robust. Ideally, a larger sample would allow analysis with more powerful statistical tools such as path analysis, which could assess the direction and strength for the effect of each contributing variable. Reasons for the limited sample size included difficulty in accessing PD patients who fulfilled all criteria and were able to complete a lengthy battery of interviews and tests.

10.2.2 Representativeness of the present sample

The model derived from the present sample may not be predictive of hallucinations in a more demented sample of PD patients, as the relationship between disease severity, global cognition and specific cognitive deficits may be different in a more impaired sample. Therefore the model may not have adequate external validity to account for hallucinations in the

Parkinson's population as a whole. It is unlikely, however, that more impaired patients would have been able to complete the neuropsychological battery, leading to possible floor effects. Furthermore, reliable assessment of hallucinations, which are by nature a subjective phenomenon, would be difficult in a sample with little insight. The present sample consisted of outpatients attending movement disorder clinics with a predominance of community dwelling patients, and individuals living in institutions were likely underrepresented. However, the sample included patients with a large range of disease duration, and individuals in both the early and late stages of Parkinson's disease.

10.2.3 Use of a non-validated questionnaire on hallucinations and sleep-related phenomena

The problems in assessing hallucinations using a single-item measure have been described. At the time the present study was designed, no scale existed for assessing hallucinations and other unusual perceptual experiences in the visual modality that had been validated for a Parkinson's population, or indeed a wider population. Although there exist inventories for assessing psychotic phenomena in dementing populations, most of these also assess hallucinations using a single item. As one of the key aims of this study was to measure the severity of hallucinations in terms of frequency, a scale was developed specifically for this purpose. The pilot study revealed that the 3 sub-scales had good internal reliability. Furthermore, factor structure within sleep items and within UPE and hallucination items was similar in both the pilot and main studies. The scale was found to be easy to administer in both self-report and semi structured interview form in a group of patients with varying degrees of cognitive impairment. The use of an equivalent scale for caregiver ratings of the patient provided an extra level of validation. Whether the factor structure remains stable in a larger

Parkinson's sample remains to be determined. As with the predictive model of hallucinations itself, relationships between variables may change if applied to a more impaired sample.

10.2.4 Suitability of actigraphy in a movement disordered population

The use of actigraphy to monitor rest-activity rhythms and sleep-wake patterns is not ideally suited to a Parkinson's population. This was demonstrated by the significant correlation between dyskinesias and overall activity levels, suggesting that the presence of certain motor symptoms may mask actual activity levels. Furthermore, self-report and actigraphy estimates of wake after sleep onset (WASO) and daytime napping showed significant discrepancies. The purpose of using actigraphic techniques in the present study was to obtain an objective index of sleep and wake pattern. Despite difficulties in interpreting the actigraphic data in the presence of motor artefacts, the study was valuable in comparing the agreement between the three methods of data collection.

Since the design of a present study an actigraphic monitor has been developed, which is designed to detect the presence of Parkinsonian tremor with its characteristic amplitude and frequency. The development of more sophisticated means of detecting movement patterns may allow for a model of the characteristic movements of dyskinesias. If more than one monitor were utilised on the same subject, with software designed to 'filter out' motor artefacts, a purer measure of rest-activity rhythm would be possible. Actigraphy is an inexpensive alternative to gold-standard measures of circadian rhythm such as cortisol and melatonin assays or body temperature monitoring equipment, and is likely to be easier to implement in a population who may be non-compliant (Van Someren et al, 1996). However, actigraphic assessment is still in its infancy, and more sophisticated models of movement would make it a more suitable means of assessment in a movement disordered population.

10.2.5 Use of error scores in analysis of neuropsychological performance

Cognitive errors and intrusions emerged as a more powerful predictor of hallucination score than did "correct" cognitive scores. However, raw error scores were low, in effect skewing the data and so percentage scores were used in their place. In the final regression composite error scores were used, partly to increase the range of scores. This may mean that results are less stable given skewing and therefore may not be replicable. Tests which provoked a greater number of intrusions and misperceptions may have improved the stability of findings. The source monitoring paradigm used by Barnes et al (2003) would have provided a wider range of scores although measuring a response bias as opposed to provoked intrusions.

10.2.6 Lack of analysis of medication

The medical model, as it was originally conceived, also incorporated medication as a key predictor. The present study, however, did not include data on medication in analyses. This was because of the difficulty in calculating L-dopa equivalent dosage across a range of DRT, particularly when some preparations act solely to prolong the effects of others (i.e. COMT inhibitors). It would be incredibly difficult to disentangle the receptor affinities for a combination of drugs in this context. Moreover, no studies have found a dose-response relationship between DRT and hallucinations, and it is likely that receptor sensitivity and upregulation are the key to any relationship between DRT and hallucinations. Furthermore, as in vivo measures of dopaminergic function were unavailable to the present study, no meaningful index of central dopaminergic function could be derived. Some studies have indicated that anticholinergic drugs may be more likely to cause hallucinations than DRT (Goetz et al, 1993; Saint-Cyr et al,

1993) but the number of patients on anticholinergics in the present sample was too small to conduct meaningful comparisons.

10.2.7 Study design – lack of longitudinal data

The results of the regression cannot be considered "predictive" in a prospective or longitudinal sense. The regression model identifies those likely to be suffering from current hallucinations using clinical, sleep-related and neuropsychological measures. It cannot, however say anything about whether these factors are related to future hallucinations. It may be that the medical model predicts more variance when applied longitudinally, although the longitudinal study by Goetz et al (2001) found that neither disease duration, severity or Mini-Mental State Examination predicted incidence of hallucinations over four years. The predictive value of neuropsychological variables over time has yet to be determined. Long term prediction of hallucinations may prove difficult in any case as frequent changes are made to medication.

10.3 Dual deficit model of hallucinations in PD

The purpose of this thesis was (i) to explore the applicability of generalised models of hallucinations to a Parkinson's disease sample, (ii) to develop a model of hallucinations in Parkinson's based on the data collected and (iii) to compare this 'psychological' model to the medical model that has dominated the literature.

Weaknesses of a clinicomedical approach included, firstly, examination of hallucinations in PD as an epiphenomenon, that is, a side effect of medication or a disease process (Bentall, 1997). Secondly, a motivation to identify 'risk factors' has meant that any theories arising about the causes of hallucinations in PD are essentially post-hoc, and not based on any coherent model

(Frith, 1992). Thirdly, neither existing theory nor paradigms were utilised to develop a model that encompassed recent neurobiological or neuropsychological models of hallucinations in other populations.

This thesis drew on models developed from studies of hallucinations in patients with visual deficits, Charles Bonnet Syndrome, dementias, narcolepsy and schizophrenia. The key findings were that disruptions to sleep processes, in particular daytime sleepiness, and both visual deficits and cognitive errors in the form of intrusions were associated with hallucinations.

The findings of the present study are remarkably similar to those published by Barnes et al (2003). Both studies found two main cognitive factors to be associated with hallucinations; firstly, a combination of deficits in visual object perception, and secondly, the presence of a tendency to make cognitive errors that suggest either a source monitoring deficit or a process of 'confabulation'. This combination implies a dual deficit theory of hallucination in Parkinson's disease. However, the nature of the cognitive errors made by hallucinators was slightly different in the two studies. The cognitive errors demonstrated in Barnes et al's (2003) sample are best defined as a *source monitoring deficit*, with a bias towards attributing internally generated mental imagery to an external source. The cognitive bias demonstrated by the present sample is best defined as a tendency to produce *material which is irrelevant to task demands*. Both of these biases are consistent with current models of cognitive errors in schizophrenic patients showing positive symptomatology, including hallucinations (Brebion et al, 1997; 1998; 1999; Bentall, 1990; Frith, 1992).

10.3.1 Fleminger's (1994) model of erroneous perception in delusional misidentification syndrome in schizophrenia

An alternative model is now presented, which draws in particular on Fleminger's (1994) model of delusional misidentification (DMS) in schizophrenia. This model is suitable for application to PD patients with hallucinations because it emphasises the role of sensory deficits and top-down visual processes in DMS, and also, because it demonstrates a role for other cognitive biases in both the selection of appropriate perceptual hypotheses, and in judgement of the validity of perceptual representations.

Fleminger (1994) presents a model of delusional misidentification in schizophrenia, whereby a familiar person is perceived as being unfamiliar. This model may be applied to any cognitive process where perception of the external world is required. Fleminger's (1994) three stage model of perception was described in section 4.5.2.1, and is presented visually below (Figure 10.2). Briefly, the process of perception is driven by the input of sensory data, with perceptual hypotheses selected at Stage 1 based on the available data, with bottom-up processes pre-dominating. Fleminger calls this stage the "Look and Select stage". At Stage 2, the hypothesis is confirmed or rejected when available data is matched to the internal representation of the hypothesised object. This "See and detect no mismatch stage" utilises both top-down and bottom-up processes. Fleminger posits that these firs two stages are "unconscious" or without awareness. The third stage represents a conscious process of decision making on the validity of the selected perceptual hypothesis based on its likelihood given current surroundings, context etc. This stage, the "Judge and accept validity" stage, can be seen as a judgement about whether the percept is real or unreal, external or internal i.e. it is a process of source monitoring. This decision then drives belief about what has been perceived, which in turn drives expectancy of what is likely or unlikely next time, and will favour the previously accepted

hypotheses over alternatives. Importantly, expectancy may affect the first and second stage of perception, as well as the third; if an expectancy is strong enough, then contradictory sensory data, or evidence that the perceptual hypothesis is unlikely, may be overridden. The strength of this model is that errors may occur at any of the three stages to produce erroneous percepts, beliefs and expectancies.

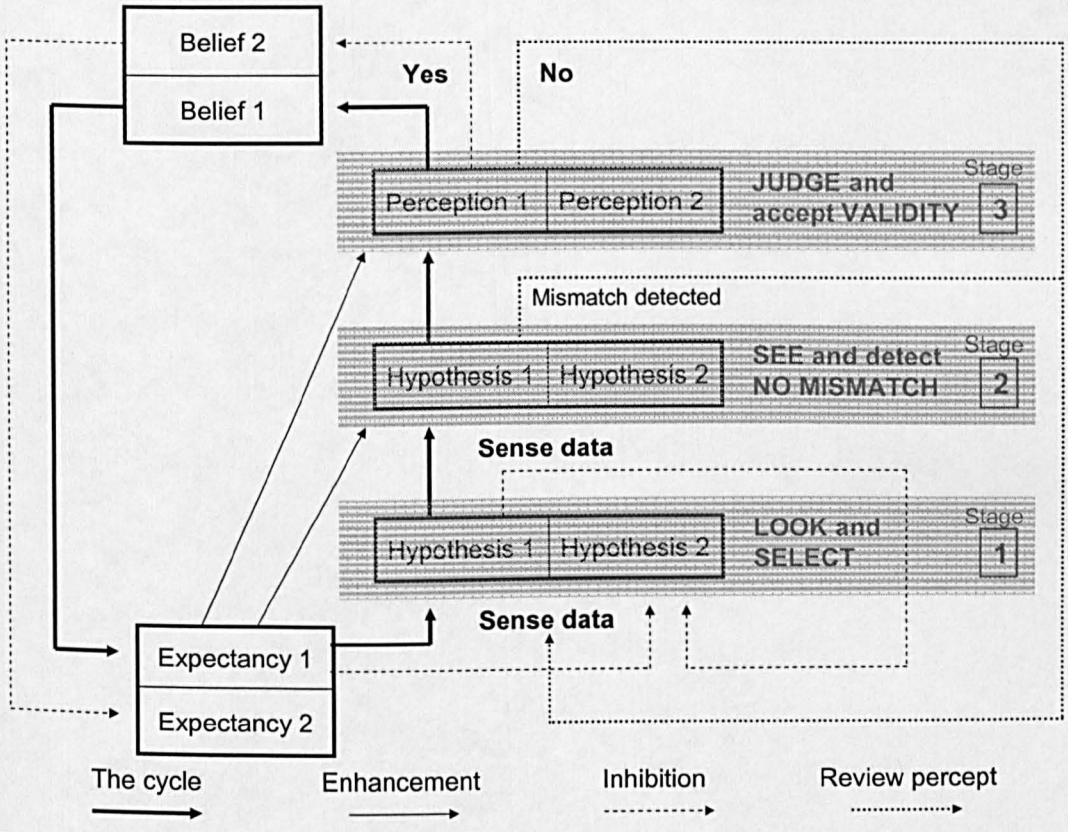


Figure 10.2 Fleminger's three stage model of perception (adapted from Fleminger, 1994)

In the context of Parkinson's Disease and in the light of the present study, errors at all three stages may result in a "hallucination" or, more correctly, an illusion. Low-level visual deficits such as poor contrast sensitivity may result in an error at Stage 1, where an erroneous hypothesis is selected on the basis of degraded incoming sensory data. At Stage 2, which

relies partly on higher-level or top-down visual processes, errors may occur if, as demonstrated by the present study, matching to an internal representation of an object is compromised. An error at Stage 3 may occur if executive processes upon which decision making relies are compromised. The cycle of previous hypotheses driving beliefs, expectancies and future hypotheses may account for the repetitive or stereotyped nature of many Parkinsonian hallucinations.

Using this model, the source monitoring bias demonstrated in Barnes et al's (2003) study can be seen as occurring at the third stage, where judgement is made concerning the validity of the conclusion an individual has come to. The role of visual deficits as found by both studies can be accounted for using this model, by the dominance of top-down visual processes when sensory data is poor and it becomes difficult to directly test a perceptual hypothesis. In this case, expectancies based on schemata and previous experience will play a key role.

The production of intrusions or irrelevant material demonstrated in the present study does not fit entirely into a source monitoring framework (i.e. problems at Stage 3), but does bear similarities to errors made at the first and second stages. Generation of task-irrelevant material implies problems at the first and second stages of Fleminger's model. In particular, that the parameters set for the search for an appropriate hypothesis or response are too wide or unfocussed.

A similar model presented by Burgess & Shallice (1996) describes the production of spontaneous confabulations in the domain of memory. Briefly, their model describes retrieval of autobiographical memories from long-term storage (LTS). The search in LTS is initiated when the "Descriptor" is activated by an input template which contains a generic representation derived from both perceptual cognitive input (akin to sensory data) and existing

semantic associations (which has parallels with the role of expectancy) of the 'type' of memory to search for. The descriptor interacts with LTS (comparable to stored perceptual representations) to facilitate a search within the parameters generated by the descriptor, and with the "Editor" which detects inconsistencies between the parameters of the descriptor and the representations retrieved. (A "Mediator" which makes an executive decision about likelihood of the memory is akin to Fleminger's third stage "Judge and accept validity). In this way the Burgess & Shallice model adds another level of complexity to Fleminger's model, and although specific to memory, has parallels with the idea of hypothesis selection and verification in perception. According to Burgess & Shallice model, one type of error producing a "false memory" is a poorly defined description, where an inappropriate retrieval is made, i.e. the production of task-irrelevant material. One explanation for poorly defined search parameters may be inadequate or degraded sensory input. Another may be an expectation which activates certain semantic associations.

The idea of unfocussed search parameters (in search for an appropriate response) may be applied across domains, whether in the case of selecting an incorrect perceptual hypothesis (i.e. incorrectly identifying an object during the VOSP test) or retrieving an incorrect memory from short or longer-tem storage (i.e. producing a novel intrusion on the logical memory test). Critically however, these types of errors arise from an earlier stage than source monitoring, which involves reviewing the validity of search results after the search process is completed. In summary, the two studies provide similar results for perceptual errors, but the task-specific errors of each study can be seen to reflect errors and biases at different stages in perception.

Fleminger's (1994) model also presents an explanation for the maintenance of delusional misidentification, where acceptance of an erroneous perceptual interpretation as being valid

increases the expectancy of a similar error being made in the future. If expectancies are driven by previous experience and belief (erroneous in this case), then perceptual hypotheses and top-down processes will come to reflect the erroneous belief, and alternative hypotheses will be suppressed. Bentall (1994) and Frith (1992) have argued that even pathological cognitive processes such as hallucinations and delusions should be examined as meaningful behaviours driven by intention. Thus, the cycle of maintenance of delusional beliefs may reflect the emotional salience of such a belief to that individual or its importance in terms of their own safety or motives (Fleminger, 1994; Bentall, 1994).

However, PD patients with hallucinations do not typically show the systematised delusions that are prominent in schizophrenic individuals, although these may be more common in DLB (Cummings, 1992; Del Ser et al, 2002). Moreover, PD patients are more likely to show insight into the fact that their hallucinations are not real (Haeske-Dewick, 1995). Therefore, Fleminger's (1994) model does not seem to account for the repetitive nature of PD hallucination, that are often stereotyped in content, occurring repeatedly in the same settings and context (Holroyd et al, 2001). Hallucinations of loved ones that occur following bereavement are thought to represent a kind of comfort phenomena, where motivation to believe that the deceased is still present in some sense may maintain hallucinations. The source of the context from which the perceptual hypothesis is derived in PD, and the cycle of maintenance is difficult to account for.

10.3.2 Adaptation of Fleminger's model to the present study

One factor that may account for content and context of hallucinations in PD, and the intention to accept them as being valid, and is compatible with the findings of the present and previous studies is the role of disturbed dream activity and daytime somnolence in hallucinating PD

patients. REM sleep and in particular SOREMs have been observed to coincide temporally with hallucinations in PD (Arnulf et al, 2000; Manni et al, 2002). If an individual awakes from a dream episode, it is likely that the ongoing dream narrative or context is still available to them, and will contribute to any perceptual hypotheses that are sought upon waking. If the individual awakes to a darkened or dimly lit room where visual sensory data is limited, and if certain visual perceptual deficits are present, then the stimuli available may indeed be matched to a perceptual hypothesis that is not based on the actual context or surroundings. If internal representations are favoured over external input, as a bias in reality monitoring would predict, then such a hypothesis may be judged as valid. Deficits in executive and attentional function may increase the likelihood of such a hypothesis being accepted, and reduce the likelihood of more plausible hypotheses being accepted. As dream content is likely to reflect issues that are pertinent and emotionally salient to the individual, then hallucinations occurring upon waking may have a similar theme, particularly if the same stimuli are present. Therefore dream narrative may account for the content and the repetitive nature of hallucinations in PD patients at the level of generating expectancies.

One final problem with the Fleminger model is that it is based on *mis*perception of *real* sensory data. Although many hallucinations in PD are better described as illusions, spontaneous hallucinations with no external sensory input do occur. It is possible that in the absence of sensory data, the same cycle of misperception may occur if background neural noise, arising from a disinhibited visual system, is sufficient to activate top down processes at Stage 2. Signal detection theory posits that given sufficient background noise and a low threshold for acceptance of a signal, false positives or misperceptions can occur. If expectancies derived from dream narrative upon waking are strong enough to drive a cognitive attempt at "effort

after meaning", then the model may be applicable in the absence of real sensory data, instead attempting to make sense of visual noise.

10.3.3 Implications and limitations of the model

The findings from the present and previous studies, and the models presented do not address all the issues pertinent to hallucinations in PD. However, they do highlight areas that deserve clarification, further investigation and also generate some further hypotheses. The model presented is essentially cognitive or neuropsychological in nature, although it does not address the location or underlying mechanisms of the cognitive processes involved. The following section addresses questions which remain unresolved

10.3.3.1 The nature of cognitive biases in PD hallucinators

The schizophrenia literature describes a rich repertoire of paradigms for exploring auditory hallucinations, and notably several investigators have attempted to provoke hallucinatory phenomena in the laboratory setting with the use of white noise (Alpert, 1985). No such approach has been applied to PD hallucinators, except in the form of pharmacological provocation (Goetz et al, 1998). The exact nature or range of cognitive biases that are present in PD hallucinators also deserves attention. Application of parallel paradigms adapted from the schizophrenia literature, such as visual signal detection tasks against a background of visual 'noise' (Heilbrun & Blum, 1984) or examination of the relationship between visual misperception and confidence in judgement (Mintz & Alpert, 1972) may be fruitful.

10.3.3.2 The underlying mechanisms of cognitive errors in PD hallucinators

The neuropsychological correlates of deficits in reality monitoring or of cognitive intrusions in PD have yet to be delineated. Both executive and attentional dysfunction may contribute to such cognitive biases, and in the context of source monitoring memory may also play a role.

Given the predominance of executive dysfunction in PD, it is likely that executive function underlies problems with allocation of attentional resources and focusing of attention, and it may also contribute to problems with retrieval (Brown & Marsden, 1990; Dubois & Pillon, 1997). Models of confabulation in amnesic patients also emphasise the role of executive function over memory loss in producing confabulations (Benson & Stuss, 1990; Johnson et al, 1991; 1993). However, Dalla Barba et al (2000) examined confabulation in AD patients, and sought other neuropsycholigcal correlates, finding that neither executive dysfunction nor source monitoring impairments were correlated with confabulations. The relationship between source monitoring deficits and cognitive intrusions and other facets of neuropsychological function in PD patients warrants investigation. If such cognitive biases were associated with other deficits, a neurobiological or neuroanatomical basis could be posited.

10.3.3.3 The contribution of bottom-up and top-down processes in visual misperception

Similarly, the precise nature of the higher-level visual deficits in hallucinating PD patients deserves consideration. Fleminger's (1994) model predicts that either poor sensory data arising from sensory deficits, or overactive disinhibited top-down processes could result in an error of matching data to perceptual hypothesis. As yet, no single study has investigated both peripheral visual deficits, lower level visual functioning, and higher-level visual functioning in hallucinating PD patients. The relative contribution of top-down and bottom-up visual processes to hallucinations warrants investigation.

10.3.3.4 Phenomenological examination of hallucinations in PD

Santhouse et al (2000) described three types of hallucination in CBS, according to content, and went on to speculate about likely neuroanatomical correlates. No such approach has yet been applied to PD patients. Studies of auditory hallucinations in schizophrenia have investigated hallucinations in terms of content, identity of the voice, perceived power or

omnipotence of the voice, and controllability. Coping mechanisms have also been studied extensively . Investigating the phenomenology of visual hallucinations in PD may be instructive in suggesting both neuroanatomical substrates, and possible interventions. The contribution of personal concerns and emotional themes to hallucinations in PD has not been formally assessed. The neurobiological model of PD, with the presence of a limbic circuit arising from the basal ganglia (Alexander et al, 1986; 1990) suggests that affect may play an important role in neuropsychiatric symptoms, and the coincidence of intense affect with hallucinations should be examined.

10.3.3.5 Limitations of a neuropsychological approach – levels of explanation

Though Manford & Andermann's (1998) theory of RAS dysfunction in hallucinating PD patients is compatible with the findings of increased RBD type behaviour and daytime somnolence, it is a neurobiological model, which cannot be easily integrated with the model presented above. The two models address different "levels of explanation" (Frith, 1992), and it is difficult to generate directly testable hypotheses from Manford & Andermann's model. Recent articles concerning neuropsychiatric symptoms in basal ganglia disorders (Ring & Serra-Mestres, 2001; Aarsland & Ehrt, 2003) have attempted to expand neurobiological models of cognitive function in PD (i.e. Darvesh & Freeman, 1996) to encompass the range of neuropsychiatric disorders found. This approach has parallels with Frith's (1992) and Bentall's (1994), and the wider schizophrenia literature. As yet specific neuropsychological models and hypotheses have not been described, but advances in brain scanning and functional imaging techniques may allow the testing of neurobiological and neuroanatomical theories, as has been most fruitfully conducted by ffyche et al (1998).

CONCLUSIONS

1. Hallucinations and other unusual perceptual experiences in Parkinson's Disease are a heterogeneous group of phenomena, as are sleep-related and motor symptoms. The value of using a phenomenological approach to seek empirical associations between disparate symptoms was reflected in the multi-dimensional factor structure of hallucinations (Frith, 1992). This approach derived a strong, internally-consistent visual hallucinations factor which appears to represent the archetypal experience of PD hallucinators. Sleep factors 'altered dream phenomena', 'sleep activity' and 'daytime sleepiness', showed a distinct pattern of association with clinical variables, and only the 'sleep activity' factor was associated with hallucinations independently of disease severity.
2. As hypothesised, increased disease severity and reduced global cognitive abilities were associated with hallucinations. This effect was independent of key covariates such as age, depression and premorbid IQ, which most previous studies have failed to covary. However, the weakness of the 'medical model' was shown as severity and global cognition explained a mere 13.7% of the variance in a hallucinations factor summed score.
3. Hallucinators showed no differences in their nocturnal sleep pattern, but rather showed a greater amount of daytime sleepiness using both self-reported sleep and a validated measure of daytime sleepiness. In the light of the existing literature this suggests that there may be mechanistic parallels with the hypnogogic hallucinations often experienced by narcolepsy patients. In group comparisons, hallucinators showed a greater disruption to their global rest-activity rhythm, with less stability across days. For day and night-time sleep, both actigraphy and diary methods appeared unreliable in this population. Daytime sleepiness and the 'sleep

activity' factor added significantly to the regression model to predict hallucinations score, demonstrating the need for more variables to be taken into consideration than disease severity and global cognition alone.

4. Hallucinators showed a specific deficit on the object decision test, with reduced ability to reject ambiguous 'pseudo-objects' as being unreal. However, they showed no executive or attentional deficits, which suggests that previous findings of impaired executive function in hallucinators are not independent of confounders such as global cognitive decline, age and disease severity. Error scores however, showed a stronger effect than any of the correct cognitive scores, demonstrating the value of using a qualitative approach to neuropsychological testing in hallucinators (Bentall et al, 1991; Frith, 1992). Similarly to schizophrenic patients, hallucinations are associated with an increased tendency to cognitive intrusions on both memory and executive tests, and increased visual *mis*perception. 'Correct' cognitive scores however, were more influenced by age, global cognition and depression.
5. The overall regression model including global cognition and disease severity as the first step, followed by sleep-related and neuropsychological variables accounted for over 56% of the variance in a hallucinations score. This model is not predictive, as data were not longitudinal, but shows that sleep and neuropsychological variables add to the model significantly. The amount of variance is all the more powerful in light of the fact that no medication data were included. The power of the combined model demonstrated the value of an integrated psychological approach, drawing on models of hallucinations and accepted paradigms in other groups, over a clinicomedical approach.

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Appendix A: Findings of studies investigating the concomitants of hallcuinations in Parkinson's Disease

Table A.1 Studies investigating global cognition and dementia-related concomitants of hallucinations in Parkinson's disease

Study	Design	N (total)	Inclusion/exclusion	Measures used	Findings
Meco et al, 1990	Clinic survey	304	MMSE <18	MMSE	8.8% hallucinators
	Group comparison	19/ 9H[1]/10NH[2]			H ↑frequency of mental deterioration than NH
Fernandez et al, 1992	Group comparison	50/ 30H/20NH	Nil	MMSE	H↑cognitive impairment than NH
Haeske-Dewick, 1995	Group comparison	36/ 16H/20NH	Psychiatric history, sensory pathology, thalamotomy, stroke, MID, AD or DLB	MMSE NART	H↑cognitive impairment than NH
Miyoshi et al, 1996	Group comparison hallucinosis and delirium	Not stated		Presence dementia CT scan EEG	Dementia was found in 64.3% of the delirium type and in 36.4% of hallucinosis type of patient
Naimark et al, 1996	Group comparison Regression	101/ 36H/65NH	PSYCHOSIS in PDD	Blessed-Roth Dementia Rating Scale Blessed Information-Memory-Concentration Test MMSE	Psychotic patients ↓ MMSE and more cognitively impaired than non-psychotic patients
Sanchez-Ramos et al, 1996	Group comparison	214/ 55H/159NH	Nil	MMSE	H ↓ MMSE than NH
Graham et al, 1997	Group comparison	129/ 32H/97NH	Idiopathic PD	CANTAB	Late H (> 5 years of onset of PD) ↓ global measures and verbal fluency task compard to late non-hallcuinators
Klein et al, 1997	Group comparison	87/ 29H/58NH	Gross sensory impairment	MMSE DSM Dementia CAT EEG	At follow-up H ↓ MMSE than NH and more dementia

[1] H - Hallucinators
[2] NH - Non-hallucinators

Table A.1 Studies investigating global cognition and dementia-related concomitants of hallucinations in Parkinson's disease (cont)

Study	Design	N (total)	Inclusion/exclusion	Measures used	Findings
Goetz et al, 1998a	Group comparison	35/ 14H/21NH	Snellen acuity <0.6	MMSE	H ↓ MMSE than NH
Goetz et al, 1998b	Longitudinal Group comparison (Early EH and late LH hall)	70/ 12EH/ 58LH		Outcomes at time II in terms of diagnostic change or autopsy (i.e to DLB or AD)	LH were less likely to develop dementia 5 years later than EH
Inzelberg et al, 1998	Group comparison	121/ 45H/76NH	Auditory only	Short mental test scores (SMT)	H↑cognitive impairment than NH
Aarsland et al, 1999	Group comparison	245/ 37H/208 NH	Exclusion: CT/MRI changes	MMSE	H ↓ MMSE than the NH and "vivid dreams" group
Fuente-Fernandez et al, 1999	Group comparison	105/ 33H/72NH		MMSE Apoε allele	H more severe Parkinsonism than NH
Kraft et al, 1999	Group comparison	30/ 15 H/15NH	Nil	MRI : atrophy and white matter lesions	No difference with regard to the total amount of white mater changes
Okada et al, 1999	Group comparison	33/ 12H/ 21 NH	Previous antipsychotics	SPECT - regional cerebral blood flow DSM criteria dementia	H showed significantly lower cerebral flow in the left temporal regions than NH
Fenelon et al, 2000	Group comps minor and formed hallns Early and late hall and non-hall Regression	216/ 86H/ 130 NH	Previously diagnosed schizophrenia	MMP DSM criteria dementia	H ↓ MMP than NH
Barnes & David, 2001	Postal survey Group comparison	44/ 21H/23NH	DLB and AD diagnosis	MMSE	H tended to show more cognitive impairment than NH (however, not statistically significant on MMSE)
Goetz et al, 2001a	Prospective longitudinal Group comparisons GEE modeling	89/ 29H/60NH	Exclusion: absence of 24-hour caregivers, concomitant strokes, AD, delirium, delusions and neuroleptic treatment	MMSE	H ↓ MMSE than the NH at baseline, but not at 4 year follow-up

Table A.1 Studies investigating global cognition and dementia-related concomitants of hallucinations in Parkinson's disease (cont)

Study	Design	N (total)	Inclusion/exclusion	Measures used	Findings
Goetz et al, 2001b	Case control study	88/ 44H/44NH	Exclusion of DLB symptoms	MMSE Apoε allele Dopamine receptor alleles	H ↓ MMSE than the NH
Holroyd et al, 2001	Prospective Group comparison (MANOVA)	102/ 30H/72NH	Atypical features suggesting PSP, DLB etc Absence of response to L-dopa DSM criteria delirium	TICS – telephone interview for cognitive status	H ↓ TICS than the NH
Nomura et al, 2002	Group comparison	22/ 14H/8NH	None	MMSE	H tended to show more cognitive impairment than NH (however, not statistically significant on MMSE)
Onofrij et al, 2002	Logistic regression	80		MMSE	Not reported
Onofrij et al, 2003	Group comparison	40/ 20H//20NH	Familial PD, dementia, psychosis or narcolepsy	MMSE NPI	H had significantly more neuropsychiatric symptoms on NPI
Barnes et al, 2003	Group comparison hall/non-hall/controls	37 PD 20 C	Diagnosis AD and DLB	MMSE NART	No differences observed
Barclay et al, 1987	Tertiary care PD population survey Group comparison	227	MMSE <18, previous psychotic disorder	Structured interview	3% of patients reported delusions, 16.1% reported visual hallucinations, 11.6% experienced illusions, 6.4% auditory hallucinations and 22.4 % reported vivid dreams (a total of 38.4% including vivid dreams, 21.4% when vivid dreams symptoms were excluded). The presence of psychotic symptoms correlate with the presence of dementia.

Table A.2 Studies investigating disease-related concomitants of hallucinations in Parkinson's Disease

Study	Design	N	Inclusion/exclusion	Methodology	Findings
Moskowiz et al, 1978	Descriptive only	88/ 27H/ 61NH	Inclusion: mild to moderate psychosis, history of nonpychotic psychiatric disorders Exclusion : severe dementia and history of psychosis	MD prior to onset psychiatric side-effects	Peaks in incidence of hallucinations (one and three years) after the initiation of Levedopa therapy
Tanner et al, 1983	Population study Group comparison	775/ 257 H/ 518NH	Nil	H&Y staging MD for diff types meds Presence fluctuations	Mean H&Y stage and mean duration of exposure to Levedopa was similar between the two groups. Mean duration of amantadine and centrally active anticholinergic agents therapy was greater in H than NH patients
Meco et al, 1990	Clinic survey Group comparison	304 9H/10NH	MMSE <18	Webster rating scale Age onset DD Med doses by type	Trend for H to score higher on WRS than NH, to be younger at the onset of PD, to be treated longer and be better educated than NH. Tendency for H to be on slightly higher doses of L-Dopa and to use anticholinergics more.
Friedman & Sienkewicz, 1991	Group comparison of PD patients with psychotic and non-psychotic symptoms	198/ 44 Psychotic/ 154 non-psychotic	Nil reported	DD + prior to therapy Age at onset + therapy	Those who developed psychotic complications were significantly older overall; older at disease onset and onset of therapy. Patients with *complex symptoms* were significantly younger at the onset of the disease. Disease duration prior to onset of psychiatric symptoms was greater than in the group of patients with *simple symptomatology.*

Table A.2 Studies investigating disease-related concomitants of hallucinations in Parkinson's Disease (cont)

Study	Design	N	Inclusion/exclusion	Methodology	Findings
Fernandez et al, 1992	Group comparison	50/ 30H/20NH	Nil reported	Hoehn & Yahr stage Fluctuations Disease duration	No differences between groups in terms of the type or duration of □arkinsonian symptoms, H&Y stage, motor fluctuations, L-dopa treatment duration or L-Dopa dose.
Haeske-Dewick, 1995	Group comparison	36/ 16H/20NH	Psychiatric history, sensory pathology, thalamotomy, stroke, MID, AD or DLB	H&Y staging DD L-dopa dose	H reported more disability (H&Y) than NH, however no differences were found in disease duration or daily L-dopa intake.
Sanchez-Ramos et al, 1996	Group comparison	214/ 55H/159NH	Nil	H&Y staging DD Medn dose by type Motor state (on vs off)	H were more disabled (H&Y stage) than NH; DD, daily intake of L-dopa and concurrent use of other anti-PD medications were not significantly different between groups. Contrary to the proposed hypothesis, the majority of patients stated that they were "on" while experiencing their hallucinations.
Miyoshi et al, 1996	Group comparison hallucinosis and delirium	Not stated		DD, MD H&Y staging	H had longer DD than NH and hallucinations were related to anti-Parkinsonian drugs. The hallucinosis type of psychiatric complications were frequent in the advanced stages (H&Y 3 and 4), whereas the delirum type of hallucinations symptoms were frequently seen in the earlier stages of PD (H&Y 1,2 and 3)
Naimark et al, 1996	Group comparison Regression	101/ 36H /65NH	PSYCHOSIS in PDD	Age at onset Age at diagnosis	Age at onset and age at diagnosis were not different in the two groups. Age, duration of PD dementia were significant predictors of psychosis.

Table A.2 Studies investigating disease-related concomitants of hallucinations in Parkinson's Disease (cont)

Study	Design	N	Inclusion/exclusion	Methodology	Findings
Graham et al, 1997	Group comparison early and late hall	129/ 32H/97NH	Idiopathic PD	UPDRS motor UPDRS ADL Type medn Specific motor symptoms DD, + prior to motor	No differences were found between H and NH on UPDRS motor or UPDRS ADL. There was a peak in onset of hallucinations within the first five years of symptoms of idiopathic PD superimposed on an increasing frequency of onset of hallucinosis with greater duration of disease. The time from idiopathic PD onset to the onset of response fluctuations was significantly shorter for H than NH. No group differences were detected on any of the mobility measures used. The early H were medicated with a significantly greater number of dopaminergic drugs than the early NH.
Klein et al, 1997	Group comparison	87/ 29H/58NH	Gross sensory impairment	Schwab-England Disability Scale UPDRS H&Y staging Webster scale DD Fluctuations	H were more disabled than NH, but no difference in Webster and H&Y scales or mean disease duration were found between groups. Significantly more H patients were treated with selegiline (no other differences in medication). No differences in on/off or dyskinisia were found between groups.
Goetz et al, 1998a	Group comparison	35/ 14H/21NH	Snellen acuity <0.6	Medication	No difference in duration, stage of PD or dosage or duration of L-dopa therapy between the two groups
Goetz et al, 1998b	Longitudinal Group comparison (early and late hall)	70/ 12EH/ 58LH		Medication	Patients with early drug-induced hallucinations had significantly greater placement to nursing homes and greater mortality; in all early H cessation of carbidopa/L-dopa led to resolution of the hallucinations.

Table A.2 Studies investigating disease-related concomitants of hallucinations in Parkinson's Disease (cont)

Study	Design	N	Inclusion/exclusion	Methodology	Findings
Inzelberg et al, 1998	Group comparison	121/ 45H/76NH	Auditory only	H&Yahr staging L-dopa	No differences were found between H and NH on duration of disease or H&Y staging. All patients with auditory hallucinations were treated with L-dopa with or without the dopamine agonists selegiline or amantadine. With few exceptions, no apparent correlation was found between the motor state and hallucinations.
Fuente-Fernandez et al, 1999	Group comparison Logistic regression	105/ 33H/72NH		H&Y staging MCS DD, MD L-dopa dose	No difference in the H&Y staging; latter age of onset of PD in H; higher scores on the MCS in H; shorter duration of treatment and lower doses of L-dopa in H
Kraft et al, 1999	Group comparison	30/ 15 H/15NH	Nil	H&Y staging LDDose DD	H were older, had shorter DD, higher doses of L-dopa and more disability (as measured by H7Y staging) than NH
Okada et al, 1999	Group comparison	33/ 12H/21NH	Previous antipsychotics	H&Y staging DD MD L-Dopa	No differences in DD, duration of medication, H&Y stage and L-dopa dose between groups.
Pappert et al, 1999	Log-linear models	126/ 33H/183NH	Inclusion: idiopathic PD. Exclusion: LBD, AD, stroke , non-use of L-dopa/ Carbidopa, non-availability of a 24-hour caregiver	UPDRS Schwab & England ADL Medn type	Parkinsonian disability (UPDRS and S&E) did not separate the behavioral subgroups; older patients predominated in the subgroup without any behavioral abnormalities; present use of L-dopa, dopamine agonists, antidepressants, bedtime Sinemet, sedatives and neuroleptics did not influence group assignment, whereas all subjects on selegeline had at least one behavioral abnormality and all those on amantadine had hallucinations.

Table A.2 Studies investigating disease-related concomitants of hallucinations in Parkinson's Disease (cont)

Study	Design	N	Inclusion/exclusion	Methodology	Findings
Arnulf et al, 2000	Group comparison	20/ 10H/10NH	Exc <24 MMSE	H&Y staging DD DD, MD pre-hall LDDose, other meds	Trend for H to be more disabled (Y&Y staging) ,longer DD and higher L-dopa daily dose.
Fenelon et al, 2000	Group comps minor and formed hallns Early and late hall and non-hall Regression	216/ 48H[1]/ 130 NH	Previously diagnosed schizophrenia	H&Y staging UPDRS motor, ADL and complications scales DD Medn type L-Dopa dose	H had a longer duration of PD, were more disabled (H&Y in "on" state, UPDRS ADL score, UPDRS motor score in "on"), more dyskinesias, were on higher daily doses of L-dopa and were less likely to b e treated with anticholinergics or selegiline than NH.
Barnes & David, 2001	Postal survey Group comparison	44/ 21H/23NH	DLB and AD diagnosis	H&Y staging L-dopa dose DD	H had a longer duration and a greater severity of illness. No difference in daily L-dopa intake was found between groups
Goetz et al, 2001a	Prospective longitudinal Group comparisons GEE modelling	89/ 29H/60NH		UPDRS motor scale H&Y staging LDDose, other meds DD	Pd duration, medications and UPDRS did not influence the incidence of hallucinations at baseline and 4-year follow-up
Goetz et al, 2001b	Group comparison on allele frequency	88/ 44H/44NH		UPDRS H&Y staging	H did not significantly differ from NH in mean daily doses of L-dopa; the mean DD was longer in H than NH; motorically, the mean UPDRS was significantly higher in H than NH
Holroyd et al, 2001	Prospective Group comparison (MANOVA)	102/ 30H/72NH	Atypical features suggesting PSP, DLB etc Absence of response to L-dopa DSM criteria delirium	UPDRS motor L-dopa dose No meds MD Medn type	H scored significantly higher on UPDRS, no difference in length of treatment or daily dose of L-dopa or other medications.
Manni et al, 2002				UPDRS	Not reported

[1] Formed visual hallucinations only

Table A.2 Studies investigating disease-related concomitants of hallucinations in Parkinson's Disease (cont)

Study	Design	N	Inclusion/exclusion	Methodology	Findings
Onofrij et al, 2002	Longitudinal Logistic regression	80	Nil	H&Y staging UPDRS Meds	Higher incidence of hallucinations in UPDRS stage 3 and 4 patients (ns , p<.06); Sleep behavior disorder was predictive of development of hallucinations independently of MMSE score, H&Y stage or UPDRS evaluation.
Barnes et al, 2003	Group comparison hall/non-hall/controls	37 PD 20 C	Diagnosis AD and DLB	H&Y staging DD L-dopa dose	H were more disabled (H&Y staging) and had longer DD than NH. No difference in daily L-dopa intake between groups
Nomura et al, 2003	Group comparison	22/ 14H/8NH		H&Y staging Age onset DD Medn	No difference in H7Y staging, age of onset, disease duration or PD medications were found
Onofrij et al, 2003	Group comparison	40/ 20H/20NH	Familial PD, dementia, psychosis or narcolepsy	UPDRS Meds	H scored significantly worse on UPDRS mental subscale and had significantly lower daily amount of dopamine agonist intake than NH
Barclay et al, 1987	Tertiary care PD population survey Group comparison	227	MMSE <18, previous psychotic disorder	H&Y staging Schwab & England ADL Presence fluctuations DD	Patients with psychotic symptoms had a longer duration of illness, tended to be in a later stage of the disease, had worse motor function both in the on and off state and were more likely to be institutionalized. Presence of psychotic symptoms correlate with the presence of dyskinesias
Shergill et al, 1988	Logistic regression	100/ 30H/70NH	PSYCHOSIS	DD LDDose Laterality EPS Age at onset	The "psychosis" group had longer DD than the "non-psychosis group". No other differences between groups were detected. Logistic regression confirmed the association between psychosis and cognitive decline and increased duration of illness. ,

Table A.3 Studies investigating demographic and psychological concomitants of hallucinations in Parkinson's Disease (Depression, Anxiety, MMPI)

Study	Design	N	Inclusion/exclusion	Methodology	Findings
Moskowiz et al, 1978	Descriptive only	88/ 27H/ 61NH	Inclusion: mild to moderate psychosis , history of nonpychotic psychiatric disorders Exclusion : severe dementia and history of psychosis	Presence of confusional and non-confusional psychosis	None reported
Meco et al, 1990	Clinic survey Group comparison	304/ 9H/10NH	MMSE <18	MMPI	H scored higher *on hypochondria, hysteria, schizophrenia* and *hypomania* scales of the MMPI than NH
Haeske-Dewick, 1995	Group comparison	36/ 16H/20NH	Psychiatric history, sensory pathology, thalamotomy, stroke, MID, AD or DLB	GDS	H significantly more depressed than NH
Buttner et al, 1996	Group comparison controls vs PD Regression to predict hallucinations	73	Colour blind individuals	BDI	Depression was predominantly correlated with achromatic contour perception
Miyoshi et al, 1996	Group comparison hallucinosis and delirium	Not stated		Presence delusions	Delusions of persecution and depressive mood are occasionally accompanied by confusional episodes
Naimark et al, 1996	Group comparison Regression	101/ 36H /65NH	PSYCHOSIS in PDD	NP symptoms + CG reported Behavioural problems	The psychotic patients had significantly more insomnia, confusion, agitation, personality changes and self-care problems than non-psychotic patients.
Sanchez-Ramos et al, 1996	Group comparison	214	Nil	History of depression	History of depression was strongly associated with the hallucinations
Graham et al, 1997	Group comparison early and late hall	129/ 32H/97NH	Idiopathic PD	BDI	No differences between groups were found
Klein et al, 1997	Group comparison	87/ 29H/58NH	Gross sensory impairment	'Mood disorder' Delusions, paranoia	No differences between groups were found

Table A.3 Studies investigating demographic and psychological concomitants of hallucinations in Parkinson's Disease (Depression, Anxiety, MMPI) (cont)

Study	Design	N	Inclusion/exclusion	Methodology	Findings
Okada et al, 1999	Group comparison	33/ 12H/ 21 NH	Previous antipsychotics	DSM criteria depression	No differences between groups were found
Fenelon et al, 2000	Group comps minor and formed hallns Early and late hall and non-hall Regression	216/ 86H/ 130 NH	Previously diagnosed schizophrenia	CES-D	H significantly more depressed than NH
Barnes & David, 2001	Postal survey Group comparison	44/ 21H/23NH	DLB and AD diagnosis	BDI	The H tended to be more depressed than the NH
Holroyd et al, 2001	Prospective Group comparison (MANOVA)	102/ 30H/72NH	Atypical features suggesting PSP, DLB etc Absence of response to L-dopa DSM criteria delirium	Psychiatric history	Visual hallucinations were associated with higher depression scores
Barnes et al, 2003	Group comparison hall/non-hall/controls	37 PD (17H, 20NH), 20 C	Diagnosis AD and DLB	VVIQ BDI	No differences on the VVIQ; H significantly more depressed than NH
Onofrij et al, 2003	Group comparison	40/ 20H/20NH	Familial PD, dementia, psychosis or narcolepsy	NPI	H higher scores on the Neuropsychiatric Inventory than NH
Barclay et al, 1987	Tertiary care PD popn survey Group comparison	227	MMSE <18, previous psychotic disorder	GDS	The presence of psychiatric symptoms were associated with depression severity

UNIFIED PARKINSON'S DISEASE RATING SCALE

I. MENTATION, BEHAVIOR AND MOOD

1. Intellectual Impairment
0 = None.
1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.
2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.
3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.
4 = Severe memory loss with orientation preserved to person only. Unable to make judgements or solve problems. Requires much help with personal care. Cannot be left alone at all.

2. Thought Disorder (Due to dementia or drug intoxication)
0 = None.
1 = Vivid dreaming.
2 = "Benign" hallucinations with insight retained.
3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.
4 = Persistent hallucinations, delusions, or florrid psychosis. Not able to care for self.

3. Depression
1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.
2 = Sustained depression (1 week or more).
3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).
4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

4. Motivation/Initiative
0 = Normal.
1 = Less assertive than usual; more passive.
2 = Loss of initiative or disinterest in elective (nonroutine) activities.
3 = Loss of initiative or disinterest in day to day (routine) activities.
4 = Withdrawn, complete loss of motivation.

II. ACTIVITIES OF DAILY LIVING (for both "on" and "off")

5. 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.

6. 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 tissue or handkerchief.

7. Swallowing
0 = Normal.
1 = Rare choking.
2 = Occasional choking.
3 = Requires soft food.
4 = Requires NG tube or gastrotomy feeding.

8. 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.

9. 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.

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

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

12. Turning in bed and 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, but not turn or adjust sheets alone.
4 = Helpless.

13. Falling (unrelated to freezing)
0 = None.
1 = Rare falling.
2 = Occasionally falls, less than once per day.
3 = Falls an average of once daily.
4 = Falls more than once daily.

14. Freezing when walking
0 = None.
1 = Rare freezing when walking; may have starthesitation.
2 = Occasional freezing when walking.
3 = Frequent freezing. Occasionally falls from freezing.
4 = Frequent falls from freezing.

15. 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.

16. 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.

17. 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.

III. MOTOR EXAMINATION

18. 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.

19. 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 facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. Tremor at rest (head, upper and lower extremities)
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.

21. Action or Postural Tremor of hands
0 = Absent.
1 = Slight; present with action.
2 = Moderate in amplitude, present with action.
3 = Moderate in amplitude with posture holding as well as action.
4 = Marked in amplitude; interferes with feeding.

22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling 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.

23. Finger Taps (Patient taps thumb with index finger in rapid succession.)
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.

24. Hand Movements (Patient opens and closes hands in rapid succesion.)
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.

25. Rapid Alternating Movements of Hands (Pronation-supination movements of hands, vertically and 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.

26. Leg Agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 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.

27. Arising from Chair (Patient attempts to rise from a straightbacked 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.

28. 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 slightly 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.

29. Gait
0 = Normal.
1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) 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, requiring assistance.
4 = Cannot walk at all, even with assistance.

30. Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders while 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.

31. Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased armswing, small amplitude poverty of movement in general.)
0 = None.
1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly rec amplitude.
2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduce amplitude.
3 = Moderate slowness, poverty or small amplitude of movement.
4 = Marked slowness, poverty or small amplitude of movement.

IV. COMPLICATIONS OF THERAPY (In the past week)

A. DYSKINESIAS

32. Duration: What proportion of the waking day are dyskinesias present? (Historical information.)
0 = None
1 = 1-25% of day.
2 = 26-50% of day.
3 = 51-75% of day.
4 = 76-100% of day.

33. Disability: How disabling are the dyskinesias? (Historical information; may be modified by office examinatic
0 = Not disabling.
1 = Mildly disabling.
2 = Moderately disabling.
3 = Severely disabling.
4 = Completely disabled.

34. Painful Dyskinesias: How painful are the dyskinesias?
0 = No painful dyskinesias.
1 = Slight.
2 = Moderate.
3 = Severe.
4 = Marked.

35. Presence of Early Morning Dystonia (Historical information.)
0 = No
1 = Yes

B. CLINICAL FLUCTUATIONS

36. Are "off" periods predictable?
0 = No
1 = Yes

37. Are "off" periods unpredictable?
0 = No
1 = Yes

38. Do "off" periods come on suddenly, within a few seconds?
0 = No
1 = Yes

39. What proportion of the waking day is the patient "off" on average?
0 = None
1 = 1-25% of day.
2 = 26-50% of day.
3 = 51-75% of day.
4 = 76-100% of day.

C. OTHER COMPLICATIONS

40. Does the patient have anorexia, nausea, or vomiting?
0 = No
1 = Yes

41. Any sleep disturbances, such as insomnia or hypersomnolence?
0 = No
1 = Yes

42. Does the patient have symptomatic orthostasis?
(Record the patient's blood pressure, height and weight on the scoring form)
0 = No
1 = Yes

V. MODIFIED HOEHN AND YAHR STAGING

STAGE 0 = No signs of disease.
STAGE 1 = Unilateral disease.
STAGE 1.5 = Unilateral plus axial involvement.
STAGE 2 = Bilateral disease, without impairment of balance.
STAGE 2.5 = Mild bilateral disease, with recovery on pull test.
STAGE 3 = Mild to moderate bilateral disease; some postural instability; physically independent.
STAGE 4 = Severe disability; still able to walk or stand unassisted.
STAGE 5 = Wheelchair bound or bedridden unless aided.

VI. SCHWAB AND ENGLAND ACTIVITIES OF DAILY LIVING SCALE

100% = Completely independent. Able to do all chores without slowness, difficulty or impairment. Essentially normal. Unaware of any difficulty.
90% = Completely independent. Able to do all chores with some degree of slowness, difficulty and impairment. Might take twice as long. Beginning to be aware of difficulty.
80% = Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness.
70% = Not completely independent. More difficulty with some chores. Three to four times as long in some. Must spenc a large part of the day with chores.
60% = Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors; some impossible.
50% = More dependent. Help with half, slower, etc. Difficulty with everything.
40% = Very dependent. Can assist with all chores, but few alone.
30% = With effort, now and then does a few chores alone or begins alone. Much help needed.
20% = Nothing alone. Can be a slight help with some chores. Severe invalid.
10% = Totally dependent, helpless. Complete invalid.
0% = Vegetative functions such as swallowing, bladder and bowel functions are not functioning. Bedridden.

Participant. no:_____
Date:____/____/____

SLEEPINESS SCALE

How likely are you to **doze off** or **fall asleep** in the following situations, in contrast to just feeling 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 situations

0	1	2	3
Would never doze off	Slight chance of dozing	Moderate chance of dozing	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 1 hour without a break	_____
Lying down to rest in the afternoon when circumstances permit	_____
Sitting and talking to someone	_____
Sitting quietly after lunch without alcohol	_____
In a car, while stopped for a few minutes in the traffic	_____

Participant no:_____
Date:____/____/____

Mood scale

Circle the best answer for how you have felt over the last week.

1. Are you basically satisfied with your life ?	YES	NO
2. Have you dropped many of your activities and interests ?	YES	NO
3. Do you feel that your life is empty ?	YES	NO
4. Do you often get bored ?	YES	NO
5. Are you in good spirits most of the time ?	YES	NO
6. Are you afraid that something bad is going to happen to you ?	YES	NO
7. Do you feel happy most of the time ?	YES	NO
8. Do you often feel helpless ?	YES	NO
9. Do you prefer to stay at home, rather than going out and doing new things ?	YES	NO
10. Do you feel that you have more problems with memory than most ?	YES	NO
11. Do you think it is wonderful to be alive ?	YES	NO
12. Do you feel pretty worthless the way you are now ?	YES	NO
13. Do you feel full of energy ?	YES	NO
14. Do you feel that your situation is hopeless ?	YES	NO
15. Do you think that most people are better off than you are ?	YES	NO

Date:____/____/___ Participant no:_____

Self-evaluation questionnaire

A number of statements which people use to describe themselves are given below. Read each statement carefully, and then circle the appropriate number, to indicate how you have been feeling recently. There are no right or wrong answers.

	Not at all	Somewhat	Moderately so	Very much so
1. I feel calm	1	2	3	4
2. I feel secure	1	2	3	4
3. I am tense	1	2	3	4
4. I am regretful	1	2	3	4
5. I feel at ease	1	2	3	4
6. I feel upset	1	2	3	4
7. I am presently worrying over possible misfortunes	1	2	3	4
8. I feel rested	1	2	3	4
9. I feel anxious	1	2	3	4
10. I feel comfortable	1	2	3	4
11. I feel self-confident	1	2	3	4
12. I feel nervous	1	2	3	4
13. I am jittery	1	2	3	4
14. I feel "high strung"	1	2	3	4
15. I am relaxed	1	2	3	4
16. I feel content	1	2	3	4
17. I am worried	1	2	3	4
18. I feel over-excited and "rattled"	1	2	3	4
19. I feel joyful	1	2	3	4
20. I feel pleasant	1	2	3	4

Section A: Quality of sleep

I'm going to ask you some questions about how you sleep. First could you tell me a bit about your sleeping arrangements...

☐	Lives alone	☐	Aids to turn over
☐	Shares bed	☐	Other aids
☐	Same room, separate beds	☐	Upstairs
☐	Different rooms	☐	Downstairs

Noise level _____

Proximity to bathroom _____

Lighting level _____

Next I'm going to ask you about your usual sleeping pattern

At what time do you take your last tablet	
Name, dose	

At what time do you go to bed ?		
How long does it usually take for you to fall asleep ?	☐	Less than 10 minutes
	☐	10 – 30 minutes
	☐	30 mins to 1 hour
	☐	More than 1 hour
At what time do you wake up in the morning ?		
At what time do you usually get out of bed ?		

Do you have problems turning over at night or pulling up sheets ?	
Do you ever switch off during the night ?	
Do you have cramps during the night ?	
Do you have pain that keeps you awake ? *(If so, what ?)*	
Are you mobile in the morning when you first wake up ?	
What time do you take your morning pill ?	

Waking in the night

How many times do you wake up during the night on average ?		
How many of these do you get up and out of bed ? *(i.e. to go to the toilet)*		
How long does it usually take you to get back to sleep if you wake in the night ?		Less than 10 minutes
		10 – 30 minutes
		30 mins to 1 hour
		More than 1 hour
How long would you estimate you spend awake during the night in total ?		
How long would you say you spend asleep on an average night ?		

Sleep Quality

How would you the quality of your sleep overall ?		Very good
		Good
		Average
		Poor
		Very poor

Daytime sleepiness

Now I'm going to ask about napping during the day

Do you often feel sleepy during the daytime ?		Yes		No
Do you have any planned siestas during the day ?				
How many times would you doze off on an average day ?				
What are you normally doing when you doze off ?				
How long do you usually spend napping during the day, in total ?				
If you feel sleepy, how easily can you resist the urge to doze off in the day ?		Not at all		
		A little		
		Quite easily		
		Very easily		
		I am not sleepy		
How much do you feel that your sleepiness gets in the way of what you want to do ?		Not at all		
		A little		
		Quite a lot		
		Very much so		

Section B: Unusual sleep symptoms

Now I'm going to ask you to think back over the last 3 months. Try and think about how often you have experienced the following symptoms in the last three months

0	1	2	3	4	5
Not at all	Once or twice	Once or twice a month	Once or twice a week	Most days	Every day

1. *Physical* fatigue during the daytime	0	1	2	3	4	5
2. Drowsiness during the daytime	0	1	2	3	4	5
3. Falling asleep during the daytime	0	1	2	3	4	5
4. Waking many times during the night	0	1	2	3	4	5
5. Vivid imagery when falling asleep	0	1	2	3	4	5
6. Vivid dreams	0	1	2	3	4	5
7. Frightening dreams or nightmares	0	1	2	3	4	5
8. States of terror or panic when half-awake	0	1	2	3	4	5
9. Confusion or disorientation on waking	0	1	2	3	4	5
10. Mumbling or crying out in your sleep	0	1	2	3	4	5
11. Restless or twitching arms and legs during sleep	0	1	2	3	4	5
12. Jerking or hitting out during sleep, which has injured you or your partner	0	1	2	3	4	5
13. Sleepwalking or wandering at night	0	1	2	3	4	5

Section C: Other 'unusual experiences'

1. Spots, or zigzag patterns before the eyes	0	1	2	3	4	5
2. Seeing flashing lights	0	1	2	3	4	5
3. Patterns appearing to move or swirl (wallpaper, curtains etc)	0	1	2	3	4	5
4. Seeing something moving from the corner of your eye	0	1	2	3	4	5
5. Thinking an object is an animal or person	0	1	2	3	4	5
6. A feeling of being 'haunted' as though someone else were in the room	0	1	2	3	4	5
7. A feeling of deja vu, as if the same thing has happened before	0	1	2	3	4	5
8. Feeling 'detached' as though things around you are unreal in some way	0	1	2	3	4	5
9. Not recognising someone familiar	0	1	2	3	4	5
10. Seeing flashbacks from a past shock	0	1	2	3	4	5
11. Memories so real you start behaving as though they were happening now	0	1	2	3	4	5
12. Seeing people, animals or objects which are not really there	0	1	2	3	4	5
13. Hearing things that cannot really be there (voices, music, etc)	0	1	2	3	4	5
14. Feeling as though something invisible is touching you or crawling on your skin	0	1	2	3	4	5
15. Smelling gas, burning, or unusual smells when they are not there	0	1	2	3	4	5

Miscellaneous items

Images from a photo or from the TV seeming as though they are real	0	1	2	3	4	5
Getting lost or unable to find your way around in your own house	0	1	2	3	4	5
Double vision (not alcohol related)	0	1	2	3	4	5
Sudden weakness or 'turning to jelly' when laughing or have strong emotions	0	1	2	3	4	5
Unable to move at all for a few minutes when trying to wake up (not related to off periods)	0	1	2	3	4	5

Other _____

Content of hallucinations _____

Could you tell me a bit more about what these images were like ?

Eyes	Open	Half-closed	Closed

Size	Miniturised	Normal	Larger than life

Duration	

Clarity	Distorted or not clear	Blurry but identifiable	Clear and focused	More vivid than reality

Colour	Congruent with darkness	Monochrome	Colourful	More intense than reality

Movement	Static	Warping	Action movement	Across visual field

Position in visual field	Focal	Peripheral	Moves with eyes

Variation	Always the same image	Some variation	Several different images	Always different

Theme	No discernible theme	Images themed	Theme from vivid dreams	Theme from external source i.e. TV, books

Theme and identity _____

Insight at time	None / Resistant	With persuasion	After first time	Full

Insight afterwards	None / Resistant	With persuasion	In retrospect	Full

Insight/ Elicited 'meaning' _____

Section D : What triggers your unusual experiences ?

I'd like to ask you a bit more about these unusual experiences and what situations they tend to happen in

Are you normally.....

Alone	With 1-2 others	In a crowded place

Very alert	As alert as normal	Drowsy	On the verge of sleep

Switched 'On'	'Wearing off'	Switched 'Off'

Is it normally.....

Morning	Daytime	Early evening	Night-time

VH only

Dark	Dimly lit	Well lit

AH only

Quiet	A bit noisy	Noisy

What do you think is the reason for your experiences ?

Do you agree with any of the following ?

- ☐ Medical illness
- ☐ Medical treatment (drugs, operations etc)
- ☐ Stress in the past
- ☐ Stress in the present
- ☐ Age-related changes
- ☐ Depression
- ☐ Mental illness
- ☐ Religious experience
- ☐ Other _____

_____

_____

_____

Section E: How much do your experiences bother you ?

1. Do you find your experiences distressing, or are they a comfort to you ?

Very distressing	Fairly distressing	Neutral	Fairly comforting	Very comforting

What is it about them that makes them...

_____

_____

_____

_____

_____

2. How much do your experiences distract you from everyday activities ?

Easy to ignore	Slightly distracting	Fairly distracting	Very distracting

3. Which of the following statements best describes your attitude towards these experiences when they happen ?

- ☐ I attempt to enjoy such experiences, or find them interesting
- ☐ I neither enjoy them or are distressed by them
- ☐ I try to ignore these things when they occur
- ☐ I try to control how often these things happen, or make them go away
- ☐ I try to explain to myself that they are unreal
- ☐ I try to stop myself getting upset when they happen
- ☐ I try to reduce the intensity or loudness of the experience
- ☐ Other _____

_____

_____

_____

_____

4. Are you able to stop these experiences when they happen ?

Not at all	Very rarely	Sometimes	Most of the time	All of the time

5. Do you feel as though you could set off such experiences or sensations if you wanted to ? (Please circle)

Not at all	Very rarely	Sometimes	Most of the time	All of the time

Section F: How do you cope with these experiences ?

Some people have techniques they use to make their experiences stop, distract themselves, or make themselves feel less anxious.

Please tell me if you've tried any of the following techniques. How useful were they ?

0	1	2	3
Never tried it	Not very useful	Fairly useful	Works very well

1. Move around or change the position you are in	0	1	2	3
2. Try to relax or go to sleep	0	1	2	3
3. Switch on the television or radio	0	1	2	3
4. Shut your eyes or cover your ears to block out the experience	0	1	2	3
5. Busy yourself with chores or useful activity (make a cup of tea, tidy things etc)	0	1	2	3
6. Distract yourself with some other activity (reading, gardening etc)	0	1	2	3
7. Walk around or exercise	0	1	2	3
8. Seek out someone to talk to	0	1	2	3
9. Tell the experiences to 'go away'	0	1	2	3
10. Talk to the things that you see or hear	0	1	2	3

Are there any other techniques that you have found useful, or that help you cope ?

Section A: Caregiver sleep quality

If you live in the same house as the person you care for, please answer the following questions about your **own** sleep

1. What sleeping arrangements do you and the person you care for have ? (Please tick)

- ☐ Share a bed
- ☐ Have separate beds in the same room
- ☐ Have different rooms

2. How many hours of sleep do ***you*** get during an average night ? (not including time spent *trying* to sleep)

_____hours

3. How many times do ***you*** usually wake up during the night ?

_____times

4. How many of these are you woken by the person you care for ?

_____times

5. How often do you get up during the night to give the person you care for *physical help* (i.e. getting out of bed, getting to the toilet) ? *(Please circle)*

Never	Very rarely	Once a month	Once a week	2-3 times a week	Every night	Several times a night

6. How often do you get up during the night to give the person you care for *reassurance or comfort* (i.e. after a bad dream) ? *(Please circle)*

Never	Very rarely	Once a month	Once a week	2-3 times a week	Every night	Several times a night

7. Do you ever stay awake purely because you need to check up on or listen out for the person you care for during the night ?

Never Rarely Sometimes Often

8. Are there any other kinds of help you give the person you care for during the night ? *(Please describe)*

_____

_____

_____

9. Overall, how would you rate the quality of your sleep at night ? *(Please circle)*

Very good Good Average Poor Very poor

10. How does the quality of your night time sleep now, compare to how it was 6-12 months ago ? *(Please circle)*

Much better now | A bit better now | About the same | A bit worse now | Much worse now

11. What do you think is the reason for this change ?

_____

_____

_____

12. How long do ***you*** usually spend napping during the day, in total ?

_____hours

Please answer the following about how well the person you care for sleeps

1. How many times does s/he usually wake up during the night ?

_____times

2. Roughly how many hours of ***sleep*** does s/he get during an average night ? (not including time spent trying to sleep)

_____hours

3. How does the quality of his/her night time sleep now, compare to how it was 6-12 months ago ? *(Please circle)*

Much better now	A bit better now	About the same	A bit worse now	Much worse now

4. How long does the *person you care for* usually spend napping during the day, in total ?

_____hours

5. How easily can s/he resist the urge to sleep in the day ? *(Please circle)*

Not at all	A little	Quite easily	Very easily	S/he is not sleepy

6. How much do you feel that his/ her daytime sleepiness affects or interrupts your plans ? *(Please circle)*

Not at all	A little	Quite a lot	Very much so

7. Does he/she sleep more or less in the day now compared to 6-12 months ago ? *(Please circle)*

Much more now	A bit more now	About the same	A bit less now	Much less now

Section B: Unusual sleep symptoms

Please indicate how often the person you care for has experienced the following symptoms in the past *threemonths*. Circle the number you think best applies to him/her.

0	1	2	3	4	5
Not at all	Once or twice	Once or twice a month	Once or twice a week	Most days	Every day

1. *Physical* fatigue during the daytime	0	1	2	3	4	5
2. Drowsiness during the daytime	0	1	2	3	4	5
3. Falling asleep during the daytime	0	1	2	3	4	5
4. Waking many times during the night	0	1	2	3	4	5
5. Vivid imagery when falling asleep	0	1	2	3	4	5
6. Vivid dreams	0	1	2	3	4	5
7. Frightening dreams or nightmares	0	1	2	3	4	5
8. States of terror or panic when half-awake	0	1	2	3	4	5
9. Confusion or disorientation on waking	0	1	2	3	4	5
10. Mumbling or crying out during sleep	0	1	2	3	4	5
11. Restless or twitching arms and legs during sleep	0	1	2	3	4	5
12. Jerking or hitting out during sleep, which has injured the person you care for or yourself	0	1	2	3	4	5
13. Sleepwalking or wandering at night	0	1	2	3	4	5

Section C: Other 'unusual experiences'

Please indicate how often the person you care for has experienced the following symptoms in the past *three months*. Circle the number you think best applies to him/her.

0	1	2	3	4	5
Not at all	Once or twice	Once or twice a month	Once or twice a week	Most days	Every day

1. Spots, or zigzag patterns before the eyes	0	1	2	3	4	5
2. Seeing flashing lights	0	1	2	3	4	5
3. Patterns or surfaces appearing to move (wallpaper, curtains etc)	0	1	2	3	4	5
4. Seeing something moving from the corner of his/her eye	0	1	2	3	4	5
5. Thinking an object is an animal or person	0	1	2	3	4	5
6. A feeling of being 'haunted' as though someone else were in the room	0	1	2	3	4	5
7. A feeling of deja vu, as if the same thing has happened before	0	1	2	3	4	5
8. Feeling 'detached' as though things around him/ her are unreal in some way	0	1	2	3	4	5
9. Not recognising someone familiar	0	1	2	3	4	5
10. Seeing 'flashbacks' from a past event	0	1	2	3	4	5
11. Memories so real s/he starts behaving as though they were happening now	0	1	2	3	4	5

0 Not at all	1 Once or twice	2 Once or twice a month	3 Once or twice a week	4 Most days	5 Every day

12. Seeing people, animals or objects which are not really there	0	1	2	3	4	5
13. Hearing things that cannot really be there (voices, music, etc)	0	1	2	3	4	5
14. Feeling as though something invisible is touching or crawling on his/her skin	0	1	2	3	4	5
15. Smelling gas, burning, or unusual smells when they are not there	0	1	2	3	4	5

If the person you care for has ***not*** seen, heard, felt or smelled things that were not really there, then you do not need to answer any further questions.

Please check that you have not left any answers blank.
Thank you for completing this questionnaire.

If you have answered positively to any of the questions on this page (12-15), i.e. the person you care for does see, hear, feel or smell things that are not there, please turn to the next page and continue

Section D: What triggers unusual experiences for the person you care for ?

This section asks about which situations unusual experiences tend to happen in.

For each question please circle the answer(s) that best suits the person you care for. You may circle more than one if his/ her experiences occur in more than one situation.

1. When s/he sees/ hears/ feels/ smells things that are not really there, s/he is usually.....

Alone	With 1-2 others	In a crowded place

2. When s/he sees/ hears/ feels/ smells things that are not really there, s/he is usually.....

Very alert	Alert	Drowsy	On the verge of sleep

3. When s/he sees/ hears/ feels/ smells things that are not really there, it is usually.....

Morning	Daytime	Early evening	Night-time

Sometimes people with Parkinson's Disease are aware that their medication is 'wearing off', and that their movement has become more difficult again. This is known as being 'off'. When medication is working well, and movement is easier, this is known as being 'on'.

4. When s/he sees/ hears/ feels/ smells things that are not really there, s/he is usually.....

'On'	'Wearing off'	'Off'

Please answer the next question only *if* the person you care for **sees** things that are not really there

5. When s/he sees things, s/he is usually in a place that is.....

Dark Dimly lit Well lit

Please answer the next questions only if the person you care for **hears** things that are not really there

6. When s/he hears things, s/he is usually in a place that is.....

Quiet A bit noisy Noisy

What do you think is the reason for the unusual experiences of the person you care for ?

Please tick all that apply to what *you* think

- ☐ Medical illness
- ☐ Medical treatment (drugs, operations etc)
- ☐ Stress in the past
- ☐ Stress in the present
- ☐ Age-related changes
- ☐ Depression
- ☐ Mental illness
- ☐ Religious experience
- ☐ Other

If you have ticked 'other' please give the reason you think has caused these experiences below

_____

_____

_____

_____

_____

_____

Section E: How much do these experiences affect the person you care for ?

1. Does the person you care for find their experiences distressing, or are they a comfort to them ? *(Please circle)*

Very distressing	Fairly distressing	Neutral	Fairly comforting	Very comforting

2. How much do the experiences distract the person you care for from everyday activities ? *(Please circle)*

They are easy to ignore	They are slightly distracting	They are fairly distracting	They are very distracting

3. Does the person you care for realise that his/ her experiences are unreal, at the time they happen ?

☐ Yes ☐ No

4. Does the person you care for realise that his/ her experiences are unreal later on, after they have finished ?

☐ Yes ☐ No

5. Could you persuade them that what they are experiencing is unreal, while the experience is happening ?

☐ Yes ☐ No

6. Could you persuade them that what they are experienced was unreal, after the experience has finished ?

☐ Yes ☐ No

7. Do you think the person you care for could stop these experiences when they happen, or make them 'go away' ? *(Please circle)*

Not at all	Very rarely	Sometimes	Most of the time	All of the time

Section F: How do <u>you</u> feel about the experiences of the person you care for ?

1. Which of the following statements best describe **<u>your</u>** feelings when the person you care for experiences something that is not really there?
   (You may tick more than one)

- ☐ It comforts me that the person I care for experiences these things
- ☐ I feel glad that these experiences keep the person I care for occupied
- ☐ I feel neither distressed or comforted that s/he has such experiences
- ☐ I feel fed up with the person I care for when the s/he has these experiences
- ☐ I feel embarrassed when the person I care has these experiences
- ☐ I feel anxious and unsure what to do when s/he has these experiences
- ☐ I feel useless or unable to help when these things happen
- ☐ I feel frightened when these things happen
- ☐ I feel angry towards the person I care for
- ☐ I feel distressed because the person I care for has these experiences
- ☐ I feel ashamed when the person I care for has these experiences

2. Which of the following statements best describes **<u>your</u>** attitudes or thoughts about the experiences the person you care for has ?
   (You may tick more than one)

- ☐ I want the person I care for to realise these things are not real
- ☐ I want to comfort or help the person I care for during these experiences
- ☐ I want the person I care for to enjoy his/ her experiences or find them interesting
- ☐ I worry that friends, family or neighbours will find out about these things
- ☐ I worry that I will not be able to look after him/ her properly
- ☐ I worry that his/ her mind is deteriorating
- ☐ I worry that s/he is becoming more ill
- ☐ I wish the person I care for had these experiences more often
- ☐ I wish the person I care for did not have these experiences at all
- ☐ I wish s/he was not upset by these experiences
- ☐ I wish s/he could control these experiences or make them 'go away'
- ☐ I wish I was not there when s/he has such experiences

Section G: What do you do when these experiences occur ?

Please read the following list of techniques people use to cope with unusual experiences.

Please tick the box for each of those you have used. If you have used a technique, please rate how useful it is to you.

Have you used this technique ? *(Please tick)*		How useful is this technique ? *(Please circle)*		
		Not useful	A bit useful	Very useful
☐	I try to tell the person I care for that these things are not real	1	2	3
☐	I pretend I can see or hear these things too	1	2	3
☐	I try to work out the underlying emotion of the person I care for at the time s/he has the experience	1	2	3
☐	I never question how real the experiences are, no matter what the person I care for tells me	1	2	3
☐	I always make sure I give the person I care for feedback about whether what s/he is experiencing is real or not	1	2	3
☐	I try to ignore any emotional reaction the person I care for has during his/ her unusual experiences	1	2	3
☐	I try to respond to the emotions of the person I care for, rather than disputing the reality of his/ her experiences	1	2	3
☐	I try to distract him/ her by talking about something else	1	2	3
☐	I try to distract him/ her by some other activity (bring him / her a cup of tea, switch the TV on)	1	2	3

Have you used this technique ? *(Please tick)*		How useful is this technique ? *(Please circle)*		
		Not useful	A bit useful	Very useful
☐	I try to ignore him/ her and get on with the things I am doing	1	2	3
☐	I make sure he/ she will not injure him/ herself if s/he gets agitated	1	2	3
☐	I try to calm him/ her down and get him/ her to relax	1	2	3
☐	I reassure him/ her that the experience will stop	1	2	3
☐	I tell him/ her s/he is safe and nothing bad will happen	1	2	3
☐	I leave the room and try not to get upset	1	2	3
☐	I get help from other people such as family or neighbours	1	2	3
☐	I try not to get upset and concentrate on how s/he is feeling	1	2	3

Are there any other techniques that you have found useful, or that help you cope when the person you care for experiences these things?

Please check that you have not left any answers blank.
Thank you for completing this questionnaire.

Please return it in the envelope provided

Please answer the following questions about how you slept last night

Daily routine

At what time did you go to bed ?	
At roughly what time did you fall asleep ?	
At what time did you wake up this morning ?	
At what time did you get out of bed ?	

Sleep Quality

How would you rate last night's sleep ? *(Please tick)*		Very good
		Good
		Average
		Poor
		Very poor
How refreshed did you feel this morning ? *(Please tick)*		Refreshed and alert
		Alert but not at peak
		Tired
		Absolutely shattered

Waking during the night

How many times did you wake up during the night ?	
How long would you estimate you spent awake during the night in total ?	
How many times did you get up and out of bed during the night ? *(i.e. to go to the toilet)*	
How long would you say you spent asleep last night ?	

Unusual experiences in the night

Please tick any which you experienced last night	
	Seeing unusual images in the dark
	Frightening dreams or nightmares
	States of terror or panic when half-awake
	Confusion or disorientation on waking
	Mumbling or crying out in your sleep
	Restless or twitching arms and legs during sleep
	Jerking or hitting out during sleep that injured you or your partner
	Sleepwalking or wandering at night

Please fill in the sleep chart below

Tick a box for each half-hour period, according to whether you were sleeping, lying awake in bed, or out of your bed during this time.

For those hours before you went to bed, and after you got up, please put a cross

(If you are unsure about what to do, there is an example sleep chart at the end of this booklet)

	P.M.							A.M.																	
	Evening							**Night**											**Morning**						
	8.30 - 9.00	9.00 - 9.30	9.30 - 10.00	10.00 - 10.30	10.30 - 11.00	11.00 - 11.30	11.30 - 12.00	12.00 - 12.30	12.30 - 1.00	1.00 - 1.30	1.30 - 2.00	2.00 - 2.30	2.30 - 3.00	3.00 - 3.30	3.30 - 4.00	4.00 - 4.30	4.30 - 5.00	5.00 - 5.30	5.30 - 6.00	6.00 - 6.30	6.30 - 7.00	7.00 - 7.30	7.30 - 8.00	8.00 - 8.30	8.30 - 9.00	9.00 - 9.30	9.30 - 10.00	10.00 - 10.30
Sleeping																												
Awake (in bed)																												
Out of bed (i.e. to visit toilet)																												

Please fill in the nap chart below

Please fill in a row for each nap you take today

There is space for five naps, although you will probably not need to use all the space

	At what time did you wake up from your nap ?	*Was this nap planned ?*	*How long do you think you were dozing for ?*	*What were you doing when you dozed off ?*	*Do you remember dreaming ?*
Nap 1		☐ Yes ☐ No			☐ Yes ☐ No
Nap 2		☐ Yes ☐ No			☐ Yes ☐ No
Nap 3		☐ Yes ☐ No			☐ Yes ☐ No
Nap 4		☐ Yes ☐ No			☐ Yes ☐ No
Nap 5		☐ Yes ☐ No			☐ Yes ☐ No

Please make a note of any times you were not wearing your actiwatch today

Please fill in the chart below, if you have had any unusual experiences or sensations today

For example, if you saw flashing lights, felt as though objects were moving or felt like someone was in the room with you. Or if you saw, heard or felt anything that was not really there.

You will probably not need to use all the space provided

	What did you see or sense ?	*Time of day*	*Were you drowsy ?*	*How long did it last for ?*	*What were you doing when the sensation happened ?*
1			☐ Yes ☐ No		
2			☐ Yes ☐ No		
3			☐ Yes ☐ No		
4			☐ Yes ☐ No		
5			☐ Yes ☐ No		

Please answer the following questions about how **you** slept last night

Daily routine

At what time did you go to bed ?	
At roughly what time did you fall asleep ?	
At what time did you wake up this morning ?	
At what time did you get out of bed ?	

Sleep Quality

How would you rate last night's sleep ? *(Please tick)*		Very good
		Good
		Average
		Poor
		Very poor
How refreshed did you feel this morning ? *(Please tick)*		Refreshed and alert
		Alert but not at peak
		Tired
		Absolutely shattered

Waking during the night

How many times did you wake up during the night ?	
How many times did you get up and out of bed during the night ? *(i.e. to go to the toilet)*	

Total time asleep and awake

How long would you estimate you spent awake during the night in total ?	
How long would you say you spent asleep last night ?	

Daytime sleepiness

Please answer he following questions about your sleepiness **during the day** today

Did you have a planned siesta or nap today ?	
How many times did you doze off by accident today ?	
How long would you say you spent napping in total today ?	

Day:_____

Please answer the following questions about how **the person you care for** slept last night You will probably need to ask for their help with most questions

Daily routine

At what time did he/she go to bed ?	
At roughly what time did he/she you fall asleep ?	
At what time did he/she wake up this morning ?	
At what time did he/she get out of bed ?	

Waking during the night

How many times did he/she wake up during the night ?	
How many times did he/she get up and out of bed during the night ? *(i.e. to go to the toilet)*	

Total time asleep and awake

How long would you estimate he/she spent awake during the night in total ?	
How long would you say he/she spent asleep last night ?	

Sleep Quality

How would he/she rate last night's sleep ? *(Please tick)*		Very good
		Good
		Average
		Poor
		Very poor
How refreshed did he/she feel this morning ? *(Please tick)*		Refreshed and alert
		Alert but not at peak
		Tired
		Absolutely shattered

Daytime sleepiness

Please answer he following questions about whethr the person you care for was sleepy **during the day**	
Did he or she have a planned siesta or nap today ?	
How many times did he/she doze off by accident today ?	
How long would you say you spent napping in total today ?	

There is also a nap chart on a later page to complete for the person you care for

Please answer the following questions about **help you provided** to the person you care for last night

Asking for help

How many times did the person you care for deliberately wake you to ask for help ?	

Physical help

How many times did you give *physical* help to him/her last night ? *(e.g. with turning over, getting to the toilet etc)*	
How long in total did you spend giving physical help ?	

Reassurance

How many times did you give *reassurance or comfort* to him/her last night ? *(e.g. after a bad dream, calming his/her worries etc)*	
How long in total did you spend giving comfort and reassurance ?	

Did you have to give any other kind of help last night ?

If so what ?

Please answer the following questions about how **the person you care for** slept last night

Unusual experiences in the night

*Please tick if **the person you care for** experienced any of the following last night*	
	Frightening dreams or nightmares
	Mumbling or crying out in his/her sleep
	Restless or twitching arms and legs during sleep
	Seeing unusual images in the dark
	Strange ideas or behaviour in the night
	States of terror or panic when half-awake
	Confusion or disorientation on waking
	Jerking or hitting out during sleep that injured you or him/herself
	Sleepwalking or wandering at night

Did he or she have any other unusual experiences last night ?

If so what ?

Please fill in the nap chart below for **the person you care for**.

Please fill in a row for each nap **he/she** takes today

There is space for seven naps, although you will probably not need to use all the space

	Was this nap planned ?		*At what time did you notice him/ her dozing ?*	*How long do you think he/she dozed for altogether ?*	*What was he/she doing when he/she dozed off ?*	*Did she/ he talk in his/ her sleep at all?*		*Was she/he aware of having been asleep ?*	
Nap 1		Yes					Yes		Yes
		No					No		No
Nap 2		Yes					Yes		Yes
		No					No		No
Nap 3		Yes					Yes		Yes
		No					No		No
Nap 4		Yes					Yes		Yes
		No					No		No
Nap 5		Yes					Yes		Yes
		No					No		No
Nap 6		Yes					Yes		Yes
		No					No		No
Nap 7		Yes					Yes		Yes
		No					No		No

Please fill in the chart below, if you think **the person you care for** had any unusual experiences or sensations today

For example, if he or she saw, heard or felt anything that was not really there.

You will probably not need to use all the space provided

	What kind of sensation did he or she experience	*How long did it last for ?*	*Time of day*	*How did s/he respond to the sensation ?*	*Was he or she drowsy ?*	*Did s/he know it was not real ?*
1					☐ Yes ☐ No	☐ Yes ☐ No
2					☐ Yes ☐ No	☐ Yes ☐ No
3					☐ Yes ☐ No	☐ Yes ☐ No
4					☐ Yes ☐ No	☐ Yes ☐ No
5					☐ Yes ☐ No	☐ Yes ☐ No

Please make a note of any times the person you care for was not wearing his/her actiwatch today

Actigraphic sleep variables derived using Actiwatch and Sleep Analysis '98

Assumed Sleep	The difference between sleep end and sleep start.
Actual Sleep Time	The amount of sleep as determined by the algorithm and is equivalent to assumed sleep minus wake time.
Actual Awake Time	The amount of time spent awake as determined by the algorithm.
Actual Sleep and Wake Time Percentages	These are displayed to the right of the Actual Sleep and Actual Wake boxes.
Sleep Efficiency	The percentage of time spent asleep whilst in bed.
Sleep Latency	The latency before sleep onset following bed time.
Number of Sleep Bouts	The actual number of episodes of sleep.
Number of Wake Bouts	The actual number of episodes of wakefulness.
Mean Length of Sleep and Wake Bouts	These figures are determined by dividing the total duration of sleep and wake by the corresponding number of sleep and wake bouts.
Number of Minutes Immobile	The total number of minutes where a score of zero was recorded during the assumed sleep period.
Number of Minutes Moving	The converse of the above being the total number of minutes where scores of greater then zero were recorded during the assumed sleep period.
Percentage of Minute Immobile and Minutes Moving	The percentage of time spent immobile or moving during the assumed sleep period.
The Number of Immobile Phases	The number of periods of continuos scores of zero being recorded in consecutive epochs.
The Number of Immobile Phases of 1 Minute	The number of Immobile phases where the duration was only 1 minute.
Percentage Immobility Phases of 1 Minute	The percentage of Immobility phases of 1 minute as a proportion of the total number of Immobility phases. This value is termed the Fragmentation Index.
Movement and Fragmentation Index	The addition of Percentage Time Spent Moving and The Percentage Immobility Phases of 1 Minute. This is used as an indicator of restlessness.
Total Activity Score	The total number of activity counts between sleep start and sleep end.
Mean Activity Score	The average value of the activity counts per epoch over the assumed sleep period.
Mean Activity Score in Active Periods	The average activity score in those epochs where scores of greater then zero were recorded during the assumed sleep period.
Average Wake Movement	The average activity score per epoch for the wake period proceeding the previous nights sleep. Derived from activity counts between sleep end in the morning and sleep start of the current day.

Explanation of and formulae for Non-Parametric Circadian Rhythm Analysis variables

The following is an excerpt from: Van Someren et al (1996) Circadian rest-activity rhythm disturbances in Alzheimer's Disease. Biological Psychiatry; 40: 259-270

The interdaily satability (IS) is the 24-hour value from the chi-square periodogram, normalised for the number of data, and gives an indication of the strength of the coupling between the rest-activity rhythm and Zeitgebers. IS is a signal-to-noise measure, calculated as the ratio between the variance of the average 24-hour pattern around the mean and the overall variance.

$$IS = \frac{n \sum_{h=1}^{p} (\bar{x}_h - \bar{x})^2}{p \sum_{i=1}^{n} (\bar{x}_h - \bar{x})^2}$$

where n is the total number of data, p the number of data per day (in this study 24), x_h the hourly means, x the mean of all data, and x_i the individual data points.

The intradaily variability (IV) gives an indications of the fragmentation of the rhythm (i.e., the frequency of transitions between rest and activity) and is calculated as the ratio of the mean squares of the difference between consecutive hours (first derivative) and the mean squares around the grand mean (overall variance). IV is based on hourly values and reflects transitions of relatively long periods of rest and activity, rather than frequent transitions of more and less activity as occurring in most daily pursuits.

$$IV = \frac{n \sum_{i=2}^{n} (x_i - x_{i-1})^2}{(n-1) \sum_{i=1}^{n} (x_i - \bar{x})^2}$$

Appendix E: Additional statistics for Chapter 8

	Total time asleep	Total time awake in night	Number of wakenings	Number of times out of bed	Nocturnal sleep latency	Self-report sleep quality	Number of unplanned naps	Total time asleep during the day	Able to resist sleep in day ?	Functional impairment caused by sleepiness	Epworth Sleepiness Scale total
Sleep latency	-0.177	0.141	0.197	0.248*	-0.022	-0.085	0.164	0.133	0.047	0.019	-0.189
Total time asleep		-0.681***	-0.312**	-0.100	-0.520***	0.432***	-0.043	-0.032	0.119	-0.053	-0.151
Total time awake in night			0.344**	0.113	0.788***	-0.594***	0.018	0.053	0.010	0.048	-0.044
Number of wakenings				0.682***	0.261*	-0.405**	0.134	0.194	-0.212	0.339**	0.234
Number of times out of bed					-0.159	-0.075	0.138	0.244*	-0.251	0.495***	0.259*
Nocturnal sleep latency						-0.725***	-0.107	-0.080	0.064	-0.058	-0.154
Self-report sleep quality							0.043	-0.007	-0.120	0.012	0.055
Number of unplanned naps								0.610***	-0.387**	0.507***	0.450***
Total time asleep during the day									-0.384**	0.460***	0.305*
Able to resist sleep in day ?										-0.456***	-0.344*
Functional impairment caused by sleepiness											0.420**

Table E.1 Internal consistency of self-reported sleep variables * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

	How long sleep last night ?	No. of awakenings ?	No. times out of bed ?	Sleep quality ?	Refreshed ?	Mean time spent napping per day	Mean nap time over all days	No. of daytime naps per day
How long awake last night ?	-0.452***	0.365**	0.136	-0.460**	-0.426**	0.214	0.191	0.254
How long sleep last night ?		-0.135	0.048	0.250	0.243	0.200	0.193	0.003
No. of awakenings ?			0.702***	-0.306*	-0.045	-0.129	-0.207	0.019
No. times out of bed ?				-0.196	0.103	-0.087	-0.118	-0.009
Sleep quality ?					0.632***	-0.234	-0.269	-0.271
Refreshed ?						-0.250	-0.131	-0.394**
Mean time spent napping per day							0.782***	0.795***
Mean nap time over all days								0.427**

Table E.2 Internal consistency between mean sleep diary variables * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

	Sleep latency	Total time asleep	Total time awake in night	Number of awak-enings	Number of times out of bed	Nocturnal sleep latency	Self-report sleep quality	Number of unplanned naps	Total time asleep during the day	Able to resist sleep in day?	Functional impairment caused by sleepiness	Epworth Sleepiness Scale total
Age at time of test	0.182	0.041	0.011	0.005	0.263*	-0.173	0.016	0.097	0.118	-0.099	0.297*	-0.169
Disease duration	0.131	0.048	-0.097	0.126	0.284*	-0.175	0.09	0.041	0.2	-0.207	0.261*	0.21
Medication duration	0.125	0.057	-0.106	0.109	0.287*	-0.185	0.101	0.046	0.205	-0.232	0.272*	0.196
MMSE total score	-0.313**	-0.014	-0.057	-0.053	-0.007	0.013	0.086	-0.395***	-0.478***	0.215	-0.125	0.027
Total for motor scale	0.256*	-0.083	0.062	0.126	0.113	0.054	-0.218	0.237*	0.330**	-0.244	0.196	0.117
Total fluctuations score	-0.021	0.062	0.048	-0.045	0.045	0.099	-0.133	0.067	0.119	-0.295*	0.267*	0.051
Ambulatory factor	0.235	0.131	-0.136	-0.016	0.159	-0.122	0.011	-0.023	0.211	-0.16	0.15	-0.074
Dexterity factor	0.035	-0.012	0.123	0.228	0.164	0.101	-0.252	0.189	0.235	-0.212	0.211	0.143
Dyskinesia factor	-0.049	0.129	-0.003	-0.105	-0.088	0.06	-0.139	-0.017	-0.004	-0.237	0.06	-0.043
Face factor	0.206	-0.12	0.033	-0.133	-0.158	-0.124	0.104	0.382**	0.187	0.023	0.028	0.107
Tremor factor	0.219	-0.219	0.086	-0.021	-0.22	0.172	-0.219	-0.057	-0.051	0.029	-0.17	0.014
Off/freezing factor	0.004	-0.041	0.093	-0.006	0.055	0.121	0.035	0.102	0.179	-0.073	0.225	0.187

Table E.3 Correlations between clinical variables and self-reported sleep variables * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

	How long awake last night ?	How long sleep last night ?	No. of awakenings ?	No. times out of bed ?	Sleep quality ?	Refreshed ?	Mean time spent napping per day	Mean nap time over all days	No. of daytime naps per day
Age at time of test	-0.006	0.056	0.022	0.104	-0.053	0.028	0.418**	0.317*	0.257
Disease duration	0.069	0.041	0.353*	0.347*	0.006	0.140	-0.089	-0.055	-0.104
Medication duration	0.071	0.034	0.360**	0.368**	-0.014	0.140	-0.071	-0.035	-0.097
MMSE total score	-0.167	-0.050	0.009	0.048	0.128	-0.020	-0.341*	-0.093	-0.288*
Total for motor scale	0.048	-0.127	-0.009	-0.056	-0.082	-0.085	0.310*	0.234	0.224
Total fluctuations score	0.195	-0.119	0.334*	0.153	-0.197	-0.121	0.175	0.224	0.152
Ambulatory factor	0.006	-0.186	0.135	-0.007	-0.191	0.064	0.165	0.269	0.082
Dexterity factor	-0.083	-0.079	0.008	-0.034	-0.076	-0.175	0.144	0.096	0.076
Dyskinesia factor	0.080	-0.108	0.290	0.036	-0.134	-0.104	0.261	0.325*	0.135
Face factor	0.238	0.098	-0.211	-0.094	0.124	0.081	0.242	0.162	0.101
Tremor factor	-0.005	-0.103	-0.158	-0.132	0.016	-0.122	0.187	0.023	0.291*
Off/freezing factor	0.482***	-0.305*	0.312*	0.238	-0.293	-0.084	-0.104	-0.209	0.055

Table E.4 Correlations between clinical variables and mean sleep diary variables * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

	Assumed sleep MEAN	Actual sleep time MEAN	Actual sleep (%) MEAN	Actual wake time MEAN	Actual wake (%) MEAN	Sleep efficiency MEAN	Sleep latency MEAN	Sleep bouts MEAN	Wake bouts MEAN	Mean sleep bout time MEAN	Mean wake bout time MEAN	Immobile mins MEAN	Immobile time (%) MEAN	Moving mins MEAN
Age at time of test	0.232	0.184	-0.089	0.144	0.089	-0.015	0.155	-0.048	-0.048	0.214	0.230	0.104	-0.132	0.176
Disease duration	0.128	0.064	-0.205	0.234	0.205	-0.082	0.101	0.024	0.026	-0.034	0.300*	0.013	-0.158	0.178
Medication duration	0.137	0.080	-0.176	0.212	0.176	-0.069	0.112	0.022	0.023	-0.031	0.274*	0.029	-0.139	0.165
MMSE total score	-0.130	-0.077	0.118	-0.147	-0.118	0.183	-0.198	-0.128	-0.126	0.069	-0.114	0.037	0.205	-0.242*
Total for motor scale	0.125	0.087	-0.085	0.112	0.085	-0.091	0.215	-0.066	-0.062	0.068	0.239	0.017	-0.125	0.157
Total fluctuations score	0.098	0.088	-0.009	0.032	0.009	-0.170	0.275*	0.013	0.013	-0.001	0.043	0.008	-0.137	0.133
Ambulatory factor	0.014	0.003	-0.012	0.030	0.012	-0.070	0.156	-0.099	-0.100	0.086	0.106	-0.034	-0.073	0.074
Dexterity factor	0.203	0.124	-0.183	0.228	0.183	-0.057	0.085	0.086	0.091	-0.005	0.293*	0.097	-0.100	0.146
Dyskinesia factor	0.123	0.143	0.070	-0.052	-0.070	-0.134	0.282*	-0.007	-0.008	-0.011	-0.038	0.068	-0.082	0.074
Face factor	-0.058	-0.014	0.097	-0.123	-0.097	-0.010	0.124	0.005	0.005	-0.234	-0.028	-0.127	-0.122	0.116
Tremor factor	-0.004	0.029	0.080	-0.093	-0.080	0.006	0.102	-0.267*	-0.263*	0.280*	0.077	0.060	0.100	-0.100
Off/freezing factor	0.099	0.086	0.000	0.039	0.000	0.008	-0.011	-0.026	-0.025	0.078	0.074	0.025	-0.082	0.106

Table E.5 Correlations between clinical variables and mean actigraphic variables * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

	Moving time (%) MEAN	No. immobile phases MEAN	Mean length immobility MEAN	1 Minute immobility MEAN	1 Min immobility (%) MEAN	Total activity score MEAN	Mean activity score MEAN	Mean score in active MEAN	Fragmentation index MEAN	Mean wake score MEAN	Mean no. actigraphic naps per day	Mean time actigraphic naps per day	Mean time all actigraphic naps
Age at time of test	0.132	0.065	0.160	0.155	0.126	0.139	0.115	0.069	0.135	-0.261*	0.262*	0.299*	0.173
Disease duration	0.158	0.123	-0.067	0.151	0.203	0.376**	0.375**	0.348**	0.191	0.228	0.068	0.171	0.034
Medication duration	0.139	0.129	-0.062	0.153	0.192	0.363**	0.359**	0.345**	0.176	0.229	0.082	0.186	0.045
MMSE total score	-0.205	-0.111	0.033	-0.161	-0.176	-0.086	-0.056	0.067	-0.198	0.080	-0.136	-0.038	0.081
Total for motor scale	0.125	-0.086	0.029	-0.076	-0.061	0.089	0.084	0.089	0.026	-0.098	0.169	0.227	0.074
Total fluctuations score	0.137	0.042	-0.015	0.028	0.039	0.086	0.051	0.035	0.088	0.444***	-0.202	-0.196	-0.260*
Ambulatory factor	0.073	0.013	0.053	0.061	0.043	0.127	0.130	0.113	0.059	0.092	-0.058	-0.075	-0.185
Dexterity factor	0.100	0.016	-0.034	0.008	-0.013	0.136	0.093	0.049	0.042	-0.186	0.209	0.280*	0.149
Dyskinesia factor	0.082	0.044	-0.008	0.020	0.009	0.008	-0.020	-0.020	0.045	0.424**	-0.259*	-0.231	-0.218
Face factor	0.122	0.042	-0.212	-0.030	0.034	-0.113	-0.057	-0.104	0.078	-0.112	0.193	0.228	0.220
Tremor factor	-0.100	-0.361**	0.274*	-0.332**	-0.275*	-0.103	-0.096	0.087	-0.202	-0.090	0.040	0.067	0.034
Off/freezing factor	0.082	0.045	-0.021	0.033	0.025	-0.035	-0.051	-0.080	0.054	0.100	-0.103	-0.074	-0.118

Table E.5 Correlations between clinical variables and mean actigraphic variables (cont.) * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

	Interdaily stability	Intradaily variability	Least active 5 hours	Most active 10 hours	Amplitude	Relative amplitude
Age at time of test	-0.029	0.411**	0.094	-0.318*	-0.338**	-0.199
Disease duration	0.186	0.135	0.370**	0.150	0.113	-0.254*
Medication duration	0.197	0.132	0.350**	0.154	0.119	-0.238
MMSE total score	0.217	-0.063	-0.058	0.188	0.200	0.323*
Total for motor scale	-0.082	0.226	0.130	-0.172	-0.193	-0.259*
Total fluctuations score	0.337**	-0.278*	0.018	0.410**	0.419**	0.175
Ambulatory factor	0.115	-0.065	0.257	0.048	0.020	-0.149
Dexterity factor	-0.106	0.276*	0.022	-0.254	-0.263*	-0.229
Dyskinesia factor	0.323*	-0.361**	-0.059	0.420**	0.438**	0.276*
Face factor	-0.227	0.193	-0.046	-0.105	-0.103	-0.097
Tremor factor	-0.150	0.191	-0.027	-0.095	-0.095	-0.047
Off/freezing factor	0.167	-0.079	-0.051	0.034	0.040	-0.040

Table E.6 Correlations between clinical variables and circadian rhythm variables * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

	Non-hall	UPE	Hall	Control	F	X^2
Sleep latency[a]	1.00	2.00	1.00	1.00		2.283
Total time asleep	6.39 (± 1.45)	6.03 (± 1.65)	6.40 (± 1.51)	6.48 (± 1.50)	0.307	
Total time awake in night	1.22 (± 1.34)	1.48 (± 1.34)	1.22 (± 1.11)	1.23 (± 1.32)	0.158	
Number of wakenings[a]	2.00	3.00	2.00	2.00		4.683
Number of times out of bed[a]	1.00	2.00	1.00	1.00		1.277
Nocturnal sleep latency[a]	1.00	1.50	1.00	2.00		1.383
Self-report sleep quality[a]	4.00	3.00	4.00	4.00		1.710
Number of unplanned naps[a]	1.00	1.00	2.00	0.50		35.121***
Total time asleep during the day	0.83 (± 0.74)	1.13 (± 1.06)	1.94 (± 1.56)	0.36 (± 0.49)	12.262***	
Able to resist sleep in day ?[a]	2.00	1.50	1.50	2.00		12.084**
Functional impairment caused by sleepiness[a]	0.00	0.00	1.00	0.00		8.617*
Epworth Sleepiness Scale total	6.18 (± 4.74)	9.57 (± 4.77)	9.24 (± 4.00)	5.16 (± 3.80)	6.526***	

Table E.7 Group comparisons for interview sleep variables [a] Median values given, and χ^2 calculated for Kruskal-Wallis non-parametric test.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

	Non-hall	UPE	Hall	Controls	F	χ^2
How long awake last night ?	80.52 (± 53.81)	67.13 (± 67.37)	69.56 (± 60.88)	60.10 (± 61.89)	0.513	
How long sleep last night ?	393.21 (± 68.33)	393.38 (± 60.55)	384.53 (± 78.60)	397.29 (± 66.50)	0.133	
No. of awakenings ?[a]	2.00	3.00	2.00	2.00		10.792*
No. times out of bed ?[a]	1.00	2.00	2.00	1.00		10.153*
Sleep quality ?	3.47 (± 0.70)	2.91 (± 0.52)	3.44 (± 0.81)	3.52 (± 0.66)	1.696	
Refreshed ?	3.04 (± 0.56)	2.73 (± 0.46)	2.95 (± 0.61)	3.04 (± 0.40)	0.918	
Time spent napping per day	23.87 (± 29.90)	46.21 (± 35.88)	39.25 (± 35.66)	11.87 (± 19.68)	5.211**	
No. of daytime naps per day	0.72 (± 0.66)	1.19 (± 0.91)	1.11 (± 0.88)	0.35 (± 0.51)	3.058*	
Nap time over all days	22.83 (± 22.28)	38.91 (± 16.01)	29.20 (± 22.19)	16.24 (± 21.09)	6.265**	

Table E.8 Group comparisons for mean sleep diary variables [a] Median values given, and χ^2 calculated for Kruskal-Wallis non-parametric test.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

	Non hallucinators		UPE group		Hallucinators		
	Mean	(Std. Dev)	Mean	(Std. Dev)	Mean	(Std. Dev)	F
Assumed sleep	427.44	(± 69.05)	458.83	(± 71.02)	435.39	(± 75.95)	0.776
Actual sleep time	399.54	(± 62.61)	412.75	(± 87.53)	394.28	(± 72.12)	0.283
Actual sleep (%)	93.69	(± 3.56)	90.03	(± 8.73)	90.57	(± 5.10)	2.944
Actual wake time	27.34	(± 16.86)	45.57	(± 44.06)	40.69	(± 20.76)	2.903
Actual wake (%)	6.31	(± 3.56)	9.97	(± 8.73)	9.43	(± 5.10)	2.944
Sleep efficiency	78.52	(± 7.42)	75.50	(± 12.00)	75.62	(± 8.97)	0.841
Sleep latency	27.65	(± 13.41)	37.91	(± 25.83)	28.22	(± 19.46)	1.400
Sleep bouts	21.37	(± 11.30)	20.72	(± 11.16)	26.41	(± 10.32)	1.891
Wake bouts	21.37	(± 11.31)	20.69	(± 11.20)	26.43	(± 10.32)	1.910
Mean sleep bout time	26.17	(± 15.62)	30.53	(± 18.48)	19.60	(± 9.13)	3.136*
Mean wake bout time	1.26	(± 0.43)	2.15	(± 1.07)	1.63	(± 0.66)	7.396**
Immobile mins	387.70	(± 61.60)	393.36	(± 94.08)	355.60	(± 81.38)	1.623
Immobile time (%)	90.88	(± 4.81)	85.50	(± 9.78)	81.75	(± 13.69)	5.330**
Moving mins	39.74	(± 22.46)	65.47	(± 48.04)	79.80	(± 59.44)	5.190**
Moving time (%)	9.12	(± 4.81)	14.50	(± 9.78)	18.25	(± 13.69)	5.330**
No. immobile phases	44.50	(± 23.66)	53.44	(± 26.90)	62.18	(± 34.13)	2.512
Mean length immobility	12.29	(± 7.75)	11.67	(± 10.66)	7.91	(± 4.72)	2.760
1 Minute immobility	13.49	(± 11.25)	19.42	(± 14.55)	23.54	(± 20.46)	2.585
1 Min immobility (%)	24.84	(± 11.14)	32.23	(± 13.44)	32.31	(± 13.26)	2.818
Total activity score	3801	(± 2873)	8706	(± 9362)	6103	(± 4014)	4.082*
Mean activity score	4.32	(± 2.98)	10.06	(± 11.80)	7.13	(± 4.44)	3.975*
Mean score in active	46.50	(± 19.81)	64.72	(± 65.62)	47.98	(± 29.70)	1.183
Fragmentation index	33.96	(± 15.65)	46.73	(± 22.62)	50.56	(± 25.88)	4.129*
Mean wake score	58.78	(± 36.64)	76.63	(± 55.81)	67.18	(± 59.07)	0.530

Table E.9 Group comparisons for mean actigraphy variables [a] Median values given, and χ^2 calculated for Kruskal-Wallis non-parametric test.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

	Sleep latency	Total time asleep	Total time awake in night	Number of wakenings	Number of times out of bed	Nocturnal sleep latency	Self-report sleep quality	Number of unplanned naps	Total time asleep during the day	Able to resist sleep in day ?	Functional impairment caused by sleepiness	Epworth Sleepiness Scale total
Summed score factor	-0.005	-0.015	-0.050	-0.005	0.004	-0.109	-0.010	0.087	0.363**	-0.174	0.136	0.237
VH factor score	-0.017	-0.069	-0.004	0.087	0.007	-0.042	-0.112	0.107	0.287*	-0.139	0.107	0.248*

Table E.10 Correlations between interview sleep variables and hallucinations scores * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

	Diary: How long awake last night ? MEAN	Diary: How long sleep last night ? MEAN	Diary: No. of wakenings ? MEAN	Diary: No. times out of bed ? MEAN	Diary: Sleep quality ? MEAN	Diary: Refreshed ? MEAN	Diary: Mean time spent napping per day	Diary: Mean nap time over all days	Diary: No. of daytime naps per day MEAN
Summed score factor	-0.041	-0.139	0.006	0.040	-0.049	-0.004	0.011	0.132	-0.030
VH factor score	-0.084	-0.197	-0.003	0.002	-0.069	0.019	-0.050	0.100	-0.065

Table E.11 Correlations between mean sleep diary variables and hallucinations scores * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

	Assumed sleep MEAN	Actual sleep time MEAN	Actual sleep (%) MEAN	Actual wake time MEAN	Actual wake (%) MEAN	Sleep efficiency MEAN	Sleep latency MEAN	Sleep bouts MEAN	Wake bouts MEAN	Mean sleep bout time MEAN	Mean wake bout time MEAN	Immobile mins MEAN	Immobile time (%) MEAN	Moving mins MEAN
Summed score factor	0.037	0.001	-0.097	0.101	0.097	-0.061	0.115	-0.006	-0.006	-0.106	0.216	-0.065	-0.162	0.158
VH factor score	-0.007	-0.079	-0.212	0.197	0.212	-0.149	0.118	0.059	0.059	-0.156	0.288*	-0.146	-0.240	0.220

Table E.12 Correlations between mean actigraphic variables and hallucinations scores * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

	Moving time (%) MEAN	No. immobile phases MEAN	Mean length immobility MEAN	1 *Minute* immobility MEAN	1 Min immobility (%) MEAN	Total acivity score MEAN	Mean activity score MEAN	Mean score in active MEAN	Fragmentation index MEAN	Mean wake score MEAN	Mean No. actigraphic naps per day	Meanl time actigraphic naps per day	Mean time all actigraphic naps
Summed score factor	0.162	0.089	-0.157	0.089	0.131	0.064	0.053	0.029	0.152	-0.051	0.092	0.089	-0.097
VH factor score	0.240	0.084	-0.190	0.103	0.179	0.131	0.129	0.025	0.216	0.047	0.005	-0.014	-0.157

Table E.12 Correlations between mean actigraphic variables and hallucinations scores (cont.) * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

	Circadian analysis - interdaily stability	Circadian analysis - intradailiy variability	Circadian analysis - least active 5 hours	Circadian analysis - most active 5 hours	Circadian analysis - amplitude	Circadian analysis - relative amplitude
Summed score factor	-0.247	0.102	0.023	-0.085	-0.091	-0.237
VH factor score	-0.238	0.058	0.106	0.018	0.005	-0.248

Table E.13 Correlations between circadian rhythm variables and hallucinations scores * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Appendix F: Additional statistics for Chapter 9

	MMSE total score	Mill Hill Vocab total score	Full NART equivalent score	Age at time of test	Geriatric Depression Scale total	State Anxiety Inventory total	Disease duration	Medication duration	Total for motor scale UPDRS	Total fluctuations score UPDRS
MMSE orientation score	0.685***	0.220	0.260*	-0.315**	0.154	0.098	0.183	0.175	-0.324**	0.164
MMSE repetition	0.276*	-0.110	-0.040	0.005	0.279*	0.176	-0.399***	-0.396***		-0.099
MMSE serial task	0.701***	0.364**	0.364**	-0.213	0.019	0.021	-0.033	-0.042	-0.213	0.019
MMSE recall	0.702***	0.425***	0.301**	-0.160	0.116	0.268	0.054	0.062	-0.337**	-0.072
MMSE object naming	0.045	-0.035	0.087	-0.034	0.320*	0.284	0.144	0.145	-0.029	0.069
MMSE three stage task	0.554***	0.201	0.218	-0.223	-0.068	0.163	-0.044	-0.038	-0.388***	-0.053

Table F.1 Correlations between MMSE subsections and clinical variables * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

	Logical memory Total Recall 1+2	Logical memory Total Recall 1+2+2	Logical memory Total Recall II	Logical memory Visit 2 story recall	Logical memory Learning slope	Logical memory Total Theme 1+2+2	Logical memory Total Theme II	Logical memory Visit 2 theme recall	Logical memory Total Recog
Hits LM recognition	0.355**	0.352**	0.427***	0.164	0.142	0.383**	0.478***	0.095	0.601***
Correct negatives LM recognition	0.702***	0.761***	0.706***	0.504***	0.444***	0.669***	0.572***	0.491***	0.857***
False alarms LM recognition	-0.688***	-0.744***	-0.698***	-0.508***	-0.429***	-0.653***	-0.558***	-0.512***	-0.852***
Misses LM recognition	-0.371**	-0.373**	-0.432***	-0.158	-0.164	-0.402***	-0.490***	-0.056	-0.599***
False alarms: correct negatives ratio	-0.586***	-0.651***	-0.626***	-0.447***	-0.406***	-0.595***	-0.513***	-0.498***	-0.757***
Recall inaccuracies new	0.048	0.075	0.000	0.062	0.118	0.098	0.084	-0.092	0.054
Novel intrusion new	-0.222	-0.221	-0.316**	-0.194	-0.172	-0.235*	-0.249*	-0.222	-0.425***
Cross-trial errors new	-0.197	-0.166	-0.247*	-0.199	0.027	-0.228	-0.311**	-0.328*	-0.020
Recall inaccuracies total	0.050	0.083	0.039	0.090	0.147	0.114	0.106	-0.084	0.060
Novel intrusion total	-0.181	-0.184	-0.271*	-0.176	-0.182	-0.201	-0.204	-0.218	-0.432***
Cross-trial errors total	-0.197	-0.166	-0.247*	-0.199	0.027	-0.228	-0.311**	-0.328*	-0.020
Percentage confabulations LM	-0.314*	-0.278*	-0.352**	-0.196	0.011	-0.266*	-0.214	-0.322*	-0.344*
Confabulations LM + intrusions VF	-0.047	-0.067	-0.185	-0.150	-0.300*	-0.033	-0.058	-0.255	-0.271*

Table F.2 Correlations between logical memory error scores and correct scores * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

	Age at time of test	MMSE total score	Mill Hill Vocab total score	Full NART equivalent score	Geriatric Depression Scale total	State Anxiety Inventory total	Disease duration	Medication duration	Total for motor scale UPDRS	Total fluctuations score UPDRS
Hits LM recognition	-0.188	0.170	0.106	-0.013	-0.316**	-0.119	0.059	0.053	-0.105	0.234
Correct negatives LM recognition	-0.217	0.569***	0.462***	0.328*	-0.384**	-0.288	0.009	-0.016	-0.178	0.052
False alarms LM recognition	0.237	-0.588***	-0.443***	-0.319*	0.415**	0.296	-0.002	0.020	0.218	-0.053
Misses LM recognition	0.154	-0.140	-0.124	-0.003	0.264	0.097	-0.068	-0.058	0.041	-0.226
False alarms: correct negative ratio LM	0.250	-0.505***	-0.332*	-0.121	0.341*	0.409**	-0.024	-0.007	0.152	-0.029
Recall inaccuracies new to trial 5	-0.011	0.033	-0.125	0.028	0.212	0.096	0.035	0.028	0.232*	-0.136
Novel intrusion new to trial 5	0.171	-0.370***	0.010	-0.003	0.164	0.314*	0.072	0.072	0.219	-0.011
Cross-trial errors new to triall 5	0.014	-0.375***	0.047	0.100	0.027	0.068	0.299**	0.303**	0.177	0.114
Recall inaccuracies total to trial 5	-0.018	0.053	-0.172	0.006	0.198	0.051	-0.022	-0.034	0.181	-0.164
Novel intrusion total to trial 5	0.154	-0.328**	0.005	0.000	0.160	0.344*	0.054	0.052	0.185	0.004
Cross-trial errors total to trial 5	0.014	-0.375***	0.047	0.100	0.027	0.068	0.299**	0.303**	0.177	0.114
Percentage confabulations LM	0.247*	-0.610***	-0.344***	-0.207*	0.358***	0.361***	0.095	0.097	0.363**	-0.051
Confabulations LM + intrusions VF	0.113	-0.175	-0.053	0.016	0.006	0.220	0.108	0.113	0.205	0.016

Table F.3 Correlations between logical memory errors and clinical variables * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

	VOSP Shape detection total	VOSP Incomplete letters total	VOSP Silhouettes total	VOSP Object decision total	VOSP Progressive silhouettes total	VOSP Grand total
VOSP Shape detection false positives	-0.623***	-0.335**	-0.231*	-0.252*	0.210	-0.342**
VOSP Shape detection false negatives	-0.846***	-0.518***	-0.317**	-0.495***	0.050	-0.444***
VOSP Shape detection confabulations	-0.512***	-0.203	-0.112	-0.162	0.126	-0.222
VOSP Incomplete letters incorrect	-0.446***	-0.798***	-0.341**	-0.361**	0.188	-0.556***
VOSP Silhouettes incorrect	-0.217	-0.278*	-0.783***	-0.373***	0.294*	-0.598***
VOSP Object decision incorrect	-0.362**	-0.408***	-0.516***	-0.813***	0.236*	-0.641***
VOSP Object decision misidentifications	-0.145	-0.130	-0.420***	-0.256*	0.366**	-0.370**

Table F.4 Correlations between VOSP error scores and correct scores * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

	Age at time of test	MMSE total score	Mill Hill Vocab total score	Full NART equivalent score	Geriatric Depression Scale total	State Anxiety Inventory total	Disease duration	Medication duration	Total for motor scale UPDRS	Total fluctuations score UPDRS
VOSP Shape detection false positives	0.143	-0.348**	-0.076	-0.013	0.127	0.314*	-0.039	-0.036	0.221	-0.002
VOSP Shape detection false negatives	0.189	-0.271*	-0.152	-0.084	0.216	0.158	-0.172	-0.177	0.148	-0.188
VOSP Shape detection confabulations	0.227*	-0.383***	-0.099	-0.113	-0.016	0.241	-0.067	-0.064	0.223	0.155
VOSP Incomplete letters incorrect	0.209	-0.211	-0.145	0.017	0.109	0.108	0.022	0.028	0.390***	-0.138
VOSP Silhouettes incorrect	0.171	-0.389***	-0.234	-0.131	0.182	0.028	-0.044	-0.045	0.218	-0.040
VOSP Object decision incorrect	0.217	-0.543***	-0.266*	-0.123	0.100	-0.031	0.008	0.014	0.286*	-0.099
VOSP Object decision misidentifications	0.219	-0.414***	-0.208	-0.127	-0.096	-0.016	0.147	0.144	0.216	0.210

Table F.5 Correlations between VOSP errors and clinical variables * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

	Overlapping figure A time to 8 (in secs)	Overlapping figure A total objects named	Overlapping figure B time to 8 (in secs)	Overlapping figure B total objects named	Total figures named OFigs A + B
Total misidentifications OFigs A + B	0.361**	-0.526***	0.372**	-0.554***	-0.577***
Percentage misidentifications OFigs	0.476***	-0.624***	0.429**	-0.643***	-0.676***
Ofigs: repetition total	0.404**	-0.214	0.380**	-0.318**	-0.288*
Ofigs: anomia total	0.174	0.059	0.150	-0.106	-0.031

Table F.6 Correlations between overlapping figures error scores and correct scores * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

	Age at time of test	MMSE total score	Mill Hill Vocab total score	Full NART equivalent score	Geriatric Depression Scale total	State Anxiety Inventory total	Disease duration	Medication duration	Total for motor scale UPDRS	Total fluctuations score UPDRS
Total misidentifications OFigs A + B	0.242*	-0.331**	-0.018	0.094	0.086	0.226	-0.011	-0.004	0.212	-0.002
Percentage misidentifications OFigs	0.253*	-0.401***	-0.074	0.082	0.124	0.254	-0.003	0.004	0.225	0.006
Ofigs: repetition total	0.168	-0.163	-0.167	-0.112	0.099	0.048	0.036	0.039	0.044	-0.023
Ofigs: anomia total	0.010	-0.135	-0.005	-0.159	-0.009	0.033	-0.123	-0.132	0.070	-0.191

Table F.7 Correlations between overlapping figures errors and clinical variables * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

	Verbal fluency letter total	Verbal fluency category total	Verbal fluency alternating letter total	Verbal fluency alternating category total	Verbal fluency alternating let/cat total	Verbal fluency grand total
Verbal fluency repetition total	0.180	-0.018	0.272*	0.057	0.032	0.113
Verbal fluency perseveration total	-0.287*	-0.156	-0.321**	-0.523***	-0.320**	-0.387***
Verbal fluency intrusion total	0.138	-0.146	0.017	-0.212	-0.115	-0.084
Cross-trial intrusions verbal fluency	0.031	-0.154	-0.125	-0.211	-0.149	-0.144
Novel intrusions verbal fluency	0.206	-0.106	0.159	-0.138	-0.034	0.006

Table F.8 Correlations between verbal flunecy error scores and correct scores * p < 0.05; ** p <0.01; *** p< 0.001

	Age at time of test	MMSE total score	Mill Hill Vocab total score	Full NART equivalent score	Geriatric Depression Scale total	State Anxiety Inventory total	Disease duration	Medication duration	Total for motor scale UPDRS	Total fluctuations score UPDRS
Verbal fluency repetition total	-0.089	0.113	0.050	-0.069	-0.060	-0.295*	-0.042	-0.057	-0.190	-0.047
Verbal fluency perseveration total	0.263*	-0.533***	-0.119	-0.208	0.228	0.081	0.047	0.037	0.262*	-0.104
Verbal fluency intrusion total	0.051	-0.061	0.006	0.008	-0.188	0.020	0.152	0.165	0.084	0.088
Cross-trial intrusions verbal fluency	0.088	-0.074	-0.030	-0.026	-0.064	-0.016	0.197	0.208	0.081	0.094
Novel intrusions verbal fluency	-0.007	-0.015	0.028	0.029	-0.225	0.040	0.065	0.073	0.071	0.063
Percentage repetition verbal fluency	-0.019	-0.010	0.019	-0.103	-0.005	-0.319*	-0.074	-0.092	-0.152	-0.099
Percentage perseveration verbal fluency	0.242*	-0.644***	-0.228	-0.183	0.317*	0.265	-0.024	-0.032	0.325**	-0.091
Percentage intrusions verbal fluency	0.136	-0.215	-0.051	0.083	-0.069	0.166	0.150	0.163	0.194	0.075
Percentage novel intrusion verbal fluency	0.054	-0.155	-0.009	0.084	-0.140	0.140	0.018	0.028	0.174	0.043
Percentage cross-trial verbal fluency	0.154	-0.178	-0.069	0.046	0.034	0.109	0.208	0.218	0.129	0.072

Table F.9 Correlations between verbal fluency errors and clinical variables * p < 0.05; ** p <0.01; *** p< 0.001

	Trailmaking A time (in secs)	Trailmaking B time (in secs)	Trailmaking A complete / 25	Trailmaking B complete / 25	Trail A time per correct response	Trail B time per correct response
Trailmaking A errors	0.572***	-0.031	-0.379**	-0.619***	0.605***	0.407**
Trailmaking B errors	0.206	0.454***		-0.101	0.206	0.177
Trailmaking A (% errors)	0.540***	-0.016	-0.711***	-0.619***	0.798***	0.414**
Trailmaking B (% errors)	0.609***	0.027		-0.784***	0.609***	0.797***

Table F.10 Correlations between trailamking error scores and correct scores * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

	Age at time of test	MMSE total score	Mill Hill Vocab total score	Full NART equivalent score	Geriatric Depression Scale total	State Anxiety Inventory total	Disease duration	Medication duration	Total for motor scale UPDRS	Total fluctuations score UPDRS
Trailmaking A errors	0.139	-0.570***	-0.432**	-0.151	0.335*	0.372*	-0.124	-0.120	0.277*	-0.114
Trailmaking B errors	0.178	-0.166	-0.086	-0.106	0.048	0.071	0.027	0.040	-0.001	-0.140
Trailmaking A (% errors)	0.070	-0.628***	-0.436**	-0.158	0.268	0.365**	-0.055	-0.052	0.290*	-0.052
Trailmaking AB(% errors)	0.255	-0.532***	-0.225	-0.164	0.248	0.287	0.032	0.045	0.257	-0.016

Table F.11 Correlations between trailmaking errors and clinical variables * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

	Novel intrusions LM + intrusions VF	%age novel intrusions LM + intrusions VF	Visual misidentifications	Percentage visual misidentifications
Age at time of test	0.116	0.233	0.251**	0.252*
Disease duration	0.126	0.101	0.035	0.033
Medication duration	0.137	0.109	0.037	0.034
MMSE total score	-0.169	-0.379**	-0.507***	-0.544***
Total for motor scale UPDRS	0.135	0.221	0.336**	0.351**
Total fluctuations score UPDRS	0.060	0.021	-0.048	-0.051
Ambulatory factor - UPD	0.212	0.306*	0.058	0.064
Dexterity factor - UPD	0.000	0.065	0.302*	0.319*
Dyskinesia factor - UPD	-0.051	-0.092	-0.096	-0.091
Face factor - UPD	-0.085	-0.118	0.085	0.100
Tremor factor - UPD	-0.054	-0.049	0.144	0.140
Off/freezing factor - UPD	-0.009	-0.030	0.081	0.051
Geriatric Depression Scale total	-0.077	0.122	0.135	0.171
State Anxiety Inventory total	0.186	0.341*	0.104	0.126

Table F.13 Correlations between composite error scores and clinical variables
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$