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Risk Factors for Visual Hallucinations in Parkinson's Disease: Investigating the Continuum

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The following pages have been redacted at the request of the University;

Appendix 7 pages 270-279

Appendix 8 page 280

Appendix 9 pages 281-282

Appendix 10 page 283

Appendix 11 pages 284-288

Appendix 12 page 289

Appendix 13-18 pages 290 – 298

Appendix 22 pages 304-305

The table 7.2 on page 137

Abstract

The present work presents a series of studies investigating neuropsychological aspects of visual hallucinations (VHs) in Parkinson's Disease (PD) and high proneness to VHs in the normal population. The aim of the thesis is to investigate whether the same risk factors are implicated in both hallucinating PD patients and in high-prone individuals from the normal population, i.e. the continuum hypothesis of VHs. To this end, new instruments were designed to assess the nature of VHs in PD and to differentiate among high and low hallucination-prone individuals. PD patients with and without VHs, age-matched normal controls, and high and low-prone normal young individuals are assessed on visual memory and executive tests from the CANTAB test battery, alongside tests examining personality factors, sleep patterns, and demographic factors. The findings suggest that VHs in PD and hallucination-proneness in the normal population are both associated with a combination of different factors, particularly aspects of visual processing and sleep patterns. Results from the five studies are interpreted with the multifactorial models of VHs, suggesting that both VHs in PD and hallucination-proneness in the normal population stem from concurrent neuropsychological dysfunctions of several processing systems. However, a specific personality profile is predictive of high hallucination-proneness in the normal population, but not in PD patients. Therefore, two different models are proposed, arguing for similar, but not identical set of risk factors in hallucinating PD patients and in high-prone normal individuals.

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...Tebi delo posvetim...

Table of Contents

List of Tables

List of Figures

"An organism with more than 100 billion neurons
is not likely to be simple."
- Anonymous

Chapter 1: Research Background

1.1 Parkinson's Disease: Background, Clinical Features and Neuropathology

James Parkinson (1755 – 1824) was a physician, social reformer and (as a hobby) a geologist and palaeontologist. But it was *"An Essay on the Shaking Palsy"* (1817) that brought him immortality. In the essay he describes "paralysis agitans" (meaning "shaking palsy"), a condition that would later be named after him. Parkinson's disease (also known as Parkinson Disease or PD) is the most common neurodegenerative disease after Alzheimer's disease (Schapira, 2004). It is largely a disease of the elderly: the prevalence increases with age from approximately 0.6% in 65-69 years-olds to 3-4% in 80-84 years-olds, with a slight male predominance (de Rijk et al., 1997; Twelves, Perkins, & Counsell, 2003).

Clinically, PD is characterized by tremor, muscle rigidity, postural instability, slowing of physical movement (bradykinesia) and sometimes a complete loss of physical movement (akinesia) (Jankovic, 2008; Serrano & Garcia-Borreguero, 2004). Neuropathologically, PD is characterized by the loss of dopaminergic neurons[1] originating from the substantia nigra, and by a prominence of atypical protein aggregates (so-called Lewy bodies) inside neurons of the substantia nigra, locus coeruleus and raphe nucleus (Dauer & Przedborski, 2003). It is estimated that 60% - 80% of the dopaminergic neurons in the substantia nigra are lost before motor symptoms of PD manifest (ibid). This means that the neurodegenerative process is already present for a number of years before the first symptoms become apparent (Scholtissen, Verhey, Steinbusch, & Leentjens, 2006).

There are eight dopaminergic pathways, but the three major ones implicated in PD are the nigrostriatal, the mesocortical and the mesolimbic pathway (see Figure 1.1).

[1] Dopaminergic neurons are neurons whose primary neurotransmitter is dopamine, a hormone and neurotransmitter involved in modulation of motor activity, cognition, motivation, reward, sleep, mood, attention and learning.

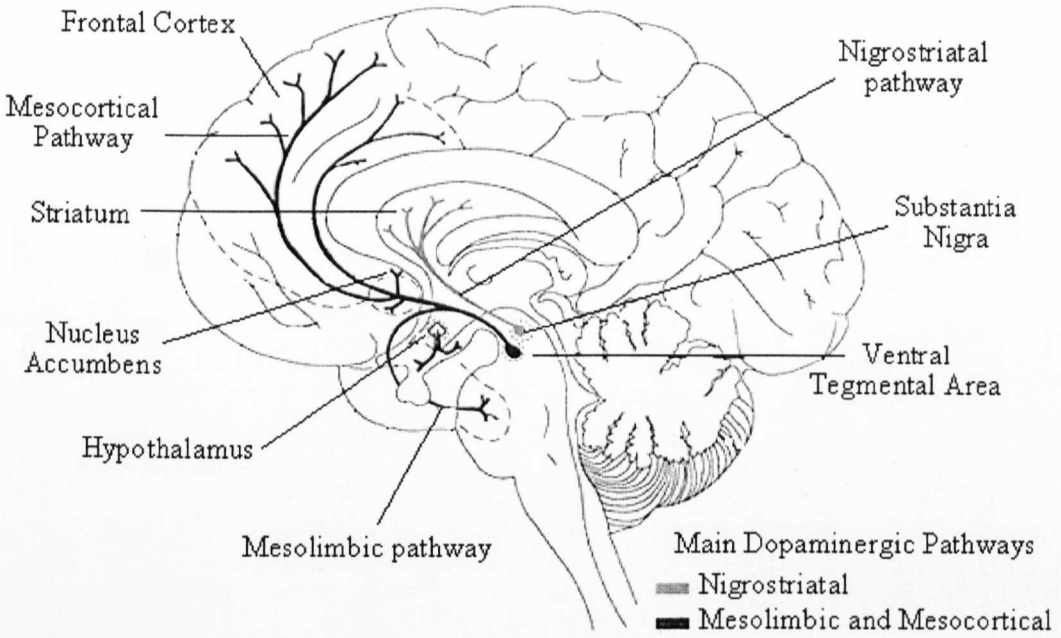


Figure 1.1. Sagittal view showing the main dopaminergic pathways.

The nigrostriatal dopaminergic pathway originates in neurons of the substantia nigra and projects to the striatum (i.e., the caudate nucleus and putamen) (Schapira, 2004). This pathway is involved in modulating smooth and coordinated movement (Contreras-Vidal & Stelmach, 1995, 1996).

The mesocortical and mesolimbic pathways originate from the midbrain ventral tegmental area neurons and target the nucleus accumbens, the limbic system, the hippocampus, and the prefrontal cortex (Chaudhuri, Martinez-Martin et al., 2006). These systems modulate a range of non-motor, mainly cognitive and emotive functions, such as reward, the psychomotor effects associated with drugs, and working memory (Chaudhuri, Healy, & Schapira, 2006; Chaudhuri, Martinez-Martin et al., 2006). Additionally, this system is associated with the ascending reticular activating system, which contributes to sleep during night and arousal during the day (Schapira, 2004).

In summary, the early dominant motor features of PD are traditionally related to dopaminergic cell death. However, the neurodegeneration extends well beyond

dopaminergic neurons even in the early stages of PD (Collerton, Perry, & McKeith, 2005; Dauer & Przedborski, 2003; Hornykiewicz & Kish, 1987). Involvement of non-dopaminergic systems result in a variety of clinical features, such as visual hallucinations, cognitive disturbances (executive, visuospatial, and memory dysfunctions), depression, autonomic abnormalities, sleep disorders, fatigue, blurred vision and weight loss or gain (Fenelon, Mahieux, Huon, & Ziegler, 2000). Indeed, the symptoms that are not traditionally related to the dopaminergic system frequently occur before the diagnosis is made and can be more prominent than the motor signs of PD (Mosimann et al., 2006). Non-motor signs of PD also add to the severity of illness, reduced life satisfaction, and shorten life expectancy (Inzelberg, Kipervasser, & Korczyn, 1998). Therefore, it is not surprising that the number of studies on the non-motor signs of PD has increased in recent years.

1.2 Phenomenology of VHs in PD

One of the most common non-motor signs of PD are visual hallucinations (VHs), occurring in approximately 30% of patients with PD (Bronnick, Aarsland, & Larsen, 2005; de Maindreville, Fenelon, & Mahieux, 2005; Fenelon et al., 2000; Gupta, Singh, Khwaja, & Mehndiratta, 2004; Holroyd, Currie, & Wooten, 2001).

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, 1994) a hallucination is "a sensory perception that has the compelling sense of reality of a true perception but that occurs without external stimulation of the relevant sensory organ" (p.767). Hallucinations are distinguished from illusions, which are misperception or misinterpretation of an actual external stimulus (ibid). VHs in PD comply with the DSM-IV definition; they are recurring spontaneous images of people, animals, or objects and are experienced as real (Barnes & David, 2001).

Fenelon et al. (2000) proposed three categories of hallucinations in PD: minor forms (a feeling of a "presence" of another being, or someone "passing-by"), formed (complex) VHs and auditory hallucinations. However, both auditory and

simple hallucinations of flashes, dots, or grids are rare and in fact suggest a differential diagnosis, independent of PD (Bodis-Wollner, 2003; Fenelon et al., 2000; Inzelberg et al., 1998; Mosimann et al., 2006).

The phenomenology of VHs in PD has been examined in detail in small number of studies (Barnes & David, 2001; Fenelon et al., 2000; Holroyd et al., 2001). However, understanding the phenomenology of VHs has important implications on the current recognition of the underlying brain structures that might be implicated in the process of experiencing VHs (see Section 1.4). Therefore, detailed studies are warranted, especially due to the difficulties in examining the brain of the hallucinating PD patients with the use of neuroimaging and electrophysiological techniques.

VHs in PD are usually described as vivid, well-formed, stereotyped and repetitive images of relatives, friends, and unknown people, but also of animals and objects (Barnes & David, 2001; Fenelon et al., 2000; Gupta et al., 2004; Haeske-Dewick, 1995; Holroyd et al., 2001). The same image is often repeated, usually in the same surrounding (Barnes & David, 2001); however, over time, many patients report experiencing a range of hallucinatory images (Fenelon et al., 2000). Similarly, the content is often ordinary, but it can range to the bizarre (e.g., unusually large body parts, half of a body part joined with furniture, images coming from a ceiling and disappearing into the floor, etc.). The images frequently move (Barnes & David, 2001), although the movement is often stereotyped and restricted (either little movement or doing the same gesture or set of moves repeatedly over time). Hallucinations are usually normal-sized, but they can also be unusually small (Holroyd et al., 2001). They can appear either black and white, in monochrome or in multiple colours (Barnes & David, 2001).

Temporal aspects of VHs have revealed the importance of the sleep generating brain functions in the occurrence of VHs in PD (see Section 1.4). Most commonly, patients experience VHs on a weekly basis: daily or monthly intervals of occurrence are rare (Barnes & David, 2001). Images usually appear for a few minutes (images that last for seconds or hours are rare), but the duration can vary according to the time of day, with longer occurrences either in the morning or in the

evening (Barnes & David, 2001; Inzelberg et al., 1998). Hallucinations are most likely to appear when the patient is drowsy or when the ambient light is dim (Goetz, Vogel, Tanner, & Stebbins, 1998; Inzelberg et al., 1998). However, images are also experienced in an alert state and most patients have their eyes open when the images appear (Barnes & David, 2001; Kulisevsky & Roldan, 2004). Both onset and offset are usually abrupt with no apparent trigger or voluntary effort (Kulisevsky & Roldan, 2004).

Once developed, VHs persist and can lose their benign, non-threatening character (Goetz, Leurgans, Pappert, Raman, & Stemer, 2001); patients with dementia may especially lose their ability to identify the images as unreal (Inzelberg et al., 1998). Fenelon et al. (2000) reported that insight was maintained in all their patients without dementia and in 64% of the patients with dementia. However, even patients without dementia who reported that they were aware of the unreality of their visions admitted that they occasionally spoke to the images because they looked real (ibid). The studies investigating VHs in PD patients with dementia can be extremely valuable in predicting the development of the illness; however, the results need to be addressed with care, because neurodegeneration is extensive in dementia and the diagnosis of PD could be incorrect. Consequently, the overall understanding of the phenomenon of VHs can be blurred.

In summary, VHs in PD are usually ordinary, stereotyped and non-threatening images of people and animals. After the first disturbing or astonishing experiences, patients usually become familiar with their presence and describe them as unpleasant but not upsetting (Barnes & David, 2001; Diederich, Goetz, & Stebbins, 2005; Fenelon et al., 2000). Emotional responses rarely include frustration, anger or fear (Barnes & David, 2001). The non-threatening nature of VHs and the preserved insight into the hallucinatory nature of their VHs are probably the main two reasons why PD patients do not spontaneously speak about VHs. Furthermore, patients often reason that reporting VHs will make people think they are "going mad" and might therefore be sent to a nursing home (Barnes & David, 2001). Similarly, patients do not want to upset their friends and carers. Mosimann et al. (2006) reported that 16% of the caregivers in their study were unaware of patients'

hallucinations. The nature of VHs in PD has immediate treatment implications, because it suggests that hallucinating PD patients as well as their carers would greatly benefit from the cognitive treatment with reassurance and acceptance.

Patients' self-awareness and shame are therefore the main reasons why VHs in PD have been long underreported. Additionally, the presence of VHs is difficult to ascertain in cases of severe dementia, when patients report about their VHs more freely but also lose the insight into of the unreality of the images (Fenelon et al., 2000; Inzelberg et al., 1998). Taking these motives into account it is now estimated that approximately one third of patients with PD have at least a transient experience of VHs in the course of their illness (Aarsland et al., 1999; Bronnick et al., 2005; de Maindreville et al., 2005; Fenelon et al., 2000; Gupta et al., 2004; Haeske-Dewick, 1995; Holroyd et al., 2001).

Several issues need to be addressed when conducting the studies with PD participants. Firstly, the sample sizes are usually relatively low. This is because of the relative rarity of the condition and the specific care that needs to be taken when working with this fragile population (the duration of tasks, medication variations throughout the day, etc.). Therefore, with the exception of Fenelon et al.'s (2000) 86 hallucinating PD patients, the studies operate with data of up to 30 participants. Small sample sizes have implications on the further analyses and caution needs to be taken when interpreting the results. Again, due to small sample sizes specific characteristics of VHs are expressed descriptively (e.g., often, rarely, the majority, etc.) rather than in exact numbers or percentages. Secondly, manifestation of PD varies greatly across patients (Paulson & Stern, 1996). Therefore, specific characteristics (e.g., age, dosage of dopaminergic and other medication, the duration of illness, side that is more affected by tremor, etc.) need to be taken into account when comparing PD patients. However, many studies do not report these characteristics, and while the issue of the small sample sizes is difficult to overcome, it is imperative that future studies are designed with greater care, taking possible independent variables into consideration and making the samples as homogenous as possible. Finally, with few exceptions (Barnes & David, 2001; Fenelon et al., 2000) the presented studies have investigated the area of VHs using

only quantitative methodologies. However, the phenomenology of VHs in PD is under-researched and greater attention needs to be directed towards qualitative descriptions of the phenomena. Similarly, except for one attempt (Diederich, Pieri, & Goetz, 2003) no studies have addressed how PD patients cope with their VHs behaviourally. Therefore, qualitative descriptions could give an insight into which strategies are most efficient in ending VHs and could easily be applied in the cognitive-behavioural strategies for PD patients with VHs.

1.3 Role of Neurotransmitter Systems and Treatment of VHs in PD

One of the most common explanations for VHs in PD is that they are simply a side-effect of dopaminergic treatment; i.e., that higher dosages of dopaminergic medication directly affect a higher incidence of VHs (Factor, Molho, Podskalny, & Brown, 1995; Fenelon et al., 2000; Inzelberg et al., 1998; Korczyn, 2001). There is a growing body of evidence, however, that suggests there is no simple association between VHs and the dose of dopaminergic antiparkinsonian medications[2]. Similarly, no association has been found between VHs and the length of levodopa[3] administration (Diederich et al., 1998; Holroyd et al., 2001).

The controversial issue of the involvement of dopaminergic medication in the occurrence of VHs could be resolved in two ways: either by examining the literature on hallucinations in PD in the "pre-levodopa" era[4] or by examining PD patients who are not taking any dopaminergic medication. Both approaches give little insight since there are very few published reports on VHs in PD before 1967 (Fenelon, Goetz, & Karenberg, 2006). Similarly, very few PD patients receive no

[2] (Aarsland et al., 1999; Barnes & David, 2001; Diederich et al., 1998; Goetz, Wuu, Curgian, & Leurgans, 2006; Graham, Grunewald, & Sagar, 1997; Haeske-Dewick, 1995; Holroyd et al., 2001; Kulisevsky & Roldan, 2004; Merims et al., 2004; Sanchez-Ramos, Ortoll, & Paulson, 1996; Santangelo et al., 2007).

[3] Levodopa is the most common dopaminergic treatment for motor symptoms of PD; it was first introduced in 1967 (Cotzias, Van Woert, & Schiffer, 1967) and has since then been the most common neuropharmacological treatment for PD.

[4] For a detailed review refer to Fenelon et al (2006).

dopaminergic medication for their illness (in fact, among other criteria, a diagnosis of PD is based on positive responses to the dopaminergic medication and is therefore one of the first treatment options when the signs of parkinsonism occur). Still, several authors report on PD patients who receive no dopaminergic treatment but have vivid VHs (Berrios, 1995; Fenelon et al., 2006; Fenelon et al., 2000; Holroyd et al., 2001). Furthermore, several authors (Fenelon et al., 2000; Goetz, Pappert et al., 1998; Holroyd et al., 2001; Korczyn, 2001; Kulisevsky & Roldan, 2004) suggested that even if VHs are a part of PD (and not due to dopaminergic administration), they are usually related to some facilitating factors, such as dementia, depression, or erratic encephalopathy, which are based on non-dopaminergic neurotransmitter systems. These risk factors will be examined in greater detail in Section 1.5.

More and more authors believe that VHs are a part of PD and that medication can worsen (but not cause) VHs. The involvement of non-dopaminergic factors has motivated research to investigate the possible roles of other neurotransmission systems in the generation of VHs in PD. Dysfunction in cholinergic[5] and serotonergic[6] systems have been commonly associated with VHs in PD.

The importance of the cholinergic system in the generation of VHs was first observed in another neurodegenerative disorder, namely dementia with Lewy Bodies (DLB). Pathologically, DLB is characterized by development of abnormal protein aggregation (Lewy bodies) throughout the brain. Clinical features include dementia and complex VHs (both occurring early in the development of the disease) and motor dysfunction, similar to that seen in PD. Cholinergic reduction has been strongly implicated in VHs in DLB (Calderon et al., 2001; Ferman & Boeve, 2007). Due to the striking pathological and clinical similarities between DLB and PD, Calderon et al. (2001) suggested that cholinergic dysfunction in PD may be important in the genesis of the VHs in the same way as in DLB. Similarly, Korczyn (2001) suggested that the disturbances of the dopaminergic-cholinergic

[5] Cholinergic neurons are neurons whose primary neurotransmitter acetylcholine is principally involved in memory.

[6] Serotonergic neurons are neurons whose primary neurotransmitter serotonin is involved in the modulation of anger, aggression, body temperature, mood, sleep, sexuality, appetite, and metabolism.

balance are implicated in the occurrence of VHs in PD. Although the exact mechanisms of a possible interaction between the two systems remain largely unknown, many studies have shown that medication based on the cholinergic system produces a modest improvement in psychotic symptoms in both PD and DLB (Assal & Cummings, 2002; Collerton et al., 2005; Fernandez, Wu, & Ott, 2003; Manford & Andermann, 1998; O'Brien, Firbank, Mosimann, Burn, & McKeith, 2005; Williams-Gray, Foltynie, Lewis, & Barker, 2006).

Finally, apart from the dopaminergic and cholinergic system, the role of the serotonergic system has been well recognized in the treatment of VHs in PD (Assal & Cummings, 2002; Scholtissen, Verhey, Adam, Weber, & Leentjens, 2006; Zoldan, Friedberg, Livneh, & Melamed, 1995). Usually, the understanding of neurotransmission involvement leads to better treatment options. However, in the case of the importance of the serotonergic system in the occurrence of VHs in PD, there seems to be the opposite trend - a link between the serotonergic system and VHs has been established because of the remarkable effect of serotonergic medication on the cessation of VHs. Although the precise nature of the interaction remains largely unknown, Zoldan et al. (1995) proposed that VHs in PD occur due to over-stimulation of serotonergic receptors.

Studies investigating the role of dopaminergic, cholinergic and serotonergic systems in the occurrence of VHs in PD suggest that all three systems are implicated in the generation of VHs in PD. While their precise functions (and possible interactions between the systems) are yet to be fully delineated, the current understanding of the underlying neurotransmission systems has had an important role in the pharmacological treatment of VHs in PD.

The first line of treatment of VHs in PD is reducing dopaminergic treatment. However, this approach is not always easy since reducing dopaminergic medication can exacerbate parkinsonism (Korczyn, 2001). Similarly, Kulisevsky and Roldan (2004) observed that controlling VHs and motor signs of PD comprises a so-called "motion-emotion" dilemma: increasing dopaminergic dosage improves motor ability but is also associated with the emergence of symptoms of psychosis. On the other hand, reducing dopaminergic dosage reduces psychosis but can adversely

affect the motor signs of PD. Due to the important role of dopaminergic medication upon motor and non-motor signs of PD, medication dosages are essential information in all studies with PD patients.

The suggested cholinergic involvement in VHs has resulted in the occasional treatment of VHs in PD by cholinergic medication (Korczyn, 2001). Although such treatment is beneficial in DLB (McKeith et al., 2000), cholinergic medication in PD is most commonly used when signs of cognitive decline are present. Furthermore, new antipsychotic drugs (based on the regulation of the serotonergic system) have already promised to be more effective and side-effect free than cholinergic medication. The "atypical" antipsychotic medications (e.g., clozapine, quetiapine, olanzapine, and risperidone) were primarily developed for the treatment of hallucinations in schizophrenia, but have been proved to be also effective in much lower doses in hallucinating PD patients (Korczyn, 2001).

Alternatively, or in combination with neuropharmacological treatment, cognitive-behavioural intervention has long been implemented in the treatment of psychosis in other disorders (Barber & DeRubeis, 1989; Carver, Scheier, & Weintraub, 1989; Delespaul, deVries, & van Os, 2002; Starker & Jolin, 1982). As discussed in Section 1.2, hallucinating PD patients would benefit from a cognitive approach based on acceptance and reassurance. However, cognitive-behavioural approaches in the treatment of VHs in PD have so far not been satisfactorily addressed (Barnes & David, 2001; Diederich et al., 2003). Therefore, many questions regarding the behavioural approach and most efficient coping strategies with VHs in PD remain unanswered (see Chapter 9). Recognizing the efficient ways of dealing with VHs pharmacologically and with cognitive-behavioural treatment could potentially improve patients' (and carers') quality of life.

1.4 Neural Substrates of VHs in PD

The growing understanding of the underlying neurotransmission systems has led to important treatment solutions for VHs in PD. Furthermore, the advent of neuroimaging techniques, and a growing understanding of neurotransmitter pathways that play a role in the generation of VHs in PD, have helped to identify the underlying neural substrates for VHs in PD.

As discussed in Sections 1.1 and 1.3, the dopaminergic system is primarily affected in PD. Further, human retinas contain dopaminergic neurons (Biousse et al., 2004). Combining both, some authors (Manford & Andermann, 1998; Rodnitzky, 1998) proposed that the dopaminergic system in PD might be affected already from the retina onwards, which would consequently affect the function of the visual cortex. This notion has been strengthened by two functional magnetic resonance imaging (fMRI) studies, showing a decreased activation in the primary visual cortex of PD patients with VHs (not hallucinating during the imaging), either during visual stimulation tasks or in resting state (Holroyd & Wooten, 2006; Stebbins et al., 2004). Furthermore, Stebbins et al. (2004) argued that the decreased activation in the primary visual cortex results in the hyperactivation of visual association cortex. Their findings were also confirmed by two single photon emission computed tomography (SPECT) studies, showing aberrant activation of the ventral visual pathways in the brain of hallucinating PD patients (Oishi et al., 2005; Okada, Suyama, Oguro, Yamaguchi, & Kobayashi, 1999). Moreover, these findings are in accordance with the complex phenomenology of hallucinatory images in PD (as described in Section 1.2). Complex, coloured and detailed images of people (sometimes in motion), objects and scenery point to the involvement of both the ventral and dorsal visual pathways in the generation of VHs in PD. Finally, a set of evidence for abnormalities in the visual association cortex of hallucinating PD patients comes from the post-mortem analyses where accumulation of Lewy bodies was evident in the visual association cortex (Harding, Broe, & Halliday, 2002; Perry et al., 1991).

Apart from the fMRI evidence of aberrant functioning of occipital-temporal and occipital-parietal association cortices, Stebbins et al. (2004) also observed degeneration of the frontal areas in hallucinating PD patients, specifically in the superior frontal gyrus and cingulate cortex. Due to a strong connection between VHs and sleep dysfunction, Manford and Andermann (1998) proposed the brainstem as one of the possible areas in generating VHs; however, its role remains largely unknown.

Taken together, the neuroanatomy of VHs in PD does not seem to be localized in a specific area; rather, there is a complex neuroanatomical and neurotransmission interaction between different brain areas, namely primary and association visual cortex, with the input from the frontal cortex and the brainstem. The lesions of the proposed areas manifest in a range of dysfunctions, which have been observed in PD patients with VHs.

1.5 The Continuum Hypothesis of VHs

VHs are a frequent psychiatric manifestation in the course of PD and specific neurotransmitter systems and neural structures have been implicated to play a role in the generation of VHs. However, VHs can also occur in a range of other disorders, characterized by a different pathology than PD. For example, VHs frequently appear in the course of degenerative disorders such as in DLB, Alzheimer's Disease and in patients with fronto-temporal dementia (Fenelon et al., 2000). Moreover, VHs can occur in a range of non-degenerative disorders, such as narcolepsy-cataplexy syndrome, peduncular hallucinosis (i.e., midbrain and pons lesions, resulting in vivid VHs), familial hemiplegic migraine (i.e., an autosomal dominant classical migraine subtype that typically includes weakness of half the body during the aura phase, which is often accompanied by vivid VHs), Charles Bonnet syndrome (VHs of the blind), schizophrenia, hallucinogen-induced states, and epilepsy (Collerton et al., 2005; Dauvilliers, Billiard, & Montplaisir, 2003; Manford & Andermann, 1998). VHs are also prevalent among hospice inpatients

(e.g., brain tumours, liver disease, epilepsy, etc.) (Fountain, 2001). These disorders arise from different underlying pathologies; yet different underlying pathologies can result in strikingly similar manifestations.

Moreover, VHs are frequent in some normal[7] individuals, usually in drowsy states of consciousness (Girard & Cheyne, 2006; Ohayon, 2000; Ohayon, Priest, Caulet, & Guilleminault, 1996). The most common occurrences of VHs in the normal participants in Ohayon et al.'s study (1996) were at sleep onset (hypnagogic hallucinations, occurring in 24.8%) and/or upon awakening (hypnopompic hallucinations, occurring in 6.6%).

Hallucinations are therefore not always indicative of pathology, as suggested by numerous studies which have established the occurrence of hallucinatory experiences in a substantial number of people from the normal population (Aleman, Böcker, & De Haan, 1999; Lopez-Rodrigo, Paino Pineiro, Martinez Suarez, Caro, & Lemos Giraldez, 1997). For example, Bell et al. (2006) reported that approximately 11% of the non-clinical sample in their study scored above the mean of psychotic inpatients on the anomalous perceptual experiences questionnaire (CAPS) (Bell et al., 2006). This provides further evidence that such experiences are not, in themselves, pathological and that a considerable percentage of the population successfully integrates anomalous percepts into their lives without necessarily leading to a psychiatric disorder. López-Rodrigo et al. (1997) emphasized that it is likely these people do not lose a sense of reality, as occurs with some clinical populations; thus, the authors suggest that the hallucinatory experiences with preserved insight would be better described as pseudo-hallucinations or hallucinosis. From this perspective, pseudo-hallucinations in the normal population are similar to VHs in PD, where patients retain insight into their hallucinations.

Moreover, this is not the only resemblance between VHs in PD and proneness to VHs in the normal population. Several authors have proposed that psychosis-like experiences exist on a continuum, ranging from mild visual disturbances in the

[7] In the present work, the term "normal population" refers to people without any known disorder or long-term illness.

normal population to the sometimes bizarre full-blown hallucinations characteristic of psychiatric illness (Crow, 1998; Slade & Bentall, 1988). This idea has been known as the continuum hypothesis, stating that psychosis-like experiences are distributed (although to varying extent) throughout the general population, and that full-blown psychosis represents the most extreme end of the population continuum[8]. Therefore, VHs in PD and proneness to VHs in the normal population might share similar predispositions, which are expressed in a lesser degree in the normal population.

Following from the continuum hypothesis, it can be argued that similar aberrant functioning is expressed across different cognitive domains in both hallucinating PD patients and in normal individuals that are high-prone to have hallucinatory experiences. This idea is in line with Lopez-Rodrigo et al. (1997) who suggested that some qualitatively different factors differentiate people from high and low-end of the continuum. To test the continuum hypothesis, the differences in cognitive functioning between hallucinating and non-hallucinating PD patients need to be compared to the differences between cognitive functioning between high and low-prone normal individuals without a history of any psychiatric disorder. Comparing VHs in a well-recognized neurological disorder to high proneness to VHs in the normal population would offer a basis for inclusion of risk factors to build a model for VHs. Consequently, such comparison would give an answer to whether a unitary model can be applied in recurrent complex VHs across different disorders that arise from various underlying pathologies.

1.6 Risk Factors for VHs

Even after a decade of research, the phenomenology and pathogenesis of VHs in PD still remain poorly understood. Apart from the aforementioned medication

[8] Hanssen et al., 2003; L. C. Johns & van Os, 2001; E. Peters, Joseph, Day, & Garety, 2004; E. R. Peters, Joseph, & Garety, 1999; Stefanis et al., 2002; Verdoux & van Os, 2002.

effect on the generation of VHs (see Section 1.3), a range of risk factors have been implicated to play a role to the occurrence of VHs. Although some studies found links between specific risk factor and VHs, and others have not, it is now believed that VHs in PD are not a simple medication effect but are probably aggravated by a number of risk factors. Even less is known why some normal individuals without a history of any psychiatric or neurological disorder are high-prone to have hallucinatory-like experiences and some are not. Stemming from the continuum hypothesis that hallucination-proneness might be related to the same risk factors, expressed in different degrees across disorders, the present section will address the role of different risk factors. Some of them are tightly related to VHs in PD (e.g., temporal factors, severity of motor disability and mood), while others have been proposed to have a role in both PD as well as in the normal population (e.g., visuo-spatial and visual imagery abnormalities, abnormalities in executive functioning, sleep disorders, genetics and some personality factors).

1.6.1 Temporal Factors

Temporal factors, such as age, duration of illness and onset of PD give inconclusive results in relation to VHs in PD. On the one hand, numerous studies have identified older age in a hallucinating PD group as a differentiating risk factor for the occurrence of VHs (Fenelon et al., 2000; Goetz et al., 2006; Haeske-Dewick, 1995). On the other hand, several studies found no such relation (Barnes & David, 2001; Diederich et al., 1998; Inzelberg et al., 1998). Further, the duration of illness was identified as an independent predictor of VHs in some studies (Barnes & David, 2001; Fenelon et al., 2000), but other studies found no difference in this respect between hallucinating and non-hallucinating PD patients (Diederich et al., 1998; Fenelon et al., 2006; Haeske-Dewick, 1995; Holroyd et al., 2001; Inzelberg et al., 1998). Finally, Graham et al. (1997) observed that VHs were not associated with age at onset of PD in their study.

As discussed in Section 1.2, PD often manifests with different symptoms at the onset of the illness, and the progress of illness can vary greatly between patients

(Paulson & Stern, 1996). Moreover, PD is a neurodegenerative disorder, ultimately leading to extensive brain pathology and to a higher incidence of both motor and non-motor complications. Therefore, it is not surprising that some studies demonstrated a higher incidence of VHs among older and longer diagnosed patients, especially in the cases of small sample sizes. However, these studies do not offer firm evidence that prolonged illness and age are a factual risk factor for development of VHs and not just a risk factor for more extensive pathology, and therefore a higher risk for psychiatric manifestations.

More tentatively, VHs are generated when specific brain areas are affected by the neurodegenerative process. Undoubtedly, pathology is extended in the later stages of PD, resulting in the generation of VHs (among other signs); however, the pathology progress is not uniform and can consequently result in an early development of VHs. Therefore, rather than to the temporal factors, effort should be put into investigating specific dysfunctions that are linked to the occurrence of VHs in PD, especially in the early stages of diagnosis, when the pathology is less extensive.

1.6.2 Motor Abilities

As with the temporal factors, there is controversy about the importance of the severity of motor disability in the occurrence of VHs in PD. Motor status was more severely affected in hallucinating than in the non-hallucinating PD patients in several studies (Aarsland, Andersen, Larsen, Lolk, & Kragh-Sorensen, 2003; Barnes & David, 2001; Fenelon et al., 2000; Haeske-Dewick, 1995; Holroyd et al., 2001); however, other studies found no such link (Diederich et al., 1998; Goetz et al., 2006; Inzelberg et al., 1998).

Extensive brain pathology results in worsening of motor and non-motor abilities (Braak et al., 2003); therefore, it is not surprising that the incidence of VHs is increased among severely disabled PD patients. However, VHs also occur in patients with mild motor dysfunctions, suggesting that specific, rather than extensive dysfunctions cause VHs in PD. Further investigations of

neuropsychological dysfunctions are therefore especially warranted in hallucinating PD patients with minor motor dysfunctions.

1.6.3 Cognitive Functioning

In line with the temporal factors and motor disability, there is inconsistency about the importance of the severity of cognitive dysfunction in the occurrence of VHs in PD. Some studies identified severe cognitive decline as the main risk factor independently predictive of VHs (Fenelon et al., 2000; Haeske-Dewick, 1995; Holroyd et al., 2001; Inzelberg et al., 1998). However, other studies found no such link (Barnes & David, 2001; Goetz et al., 2006). Fenelon et al. (2000) suggested the discrepancy occurs because PD patients with impaired cognition are not so self-conscious and therefore report on their VHs more often than PD patients without dementia; at the same time, patients without dementia are usually aware of the stigma related to VHs, and therefore do not report having VHs unless explicitly asked.

In line with the neuroimaging evidence of aberrant frontal functioning (Matsui, Nishinaka et al., 2006b; Nagano-Saito et al., 2004; Stebbins et al., 2004), several studies found reduced performance in executive functioning[9] in hallucinating PD patients without dementia (Aarsland et al., 2003; Athey, Porter, & Walker, 2005; Barnes & Boubert, 2008; Grossi et al., 2005; Meco, Bonifati, Cusimano, Fabrizio, & Vanacore, 1990; Santangelo et al., 2007). According to these studies, executive functions might be an important substrate for occurrence of VHs even when dementia is not yet apparent. It is also in line with two longitudinal studies where VHs were recognized as a risk factor for a later development of dementia (Aarsland et al., 2003; Santangelo et al., 2007). However, other studies suggested that since executive dysfunctions are noticeable even in the early stages of PD, it is the executive dysfunctions that predict the occurrence of VHs, and not

[9] Executive functions are defined as a set of brain processes, such as planning, abstract thinking, rule acquisition, initiating appropriate responses and inhibiting inappropriate responses.

the other way around (Barnes & Boubert, 2008; Grossi et al., 2005; Meco et al., 1990; Sanchez-Ramos et al., 1996).

However, the main limitations of these studies are the methodologies, which were used as the indicators of executive dysfunctions. The tasks were either brief screening techniques (e.g., Mini Mental State Examination, Cambridge Cognitive Assessment, Telephone Interview for Cognitive Status, etc.) or too specific (tests of semantic and verbal fluency). Some tasks were reliable and valid measures of reasoning and memory (Raven's 47 Coloured Progressive Matrices and Rey Auditory Learning Test); however, the differences between hallucinating and non-hallucinating PD patients on these tasks were not significant (Grossi et al., 2005; Santangelo et al., 2007). Therefore, in order to explore the link between VHs and executive dysfunctions, further studies using reliable, valid and standardized tasks are warranted.

1.6.4 Visuo-Spatial Functioning

The aforementioned retinal dopaminergic deficiency in PD (see Section 1.4) may alter a range of visual abilities in PD patients (Biousse et al., 2004; Manford & Andermann, 1998; Rodnitzky, 1998), which can in turn facilitate the occurrence of VHs. However, despite the intuitive reasoning that visual disturbances are associated with VHs, surprisingly few neuropsychological and neuroimaging studies have addressed this issue in hallucinating PD patients (Barnes, Boubert, Harris, Lee, & David, 2003; Diederich et al., 1998; Ramirez-Ruiz, Junque, Marti, Valldeoriola, & Tolosa, 2007; Uc et al., 2005). The studies have investigated the following visuo-spatial functions: incidence of ocular disorders, visual acuity, colour and contrast discrimination, visual object perception and visual memory for faces.

Fenelon et al. (2000) suggested that a higher incidence of ocular disorders (such as abnormal eye and eyelid movements, blurred vision, double vision, etc.) in hallucinating PD patients facilitates the development of VHs. Three studies (Chapman, Dickinson, McKeith, & Ballard, 1999; Holroyd et al., 2001; Uc et al.,

2005) suggested it is a significantly reduced visual acuity in the better eye that predisposes PD patients to VHs. However, Diederich et al. (1998) studied ocular pathology in PD patients with normal visual acuity. They found more deficits in colour and contrast discrimination in hallucinating patients. This visual deprivation might consequently be the facilitating factor for the occurrence of VHs in PD (Diederich et al., 1998). Similar ideas have been proposed by other authors (Barnes & David, 2001; Korczyn, 2001), who noted that VHs are especially frequent in the evenings and when the light is dim – in other words, when sensory inputs are degraded. In their view, disturbances of the visual input result in hyper-activation of the visual system, which gives rise to the generation of VHs (Barnes & David, 2001; Chapman et al., 1999; Diederich et al., 1998; Holroyd et al., 2001; Uc et al., 2005). The idea that poor visual input can facilitate the occurrence of VHs seems especially plausible, because VHs have been also reported in healthy individuals who experienced vivid VHs after sensory deprivation (Solomon, Leiderman, Mendelson, & Wexler, 1957; Suedfeld & Vernon, 1964) as well as in the states of low arousal and sleep deprivation, when the visual input is reduced or disturbed (Babkoff, Sing, Thorne, Genser, & Hegge, 1989; Hidalgo & Caumo, 2002; Kollar et al., 1969). Risk factors related particularly to sleep will be further addressed in Section 1.5.8.

Apart from the ophthalmologic studies, few studies have addressed the role of visuo-spatial functioning in the occurrence of VHs in PD. Barnes et al. (2003), for example, found that hallucinating PD patients are impaired on object recognition tests. They suggested that the failure to extract information from the stimuli might be the facilitating factor in the occurrence of VHs. Similarly, the results are in accordance with Ramirez-Ruiz et al. (2007) who, in addition to the failure of recognition function, found deficits in visual memory for faces in hallucinating PD patients. Both dysfunctions of the visual system in hallucinating PD patients (object recognition and visual memory for faces) point to a degeneration of the association cortex, which is in accordance with the evidence from the neuroimaging studies (as described in Section 1.4). However, more studies need to address the role of the

visual system in the generation of VHs in PD, using reliable and valid measures of perceptual functioning.

1.6.5 Visual Imagery

A specific visual processing function often related to VHs is visual imagery. Vividness of mental imagery is defined as the degree of similarity of a mental image to actual perception; the more vivid the image, the closer the experience is to an actual perception of sensory input (Aleman et al., 1999). The idea that increased vividness of mental imagery may be associated with hallucinatory experiences was already expressed more than hundred years ago by Francis Galton (1883). However, the results from both the normal population and schizophrenia patients remain inconclusive; some authors reported that visual imagery is related to the occurrence of VHs, and some found no relation between visual imagery and occurrence of hallucinations (Aleman, Nieuwenstein, Bocker, & de Haan, 2000; Bocker, Hijman, Kahn, & De Haan, 2000; Lopez-Rodrigo et al., 1997; Sack, van de Ven, Etschenberg, Schatz, & Linden, 2005).

Despite the relatively long tradition of investigating the role of mental imagery in schizophrenia and in the normal population high-prone to have VHs, only one study has addressed the role of mental imagery in the generation of VHs in PD (Barnes et al., 2003). In this study, the performance of hallucinating and non-hallucinating PD patients was comparable, but hallucinating PD patients expressed a higher tendency to report imaged stimuli as percepts. Therefore, the role of mental imagery in the generation of VHs remains unclear, and calls for a further investigation.

1.6.6 Mood

Of all the risk factors, the role of depression in the occurrence of VHs gives the most contradictory results. In 1995, Haeske-Dewick et al. (1995) found no significant difference in depression between hallucinating and non-hallucinating PD

patients. Conversely, Aarsland et al. (1999) and Sanchez-Ramos et al. (1996) found the hallucinating PD patients in their groups scored higher on different depression scales than the non-hallucinating PD patients. Similarly, hallucinating PD patients had significantly more depressive symptoms than non-hallucinating patients; however, none of the groups reached a cut-off criterion for depression (Holroyd et al., 2001), using the Geriatric Depression Scale (Yesavage et al., 1982). Some authors suggested that in patients who have been diagnosed with PD for more than 5 years, depression is statistically related to VHs (Fenelon et al., 2000); however, another study found that depression was statistically related to VHs in patients with shorter (and not longer) disease duration (Graham et al., 1997).

In summary, the studies give contradictory results and even in the cases where depression is statistically related to VHs, the authors concluded that depression might be a facilitating, but not a predictive factor for the occurrence of VHs (Fenelon et al., 2000; Holroyd et al., 2001; Inzelberg et al., 1998). Furthermore, the results of the studies give evidence that the role of depression is more complex than initially thought and future studies need to address this issue in a more sophisticated way. One possibility, for example, is to explore the link between depression and specific behavioural coping strategies, which PD patients use in order to manage their VHs. A more qualitative approach to the topic would give an insight into whether specific behavioural techniques are linked to a better mood. If that is the case, applying specific behavioural-cognitive management could have a beneficial effect on the mood modification in hallucinating PD patients.

1.6.7 Personality

Personality traits are one of the least explored risk factors for the occurrence of VHs. Several authors (Cangas, Errasti, Garcia-Montes, Alvarez, & Ruiz, 2006; Jones & Fernyhough, 2006; Laroi & Van der Linden, 2005; Morrison et al., 2000) proposed that meta-cognitive beliefs about thoughts can be implicated in predisposition to VHs in both clinical and non-clinical populations. In their view, hallucination-proneness in the normal population as well as full-blown

hallucinations in psychiatric patients stem from over-reliance on the internal meta-cognitive processes rather than on externally generated information that is obtained from the sensory receptors. Furthermore, logistic analysis in another study indicated that fantasy proneness was the best predictor of hallucinatory reports in the normal population (Van de Ven & Merckelbach, 2003); however, the authors admit that the precise nature of the link remains unclear. They suggest that the link could reflect a general bias to endorse bizarre items or a subtle reality-testing deficit[10].

In summary, there is some evidence that specific personality traits are related to hallucination-proneness in both clinical and normal population. However, the presented studies stem from clinical populations with auditory and not visual hallucinations. Therefore, future studies need to address the role of personality features in proneness to VHs. Further, although the studies give some evidence for the importance of the top-down processing in schizophrenia, to date no study has explored the implication of personality factors in hallucinating PD patients. Therefore, future studies need to provide evidence that fantasy proneness and meta-cognitive beliefs are implicated not only in schizophrenia, but in other disorders suffering from VHs as well.

1.6.8 Sleep

As explained in Section 1.3, the neurodegeneration of PD extends beyond the dopaminergic system and affects the serotonergic system and its sleep functions as well. A number of studies have recognized a link between VHs and specific sleep disturbances, pointing to the extended neurodegeneration of the midbrain neural mechanisms (Chaudhuri, Martinez-Martin et al., 2006; Comella, Tanner, & Ristanovic, 1993; Fenelon et al., 2000; Gupta et al., 2004; Manni et al., 2002; Pacchetti et al., 2005). Furthermore, the link between sleep and VHs in the normal population has been established in sleep deprivation studies and in disorders such as narcolepsy-cataplexy, sleep paralysis, or even hypnagogic and hypnopompic

[10] Reality testing is an ability to distinguish internally generated images and external percepts (Johnson & Raye, 1981).

hallucinations (Collerton et al., 2005; Dauvilliers et al., 2003; Girard & Cheyne, 2006; Manford & Andermann, 1998; Ohayon, 2000; Ohayon et al., 1996). Some authors have suggested that particularly the dysfunction of the arousal system causes unfaithful transmission of visual input, which together with the low environmental luminance creates an ideal situation for misinterpreting visual stimuli as real images (Chaudhuri, Martinez-Martin et al., 2006; Comella et al., 1993; Fenelon et al., 2000; Manni et al., 2002). However, the exact mechanisms of the link between sleep patterns and VHs are not fully understood, and future studies need to address this issue. Specifically, the advent of new objective measures of sleep patterns promises a more elegant approach to sleep research, avoiding the disadvantages of the laboratory-based polysomnographic settings.

1.6.9 Genetics

Finally, the presence of the apolipoprotein E e4 allele was found to be the first genetic risk factor for drug induced VHs in PD (de la Fuente-Fernandez, Nunez, & Lopez, 1999; Feldman, Chapman, & Korczyn, 2006). Genetic predispositions to VHs are outside the scope of the present study; however, further research in this area is warranted.

1.6.10 Summary

VHs in PD, as in other pathologies, and hallucination-proneness in the normal population are a complex phenomenon and their aetiology is far from understood. A number of risk factors have been put forward as facilitating factors in the occurrence of VHs in both PD and the normal population. However, it remains unclear whether the same risk factors predispose PD patients to VHs and the normal individuals to high hallucination-proneness. Further research is therefore needed to establish the link, which could provide a basis for the possible holistic model for the generation of VHs. As opposed to focusing attention on only one risk factor, the following section will address the studies that tried to encompass several risk

factors into a model of VHs in PD; however, no model has been proposed for hallucination-proneness in the normal population to date.

1.7 Models of VHs

Putting different risk factors together, several hypotheses and models have been put forward as a possible mechanism to explain which risk factors are implicated in the occurrence of VHs in PD. In this section, the most cited and comprehensive models of VHs are discussed.

1.7.1 VHs as a Release Phenomenon

Cogan (1973) proposed that VHs (regardless of the clinical diagnosis) are caused by disruption of the normal flow of visual impulses, with subsequent release of endogenous cerebral activity from the visual system. As described in Sections 1.3 and 1.4, ocular pathology in PD (especially dopaminergic deficiency in the retina) can affect the primary visual cortex. Next, the lack of input from the primary visual cortex results in over-activation of the associative visual cortex, and consequently VHs occur (Stebbins et al., 2004). Cogan's model can thus be applied to explain the genesis of VHs in PD, describing VHs as a release phenomenon, i.e., as a disinhibition of neural structures, with increase in the excitability and spontaneous activity of the disinhibited neurons. Although the model adequately describes the pathology of the visual pathways, it is nonetheless relatively static, and does not account for other risk factors, as described in Section 1.5 (e.g., mood and personality, imagery, executive and sleep dysfunction).

1.7.2 VHs as a Brainstem Modulation

Building up from the release theory, Manford and Andermann (1998) expanded the model by including a set of risk factors for occurrence of VHs. They suggested that

three basic mechanisms, alone or in combination, underlie VHs with widely differing causes: irritative processes acting on higher visual centres or pathways; defective visual processing; and brainstem modulation of thalamocortical connections (ibid). As discussed in Section 1.5.8, brainstem lesions are especially implicated in PD, affecting ascending cholinergic and serotonergic pathways. The brainstem abnormalities are often associated with disturbances of sleep and may cause defective modulation of thalamocortical relationships, leading to a release phenomenon (Manford & Andermann, 1998).

The main contribution of Manford and Andermann's model (1998) is the acknowledgement that apart from the abnormalities of the visual system and abnormal cortical release phenomenon, VHs can be attributed to abnormalities of the ascending cholinergic and serotonergic brainstem (and thalamic) pathways involved in the control of sleep-waking state. In support of this explanation, disturbances of rapid-eye-movement (REM) sleep and intrusions of dream images into waking state have been often associated with VHs in PD patients (Arnulf et al., 2000; Manni et al., 2002; Nomura et al., 2003; Onofrj et al., 2002; Pappert, Goetz, Niederman, Raman, & Leurgans, 1999). However, the model fails to address the recently proposed frontal dysfunctions in hallucinating PD patients, as described in Section 1.5.3.

1.7.3 Integrative Models

The integrative model of Diederich et al. (2005) is the most comprehensive model accounting for VHs in PD to date. Similarly to the models based on the brainstem modulation mechanisms, the model focuses on visual impairment, probably reflecting dopaminergic retinal dysfunction, and on sleep/vigilance abnormalities, probably reflecting dysfunctions of the ponto-geniculo-occipital system regulating REM sleep. In addition, Diederich and colleagues (ibid) suggested that a model of VHs in PD should also include aberrant activation of frontal cortex and lack of suppression or spontaneous emergence of internally generated imagery through the ponto-geniculo-occipital system. Further, the importance of the frontal lobe

functioning was also recognized by Barnes et al. (2003) who proposed a multi-factorial model, which includes a combination of degraded visual information about the environment, impaired and perhaps fluctuating source monitoring in episodic memory and an over-reliance of previously stored schemas.

The strongest advantage of the integrative models is that they are based on the evidence from the studies on PD, and are not simply extrapolated from the evidence about the risk factors in other disorders. Further, the models adequately address a number of risk factors that predispose the occurrence of VHs in PD patients; however, further empirical examination is needed to confirm the models, especially the role of executive dysfunctions in the generation of VHs. The models' weakness, however, is that they do not address the role of top-down, internally-driven processes.

1.7.4 The Perception and Attention Deficit (PAD) Model

The recently proposed PAD model (Collerton et al., 2005), primarily designed for DLB, has aimed to account for all recurrent complex VHs across different conditions. The authors suggested that VHs in different disorders are related to the coexistence of attentional and visual perceptual impairments, mainly through the disturbances in the lateral frontal cortex and the ventral visual stream system. The model offers a tentative idea for inclusion of attention as a risk factor in occurrence of VHs; however, the attention component of the model needs both theoretical and empirical improvements, as it offers neither neurobiological accounts nor empirical evidence for the existence of attention deficits across different disorders related to VHs (Castelo-Branco, 2005; Halliday, 2005; Kirov, 2005; Mast, 2005; Morrison & David, 2005; Smythies, 2005; Spencer & McCarley, 2005). The main limitation of the model is that it fails to achieve its aim to be incorporated in any clinical disorder presented with VHs (Dror, 2005; Ffytche, 2005a; Morrison & David, 2005; Samsonovich, 2005; Tadin et al., 2005). Although exploration of attention components is outside the scope of the present study, the model needs to be empirically verified in future studies.

1.7.5 Summary

Section 1.6 described the risk factors that can be argued to play an important role in the occurrence of VHs, and Section 1.7 presented the studies that tried to incorporate those factors in the models. From a one dimensional model, believing that VHs in PD are a simple medication effect, the models have developed and today most authors are in favour of the integrative models (Barnes et al., 2003; Diederich et al., 2005). However, further studies are needed to give firm empirical evidence indicating which risk factors are implicated in both the occurrence of VHs in PD as well as hallucination-proneness in the normal population. The present thesis aims to address the issue of whether the same risk factors are implicated in both hallucinating PD patients and high-prone normal individuals. The next section will delineate the studies that will explore the risk factors. On the basis of the empirical results, a new model to best explain VHs in PD and in the normal population will be postulated.

1.8 Structure of the Thesis

VHs occur in a range of clinical disorders and in the normal population; different aetiologies can therefore manifest in strikingly similar symptoms. Despite different origins, similar risk factors have been suggested to play a role in the occurrence of VHs in both PD and the normal population (see Section 1.6). However, to date no studies have systematically explored the role of different risk factors from a continuum hypothesis, stating that VHs are expressed in varying degrees across clinical and non-clinical population. The aim of the present thesis is therefore to explore whether the same risk factors are involved both in hallucinating PD patients as well as in high-prone individuals from the normal population. Consequently, the main contribution of the present work is to explore whether a unitary model can be proposed for the occurrence of recurrent complex VHs in PD and for high hallucination-proneness in the normal population.

The present chapter has described PD, with a special focus on different domains of VHs in PD: phenomenology of VHs in PD, the neurotransmitters and neural substrates that are implicated in the generation of VHs. Next, the chapter has introduced the idea that there are core similarities between hallucinating PD patients and high-prone normal individuals without any history of psychiatric disorder. The aim is to explore whether the same risk factors (and consequently a unitary model) can be postulated for VHs.

The first part of the thesis (Chapters 2 and 3) presents both phenomena: VHs in PD and hallucination-proneness in the normal population. Chapter 2 concentrates on how VHs are expressed in PD and gives a detailed phenomenological description of both the phenomena, as well as the important characteristics of hallucinating PD patients. Similarly, the aim of Chapter 3 is to explore how hallucination-proneness is expressed in the normal population, and how it is measured. The aims of Chapters 2 and 3 are therefore to give a clear description of both groups (PD and the normal individuals) and the characteristics of both phenomena (VHs and proneness to VHs).

Next, the thesis presents a series of five experimental chapters (Part II), exploring specific risk factors for the occurrence of VHs in PD and proneness to VHs in the normal population as described in Section 1.6: the role of perception and executive functioning (Chapters 4, 5, and 6), the role of personality processes (Chapter 7) and the role of specific sleep patterns (Chapter 8).

Chapters 4, 5 and 6 aim to examine the role of different aspects of the visual-executive functioning in the occurrence of VHs in both PD and high-prone individuals. In particular, Chapter 4 aims to investigate the role of visual memory and visual imagery in the occurrence of both VHs in PD and high proneness to VHs in the normal group, using highly reliable and valid tasks (the Cambridge Neuropsychological Test Automated Battery - CANTAB). Chapter 5 is the first study to date to address the early visual processing components in high-prone normal individuals using an electrophysiological tool (electroencephalogram). Executive tasks from the CANTAB neuropsychological battery are used in Chapter 6, with the aim to explore executive functioning in both hallucinating PD patients

and high-prone individuals. All three studies provide a novel account in exploring the role of the association visual cortex and frontal functioning in the generation of VHs in PD and proneness to VHs in the normal population.

Chapters 7 and 8 aim to investigate the role of specific sleep patterns and personality factors in relation to VHs in PD and to hallucination-proneness in the normal population. Chapter 7 examines which (if any) top-down processes characterize hallucinating PD patients and high-prone normal individuals. This is the first study to address the role of internally-driven processes in the generation of VHs in both hallucinating PD patients and high-prone normal individuals. Chapter 8 examines specific sleep patterns that are implemented in the generation of VHs in both PD and the normal population. It is the first study to provide such evidence using actigraphy, an objective measure of sleep.

Finally, the aim of the last chapter (Chapter 9) is to provide the first detailed description of how PD patients cope with their VHs, using a semi-structured interview, which addresses the role of different coping strategies. The study also explores the link between the level of depression and specific coping strategies. The aim of the study is to extrapolate the coping strategies that are most efficient in dealing with recurrent complex VHs in PD.

The conclusions and recommendations for future research are discussed in Chapter 10 with special attention to improving the understanding of VHs in PD. Models for VHs in PD and for proneness to VHs in the normal population are proposed and future perspectives of the studies are discussed.

Part I

Chapter 2: VHs in PD: Phenomenology

Chapter 3: Proneness to VHs in the Normal Population

Chapter 2: VHs in PD: Phenomenology

2.1 Introduction

VHs are a common psychiatric manifestation in PD, affecting as many as 30% of patients with PD (Fenelon et al., 2000; Gupta et al., 2004; Sanchez-Ramos et al., 1996). Fenelon et al. (2000) note that when minor forms of VHs (e.g., sensations of a presence, a sideways passage or illusion) are included in the count, the incidence could reach 40%. Moreover, increased nursing home placement and, ultimately, mortality rates are related to hallucinations (Goetz & Stebbins, 1993, 1995). These links have greatly contributed to the increased attention to VHs in research. Goetz and Stebbins (1993; 1995) emphasize that managing hallucinations in an efficient way would be beneficial to patients, reducing the need for placement in nursing homes. Also, the recent discovery of the importance of new antipsychotic drug treatment of VHs in PD has also contributed to increased attention to the topic in the past decade. VHs are therefore vital for differential diagnosis and prognosis (Mosimann et al., 2008).

However, despite the increase of (mainly neuropharmacological) interest in VHs in PD, the subject of the precise nature of VHs has been neglected in the studies of PD. While it is understandable that the advances in neuropharmacology are motivated with the aim to develop effective methods to eliminate hallucinations, Giorgi (2003) argues that these motives are challenged when it comes to understanding the phenomena by those experiencing hallucinations. Hallucinations, but also delusions, illusions, false memories and so on imply falsehood; however, true understanding of what the hallucinations represent to the individual could help eliminate hallucinations by transforming their meaning (ibid).

Further, other advantages of detailed phenomenology of VHs in PD lie in the understanding of the motives and dynamics of the phenomena. One question, for example, is whether VHs are pathologies of bottom-up processes or, maybe, they are pathologies of the imagination. If there are top-down components involved, how do they affect VHs in PD? Giorgi (2003), for example, wonders as to whether

hallucinators see "a real thing that is not there, or are they merely seeing a quasi-thing or a pseudothing" (p.209). Specific phenomenological qualities of VHs might be therefore one of the reasons why PD patients with VHs have insight into the hallucinatory nature of the images. Therefore, detailed description of the phenomena of VHs in PD gives rise not only to hermeneutics of it, but can also offer suggestions for coping strategies.

Despite these potential benefits of the phenomenological approach, apart from a few exceptions, which were addressed in Section 1.2 (Barnes & David, 2001; Fenelon et al., 2000; Holroyd et al., 2001), previous literature does not provide detailed descriptions of VHs. Similarly, there is no gold standard available to assess VHs in PD: e.g., Parkinson's Psychosis Rating Scale (PPRS) (Friedberg, Zoldan, Weizman, & Melamed, 1998), the PD – Psychosocial Questionnaire (SCOPA-PC) (Visser et al., 2007) and the non-motor symptom questionnaire (NMSQuest) (Chaudhuri, Martinez-Martin et al., 2006) either assess hallucinations only in a few sub-items (Papapetropoulos et al., 2008)[11] or are not specific enough for PD-related hallucinations (e.g., the Neuropsychiatric Inventory, Cummings et al., 1994).

The aim of the present study is therefore to offer detailed description of VHs in PD from a more qualitative perspective and clarify the characteristics of VHs as described by the patients themselves. A thorough examination of the phenomenology of VHs can offer predictions about the underlying mechanisms and how hallucinations relate to other functions (e.g., to sleep, to ocular pathology, etc.) which may open new paths to manage VHs behaviourally. Furthermore, in order to better understand the phenomenon of VHs in PD, the study will determine whether there is a set of demographic factors (such as age, dopaminergic dosage, disability stage, etc.) upon which the frequency of VHs could be predicted. Finally, the study aims to explore whether specific characteristics of VHs might predict the frequency of VHs in PD.

[11] A recently published questionnaire-based study of hallucinations in PD has been developed independently from the present research and comprises similar, although much fewer, items (Papapetropoulos et al., 2008).

2.2 Methods

2.2.1 Participants

23 PD patients with VHs (16 male and 7 female) were recruited to participate in the study about the phenomenology of VHs in PD. All patients were members of the PD societies in the UK, with normal hearing and normal or corrected-to-normal vision. Similar to Barnes et al.'s study (2001), criteria for eligibility were a clinical diagnosis of PD as assessed by their GPs and recurrent complex VHs, reported by the patients at least once per week in the previous month. No retrospective data were included in the study, in order to collect unambiguous reports; therefore, patients who experienced recurrent complex VHs in the past, but not at the time of the study, were not included. Of the present sample of hallucinating PD patients, 6 experienced VHs more than 5 times a week, 9 of them experienced VHs 2-5 times a week, and 8 of them experienced VHs once per week. Based on the risk factors stated in Section 1.6.3, exclusion criteria were a moderate or severe stage of dementia, confirmed by the carers of the PD patients, and the loss of independent maintenance of daily living activities, also reported by the carers.

In order to predict the frequency of VHs, several independent variables were taken into account (see Section 1.6): age, amount of daily levodopa medication and the use of any other medication, years since their diagnosis, side more affected by PD (left, right, or both sides), and Hoehn and Yahr (1967) motor disability stage (HY). HY is a frequently used system to express the progress of PD symptoms. The scale assigns stages from 1 to 5 to specify the relative stage of disability:

- Stage one: Symptoms on one side of the body only;
- Stage two: Symptoms on both sides of the body. No impairment of balance;
- Stage three: Balance impairment. Mild to moderate disease. Physically independent;
- Stage four: Severe disability, but still able to walk or stand unassisted;
- Stage five: Wheelchair-bound or bedridden unless assisted.

Finally, in order to take alternative facilitating factors for the occurrence of VHs into account, the presence of frequent migraines and ocular pathology (excluding correction glasses) were taken as additional independent variables in the study.

The mean age of hallucinating PD patients in the present study was 68 years (SD = 7.42). The mean daily levodopa dose was 498.86 mg (SD = 270.63). 2 participants were taking sleep medication and four other patients were taking antidepressants at the time of the study. Years since diagnosis varied from one to 27, with the mean of 10 years (SD = 6.42). The mean HY disability stage was 2.08 (SD = .93), which specifies a relatively mild motor disability (symptoms were bilateral, but there was no impairment of balance and patients could move around independently). There was no difference in the side more affected by tremor: 10 patients reported more severe disability on their left side of the body, 8 reported their right side was more affected by PD, and 5 patients reported having both sides equally affected. Therefore, the majority of patients were not severely (bilaterally) affected by tremor. In further accordance with the relatively low HY disability stage, 20 patients (87%) were able to move around the house unassisted. In addition to PD, half of all patients (12) suffered from another long term illness. Apart from VHs, 10 patients had other vision related problems (mainly double vision, but also loss of focus, cataract and conjunctivitis); however, only three patients reported having frequent migraines. Detailed demographics are displayed in Table 2.1.

Table 2.1. Participants' demographics.

Patient	Gender	Age	Levodopa (mg)	Years since diagnosis	HY	Other illness	Visual problems	Side
1	M	80	600	5	3	No	Cataract	Both
2	M	79	800	10	2	Osteoarthritis	No	Both
3	M	71	1000	11	2	High blood pressure	Double vision	Both
4	M	80	300	10	2	High blood pressure	No	Left
5	M	68	400	16	1	No	No	Right
6	M	54	900	3.5	1	No	No	Right
7	M	67	600	6	3	Pulmonary disease, diabetes	Loss of focus	Left
8	F	65	600	10	2	Osteoarthritis	Double vision	Left
9	M	59	600	1	4	Stroke	Double vision	Right
10	M	59	100	3.5	2	High blood pressure, diabetes	Unspecified	Left
11	M	74	550	6	2	No	No	Both
12	M	62	525	6.5	1	Coronary heart disease	No	Right
13	M	72	350	1	3	Cancer	No	Both
14	F	72	200	11	2	Osteoporosis	Cataract	Left
15	F	62	700	20	2	No	Double vision	Left
16	F	63	100	27	-	No	No	Left
17	M	65	700	6	1	No	No	Left
18	M	78	600	19	3.5	Infection hepatitis	Conjunctivitis	Right
19	M	67	200	9	1	No	Unspecified	Right
20	M	66	300	10	1	No	No	Right
21	F	-	800	10	2.5	No	No	Left
22	F	61	50	11	2.5	Lumbar disc prolapsed	Loss of focus	Left
23	F	61	-	18	-	No	No	Right

"Side" refers to the side of the body that is more affected by PD; "Levodopa" refers to daily levodopa dosages (in mg), and "HY" refers to Hoehn and Yahr (1967) disability scale. " - " indicates missing data.

2.2.2 Assessments

VHs questionnaire

The aim of the VHs questionnaire (see Appendix 1) was to extract detailed information about the content of VHs in PD. The VHs questionnaire was designed based on the existing phenomenological studies of VHs in PD (Barnes & David, 2001; Diederich et al., 2005; Fenelon et al., 2000) and with the aid of local PD gerontologists[12]. As discussed in Section 2.1, the subjective nature of the hallucinatory phenomena requires an approach where people with hallucinations can freely report about their experiences. Giorgi (2003) stressed that "hallucinatory phenomena are not to be analysed in terms of objective criteria" (p.215). In order to rely on the previous findings and knowledge from experienced PD gerontologists as well as on the spontaneous reports from the patients themselves, the VHs questionnaire utilizes a semi-structured questionnaire.

The VHs questionnaire is comprised of 9 demographic questions (for a detailed description see 2.2.1 and Appendix 1, Questions 1 – 9) and 18 questions related to the nature of VHs (see Appendix 1, Questions 10 – 27). The latter request a precise description of the images: how they appear, the ambient light when the images appear, how the images are perceived by patients, etc. The majority of questions are based on multiple-choice answers; however, several questions allow patients to elaborate their answers in their own words (e.g., details of the most common images patients see, how the images are distorted, what the patients believe is the cause for hallucinations, etc.). The questionnaire took approximately 10-15 minutes to complete.

[12] With the assistance of Dr Hilary Hart and Dr Sudhir Singh, John Radcliffe Hospital, Parkinson's Disease Outpatient Clinic, Oxford.

2.2.3 Procedure

The study was introduced verbally and information sheets (see Appendix 2) were given out at the monthly meetings in various PD societies throughout the UK between October 2006 and September 2007. Potential participants with VHs were encouraged to take part. Those who decided to participate contacted the researcher at the end of the meeting. Patients individually agreed on a convenient meeting time with the researcher either in their own homes or at the society meetings venue. All participants were then given the VHs questionnaire and were asked to fill it in before the scheduled meeting. In accordance with the university research ethics, completing the questionnaire was taken as a written informed consent. Questionnaires were returned at the next meeting and further questions were asked if the patient's responses were ambiguous. A debriefing document was sent by post to the patients at the end of the study.

The present and all the following PD studies were approved by the University Research Ethics Committee (see Appendix 3).

2.2.4 Analysis

The aim of the study was to provide detailed descriptions of the images experienced by PD patients with VHs. Therefore, the participants' answers were taken as qualitative descriptions of the phenomena. In order to identify the most prominent characteristics of VHs in PD, specific characteristics of VHs were presented to the patients in the form of multiple-choice questions and were analysed using the non-parametric chi-square test. Further, all statistically significant characteristics (variables) from the chi-square analysis were used in the multivariate analysis and a logistic regression analysis was performed to predict the frequency of hallucinations. Similarly, the demographic variables (temporal factors, medication dosage, HY disability stage, etc.) were used to perform a logistic regression analysis, upon which the frequency of VHs could be predicted.

All quantitative analyses were performed using SPSS for Windows version 15.0 (SPSS Inc, Chicago, Ill., USA).

2.3 Results

Once the demographic information of the VHs questionnaire was completed (see Section 2.2.1), patients were asked to describe the form(s) of their VHs (see Appendix 1 - Question 10). The patients' responses and descriptions are presented in Table 2.2. The most common reports were the images of people (15 reports) and animals (10 reports). There were 2 reports of simple shapes and patterns (on top of seeing faces) and only one report of seeing trees and buildings. Four people reported that the images they see have no particular form (e.g., unspecified or blurred images).

Table 2.2. Descriptions of VHs.

Patient	Description of VHs
1	Ordinary people and animals.
2	Ordinary people. Despite images being sharp, cannot distinguish faces.
3	My wife.
4	Animals, children, insects.
5	Spiders, ordinary people.
6	If I see a mark on the carpet, the more I look at it, the more I can see a spider with its legs kicking. I can look at an object and my mind tells me that I can see things within the object that I know are not really there. It is like seeing a picture but the picture can change into something completely different with the blink of an eye.
7	Shadows of people around cars, animals, children.
8	People, a dog.
9	Ordinary middle-aged people.
10	Hallucinations are blurred and cannot focus the details.
11	Shadowy animals, usually small rodents (mice) and spiders.
12	Mainly human faces or animal shapes. I do quite often pick out outline shapes in things like carpets or other patterned materials/things, pictures, shadows on the ground, etc. The best way to describe this is to use the analogy of the young girl/old lady pen and ink drawing, where depending on how you look at the drawing, you see either a young girl or an old lady. These "images", will only last for seconds, and are not at all disturbing to me. I have always seen some of these images, but I do think the problem has got much worse/more frequent, since starting to take levodopa. An example: when looking at a friend's picture of some old houses, yesterday evening, I saw in the pattern of clouds in the sky of the picture firstly a man's face, and then a dog. Both "images" disappeared after a few seconds. I also pick up, sometimes, what I think are reflections from the edges of the lenses, which can appear as bright flashes in the corner of my vision, or alternatively, dark patches sometimes.
13	Fine pattern of fine lines on bright white background. The pattern moves back and forward. People.
14	People. Shapes – usually bright light or fireworks.
15	People.
16	People trying to harm me. People (sometimes recognizing family members) being buried. Images are often coming towards me and trying to "get" me.
17	Hallucinations are blurred and cannot focus the details.
18	A girl sitting in a settee. A girl has thin legs, huge knees (like swollen) and big head. A dog. People walking up and down the street, but the faces are not distinguishable.
19	Mainly people and insects. When I am watching TV, I sometimes see people wearing glasses or having a moustache which later disappear. I mistakenly see people sitting in an empty car. I think my brain misinterprets what my eyes see.
20	Hallucinations are blurred and cannot focus the details.
21	People standing. People coming down from ceiling, when they hit the floor, they disappear.
22	People's faces. Trees. Buildings.
23	Hallucinations are blurred and cannot focus the details.

Table 2.3 displays frequency and percentage reports about different characteristics of VHs reported in the VHs questionnaire (see Appendix 1 – Questions 11-27). Significantly different distributions of the answers from each of the multiple-choice questions are asterisked (using chi-square analysis).

Table 2.3. Characteristics of VHs in PD.

Variable	N	%
Frequency of VHs		
>5/week	6	26
2 to 5/week	9	39
1/week	8	35
Number of images		
One	7	30
2 to 5	9	40
More than 5	7	30
Content		
Stereotyped	9	39
Always different	10	44
Missing data	4	17
Clarity		
Sharp	9	40
Blurry	8	35
Transparent	1	4**
Variable	5	21
Distortion of images		
Present	9	39
Absent	12	52
Missing data	2	9
Reality of images		
Seem real	10	43
Seem unreal	8	35
Not sure	5	22
Colour		
Black and white	7	30
Single colour	4	17
Multiple colours	12	53
Movement		
Present	19	83**
Absent	4	17**
Eyes		
Open	15	66*
Closed	4	17*
Both	4	17*
Vision field		
Complete	8	35
Partial	14	61
Missing data	1	4

Variable	N	%
Onset		
Sudden	17	74*
Gradual	4	17*
Missing data	2	9
Trigger		
Starts with percept	8	35
Starts without percept	14	61
Missing data	1	4
Duration of VHs		
Hours	6	26
Minutes	8	35
Seconds	7	30
Missing data	2	9
Time of day		
When waking up	4	17
When falling asleep	3	13
In the morning	4	17
In the afternoon	5	22
In the evening	7	31
Lighting		
Bright	5	21
Dim	10	43
Dark	2	9*
Variable	6	27
Images talk to		
The patient	1	4**
Each other	2	9*
Do not talk	20	87**
Images accompanied by		
Voice	3	13*
Smell	1	5**
Touch	1	5**
Nothing	18	77*
Disturbed because of VHs		
Yes	5	21**
No	18	79**
Perceived control		
Yes	12	52
No	8	35
Missing data	3	13

* $\chi 2$; significant difference in distribution of responses from chance, $p<0.05$.
** $\chi 2$; significant difference in distribution of responses from chance, $p<0.01$.

The most noticeable characteristics of VHs from the present sample were:

(a) Sudden appearance of "solid" images (either sharp or blurred clarity, but not ghost-like, transparent images);

(b) Hallucinations were almost invariably perceived in the visual modality only (hallucinations in other modalities were rare); similarly, the images did not communicate either with the patients or (in the cases of multiple images) to each other;

(c) Images were frequently in motion;

(d) The images were most commonly experienced when the patients had their eyes open, and

(e) Although half of all patients reported having control over their VHs and being able to make them disappear, the majority of patients (N=18) were not at all disturbed by the images. One patient described the images as *"not scary, just annoying when wanting to fall asleep"*. Finally, one of the patients reported he liked the images because *"they keep me company"*.

Regression Analysis

The statistically significant variables (sudden onset, hallucinations in the visual modality, moving images, open eyes, and non-threatening nature of the images) were submitted to a regression analysis; however, no model could predict the frequency of VHs on the basis of these variables ($p = .742$). Furthermore, using regression analysis, no model could predict the frequency of VHs (i.e., more than 5 times per week, 2-5 times per week or once per week) based on the range of demographic variables (temporal factors, HY disability stage, the amount of daily levodopa dosage, etc.) ($p = .786$).

Finally, there were no statistically significant differences on a number of independent variables between PD patients with and without ocular problems (see Table 4.2). PD patients with ocular problems in the current studies were not at a higher risk for developing VHs than PD patients without ocular problems. In addition, the possible

role of ocular problems in development of VHs was also excluded, as there were no statistically significant differences between PD patients with and without ocular problems on the CANTAB visual memory and executive functions tests.

Table 2.4: Differences between PD patients with and without ocular problems: Means, SDs, and p-values.

	PD with ocular problems	**PD without ocular problems**	*t*	*df*	*p*
Age	72.50 (7.79)	71.27 (6.96)	.338	19	.726
Gender	1.50 (.55)	1.31 (.48)	.739	20	.440
HY Disability Scale	2.38 (1.60)	2.11 (1.02)	.317	20	.687
Years since diagnosis	8.70 (6.60)	6.38 (5.57)	.766	20	.416
Side more affected by tremor	1.67 (.82)	2.06 (.93)	-.974	20	.370
Frequency of VHs	2.33 (.58)	2.00 (.82)	.632	20	.576
IED					
- total errors (adjusted)	-.61 (1.59)	-.08 (.65)	-1.111	21	.279
- total errors (raw)	-.39 (.95)	-.37 (.97)	-.048	21	.962
- completed stage errors	.39 (.73)	-.20 (1.38)	.395	21	.697
- completed stage trials	.64 (.83)	.24 (1.29)	.825	21	.419
- ED errors	-.57 (1.17)	-.86 (1.09)	.608	21	.549
- ID errors	.08 (1.25)	.59 (.26)	-1.484	21	.153
- stages completed	-.78 (1.46)	-.16 (.75)	-1.330	21	.198
- total trials	.03 (.77)	-.18 (.86)	.589	21	.562
- total trials (adjusted)	-.65 (1.49)	-.17 (.70)	-1.055	21	.303
SOC					
- problems solved in minimum moves	-.33 (1.92)	-.38 (1.14)	-.079	21	.938
SWM					
- between errors	.15 (.68)	-.02 (.97)	.413	18	.684
- double errors	.42 (.58)	.34 (.93)	.203	18	.841
- strategy	-.25 (.37)	-.38 (.77)	.486	18	.633
- total errors	-.14 (.67)	-.34 (1.06)	.439	18	.666
- within errors	.44 (.42)	.37 (.94)	.204	18	.841
DSM					
- percent of correct answers	-1.60 (2.33)	-.84 (1.46)	-.922	19	.368
- percent of correct simultaneous answers	-.99 (2.47)	-.43 (1.45)	-.650	19	.524
- probability of a double error	-1.54 (1.56)	-.62 (1.12)	-1.572	19	.133
PAL					
- total number of errors	.41 (.47)	-.06 (.64)	1.532	12	.152
- average trials for a successful solution	.40 (.64)	.09 (.65)	.874	12	.399
- average number of completed stages	.33 (.67)	.11 (.53)	1.012	12	.331
PRM					
- percent of correct answers	-.08 (1.16)	-1.18 (1.50)	1.874	21	.075
SRM					
-percent of correct answers	-.33 (1.00)	-.88 (.83)	1.419	20	.171

2.4 Discussion

Providing detailed characteristics of VHs in PD has important implications for the new research directions: understanding of both the underlying neural and functional processes involved in the generation of VHs and, consequently, about the methods to eliminate hallucinations (or at least effectively cope with them). Therefore, the aim of the present study is to offer a detailed description of VHs in PD.

The patients from the study varied greatly according to their age, daily levodopa dose, years since diagnosis, HY disability stage and the side of the body that was more affected by tremor (as described in Table 2.1). There is therefore no "typical" PD patient, as PD is expressed in different ways across patients (Paulson & Stern, 1996). However, half of all patients (N = 11) had some form of ocular pathology in the current study (see Table 2.1), which is comparable to the estimated 50% of ocular problems in old age in Great Britain (Government Statistical Service, 1988). Most of the reported pathologies affected visual acuity of patients (e.g., loss of focus and double vision) and two reported having cataract. Visual acuity and cataracts were independently associated with VHs in age related eye disease (Berrios & Brook, 1984; Teunisse, Cruysberg, Hoefnagels, Verbeek, & Zitman, 1996), in Alzheimer's Disease (Chapman et al., 1999) and in Charles-Bonnet Syndrome (Jacob, Prasad, Boggild, & Chandratre, 2004; Rosenbaum, Harati, Rolak, & Freedman, 1987). Levine (1980) reports on association between VHs and cataract. Moreover, even in PD, VHs were reported to disappear after cataract surgery (Matsui et al., 2004). As discussed in Chapter 1, the dopaminergic system, which is affected in PD, has projections to the human retina (Biousse et al., 2004) and can affect all subsequent processing from the level of retina onwards. While the results from the present study cannot postulate a causal link between ocular problems experienced by the patients and VHs, the results suggest that age-related vision problems present an additive problem on top of the impoverished dopaminergic visual system.

If this is really the case, then the projections from the retina to the thalamus and the primary visual cortex are additionally suboptimal due to the ocular

pathology observed in the present sample of hallucinating PD patients. The impoverished visual input in the primary visual cortex consequently alters all further visual processing. Rosenbaum and Freedman (1987) and Lalla and Primeau (1993) argued that a number of ocular pathologies, but also post-surgical eye patching or sensory deprivation, may cause a lack in the usual afferent inputs, producing spontaneous nerve impulses and visual experiences at any of the various levels of visual processing. This hypothesis is in line with two other studies (Manford & Andermann, 1998; Rodnitzky, 1998) which suggest that the compromised dopaminergic system in the retina consequently affects the functioning of all subsequent processes in the visual system, namely the ventral and the dorsal visual pathways. In addition, impoverished data might give rise to more top-down processing, and hence the tendency to generate things that are not really there.

The descriptions of VHs in the present study were similar to those described in the previous studies of hallucinating PD patients (Barnes & David, 2001; Fenelon et al., 2000; Holroyd et al., 2001; Manford & Andermann, 1998). Patients described the sudden onset of well-defined images (mainly people and animals) and were able to recollect the features of the images as clearly as if they were actually looking at them. The images were often moving around, although the movement was usually rather restricted (e.g., the images repeated the same sequence of gestures or moves). The finding about the clear, well-formed and moving images supports the hypothesis about the early dysfunctions of the visual system, and suggests that both the ventral and dorsal pathways, stemming from the primary visual cortex, might be affected as a result, and involved in the generation of VHs in PD.

Goodale and Milner (1992) pioneered the work on the processing of visual information. They suggested that visual perception depends on two systems: a ventral stream of projections from the primary visual cortex to the inferior temporal cortex, playing a major role in the perceptual identification of objects and form representation, and a dorsal stream of projections from the primary visual cortex to the posterior parietal cortex, involved in spatial awareness, guidance of actions, and detecting and analyzing movements (ibid). Ffytche et al. (1998) provided firm fMRI

evidence that the content of the hallucinations of patients with Charles-Bonnet syndrome (VHs of the blind) reflects the functional specializations of the region. Patients with Charles-Bonnet syndrome often perceive images of faces and objects, and such hallucinations correlate with cerebral activity in the ventral visual cortex. Although no neuroimaging studies have been done in PD patients during hallucinations, some neuroimaging studies showed relatively increased activation of the ventral stream in hallucinating PD patients in the resting (non-hallucinating) state, compared to the non-hallucinating counterparts[13]. The dysfunction of the parietal-dorsal stream in the hallucinating PD patients in the resting state has been suggested in several neuroimaging studies, where the authors found hypoperfusion in the parietal lobe using PET (Matsui, Nishinaka et al., 2006b), grey matter volume reduction using MRI (Ramirez-Ruiz, Marti et al., 2007), and significantly higher density of the Lewy bodies in the dorsal areas using a clinical-pathological comparison between the brain of hallucinating and non-hallucinating PD patients (Papapetropoulos, McCorquodale, Gonzalez, Jean-Gilles, & Mash, 2006).

Putting the phenomenological descriptions from the present study (see Table 2.2) together with the neuroimaging and pathological findings, it can be hypothesized that the nature of VHs in PD reflects the functional specializations of the ventral and dorsal pathways. Thus, well-defined images of mainly people and animals could reflect the activation of the ventral visual pathway and the reports of the movement of the images (although restricted in nature) could suggest the activation of the dorsal pathway during hallucinations in PD patients. However, although a similar idea is expressed in two other studies (Boecker et al., 2007; Mosimann et al., 2006), this hypothesis is based only on the phenomenological results and the results from another disorder affected by VHs (Ffytche et al., 1998). These speculations need to be supported by empirical evidence from PD patients during their hallucinating states, as well as by a neuropsychological assessment of functioning of the association visual cortex, which will be addressed in Chapter 4.

[13] Aberrant activation of the ventral stream in hallucinating PD patients has been suggested by Harding et al. (2002), Matsui et al. (2006b), Oishi et al. (2005), Okada et al. (1999) and Stebbins et al. (2004).

Furthermore, the hallucinating PD patients from the present study often reported experiencing non-threatening hallucinations in the visual modality only. Thus, VHs were rarely accompanied by voice, smell or touch (see Table 2.3). Likewise, the images were rarely talking to each other or to the patient. The results are in line with other studies reporting that hallucinations in other sensory modalities are rare in PD (Diederich et al., 2005; Fenelon et al., 2000; Haeske-Dewick, 1995; Inzelberg et al., 1998; Tousi & Frankel, 2004). Fenelon et al. (2000) reported that in the very few cases where auditory verbal hallucinations were present, they were always neutral and clearly different from the threatening auditory hallucinations characteristic of schizophrenia. Moreover, Bodis-Wollner (2003) suggested that the presence of auditory hallucinations in PD (especially without VHs) raises a suspicion of an underlying primary psychiatric disorder. Mainly visual and non-threatening hallucinations in PD patients from the present study therefore indicate that VHs are not caused by a coexisting psychiatric disorder. However, due to the neutral emotional response to VHs, the study raises the question of how PD patients cope with their VHs (see Chapter 9) and whether there are specific characteristics of the images that influence their responses.

The detailed descriptions of VHs of PD patients presented in the current study revealed that despite the occasional bizarre appearances, the majority of the images were non-threatening, repetitive and stereotyped, and provoked little or no emotional response in the patients. All patients had preserved insight into the hallucinatory nature of the images they saw. Therefore, it is not surprising that the majority of the patients were not disturbed by or worried about their VHs. Additionally, although some characteristics of VHs were not statistically significant, the present study offers a line of alternative motives for patients' clear insight and undisturbed response to the images. Firstly, the images were experienced relatively often, occurring at least once a week (see Table 2.3). With time, the patients may have learned that the images do not harm them and perceive them as a part of their everyday life. Their emotional responses to the images might therefore become neutral quite quickly. There are also a number of visual cues that helped the patients to recognize the image as a hallucination, e.g., the clarity of the

images might be different to the clarity of other objects in the environment (images are often blurred, see Table 2.3), the images may occur in different colour than the environment (e.g., in black and white or in a single colour), the images may suddenly appear, where there was nothing before, starting without any percept. The images are often stereotyped, occurring always at the same time and place. Finally, some patients experienced the images as somewhat distorted, giving them the qualities of the unreal percepts. Taking these visual cues into consideration, it is not surprising that a substantial number of the patients (N = 13) reported that the images they perceive look unreal.

The phenomenology of the VHs experienced by the PD patients from the present study offers new insight into the nature of the images. There are a number of cues that can be used by PD patients as indicators for recognizing the images as unreal, and together with the unexciting content, offer a base for a non-emotional and neutral response towards the images. The study raises the possibility of whether specific characteristics of the images influence not only emotionally neutral responses, but also moulding the behavioural coping responses of patients. These questions will be addressed in detail in the context of patients' personality traits (e.g., emotional responsiveness, self-control, self-consciousness, etc.) in Chapter 9.

Finally, apart from studying the characteristics of VHs in PD, the aim of the present study was also to identify whether the frequency of VHs can be predicted on the basis of the statistically significant characteristics of VHs (see Table 2.3) or on the basis of the demographic variables (e.g., temporal factors, levodopa dosage, disability stage, etc.). No model could adequately predict the frequency of VHs on the basis of these variables in the current study. The results from the study support the claim that the frequency of VHs is independent of the nature of VHs experienced and of any other demographic data. VHs in PD are therefore more likely to be related to more cognitive factors.

2.4.1 Limitations

PD patients were selected on the criterion of absence of dementia; however, dementia was evaluated on subjective measures, such as gathering reports from the carers and asking about maintenance of activities of daily living. This poses a problem as a more objective measure of cognitive decline should be accounted for in studies with PD populations.

The Mini-Mental Status Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) is the most routinely administered orientation measure used by neurologists to screen for orientation and cognitive impairments informally (York & Alvarez, 2008). It is sensitive to the presence of dementia, particularly in those with moderate to severe forms of cognitive impairment; however, the MMSE appears to be less than ideal when those with mild cognitive impairment are evaluated (Kuslansky, 2004; Nys et al., 2005). In some patient groups, such as PD, using the MMSE as the only method of cognitive assessment might not only be inappropriate, but even misleading; a normal MMSE is likely to lead to the false assumption of preserved cognitive status while in fact the patient might have severe frontal dysexecutive or visuospatial symptoms (Bak & Mioshi, 2007). MMSE has been criticized for being insensitive to differences between dementing disorders, and particularly to cognitive decline in subcortical dementias, such as PD (Huber & Bornstein, 1992; Jefferson et al., 2002). In a recent study defining cognitive dysfunction as impaired performance on at least three neuropsychological tests, there was no difference found in MMSE scores between cognitively intact and cognitively impaired PD patients (Muslimovic, Post, Speelman, & Schmand, 2005). Therefore, cognitive deficits are common in PD patients with "normal" cognition based on MMSE performance, suggesting that mild cognitive impairment is under-recognized in clinical practice due to routine use of insensitive screening instruments (Mamikonyan et al., 2009).

Therefore, some other measures of cognitive decline should be used; some authors suggest measures such as the Dementia Rating Scale (DRS) (Mattis, 1988), which were designed to assess early cognitive impairment and was showed to be a valid mental status screening test of cognitive functioning for individuals with PD

(Brown et al., 1999), 1999). The other possibility is The Montreal Cognitive Assessment (MoCA), which is more sensitive to subtle cognitive deficits in patients with PD (Nasreddine et al., 2005). In summary, future research needs to take some cognitive measures of dementia into account for early signs of dementia as important covariates in the assessment of cognitive functioning.

2.4.2 Conclusions

Age-related ocular problems were a frequent complication factor in the hallucinating PD patients from the present study, probably affecting the already compromised dopaminergic-based visual processing. The impoverished data from the early stages of visual processing onwards gives rise to aberrant subsequent visual processing, as well as to more top-down processing. Well-formed and moving images suggest suboptimal functional specialization of the ventral and dorsal visual system in the hallucinating PD patients; however, this hypothesis is strictly speculative and needs to be addressed by the means of using neuroimaging techniques during the hallucinating state. Five specific features characterized VHs in PD: sudden appearance of "solid" images, frequent movement of the images, non-threatening nature, and images were experienced with the eyes open and in the visual modality; however, these characteristics could not predict the frequency of hallucinations using the regression analysis. Further, hallucinating PD patients probably use a range of visual cues to preserve the insight into the hallucinatory nature of the images and the nature of VHs in PD was probably reflected in a composed emotional response; however, this is a significant finding and deserves further investigation in greater details (see Chapter 9). Finally, the demographic characteristics of the hallucinating PD patients could not predict the frequency of VHs using regression analysis, and suggest the importance of other, more cognitive, factors in the generation of VHs in PD.

Chapter 3: Proneness to VHs in the Normal Population

3.1 Introduction

Chapter 2 investigated the detailed phenomenology of VHs in PD and explored how the characteristics of the images relate to each other and to the demographics of the hallucinating PD patients. VHs in PD do not only constitute well-formed images, but also include "hallucinatory-like" experiences such as sensations of a presence, a sideway passage, etc. (Fenelon et al., 2000). However, while hallucinatory-like experiences are a frequent manifestation in clinical populations, they also occur in the normal population, without any history of psychiatric disorders. Several authors (Hanssen et al., 2003; Johns & van Os2001; Lopez-Rodrigo et al., 1997; Slade & Bentall, 1988; Stefanis et al., 2002; Verdoux & van Os, 2002) have proposed that such experiences range from mild visual disturbances to full-blown hallucinations, characteristic of psychiatric illness. Stemming from the continuum hypothesis (ibid), the present chapter aims to investigate the expression of visual images further and explore how hallucinatory-like experiences are expressed in the normal population.

One of the first attempts to measure psychosis proneness was with the psychoticism dimension as a personality feature (Eysenck, 1952; Eysenck & Eysenck, 1976). According to this standpoint, psychosis proneness is a dimensional construct ranging from normality (defined in culturally relative terms) to psychosis (a similar idea to the continuum hypothesis). Psychosis proneness was later developed into a multidimensional construct, promoting the development of the schizotypy scale of Oxford and Liverpool Inventory of Feelings and Experiences (O-LIFE) (Claridge et al., 1996; Mason & Claridge, 2006). Other approaches, however, aimed to measure subtle psychotic symptoms in the general population, most commonly delusion and hallucination-proneness. Two common scales, for example, are the Cardiff Anomalous Perceptions Scale (CAPS) (Bell et al., 2006) and the Launay-Slade Hallucinations Scale (LSHS) (Morrison et al., 2000;

Morrison, Wells, & Nothard, 2002). These scales are often used as measures of hallucination-proneness, because they consider not only clear visual hallucinations, but mainly rely on subjective experiences (e.g., a feeling of a presence of another being). However, a shortcoming of the scales is the over-emphasizing of hallucinatory experiences in the visual and auditory modalities, and consequently leaving the relationship between different modalities under-researched.

In order to investigate the nature of hallucination-predisposition in the healthy young population, the aim of the present study is two-fold: firstly, to construct a valid and reliable measure of hallucination-proneness taking visual, auditory and other sensory modalities into consideration; and secondly, to investigate how hallucination-proneness is expressed in the normal population using a constructed hallucination-proneness questionnaire. The study will give evidence as to whether such an approach is useful in differentiating people from the normal population who are extremely high and extremely low-prone to have hallucinatory-like experiences. Following from the hypothesis about qualitative differences between high and low-prone individuals (Lopez-Rodrigo et al., 1997), the present study will proceed to offer a basis for following studies, investigating whether the cognitive differences between high and low-prone normal individuals correspond to the same cognitive differences between hallucinating and non-hallucinating PD patients.

3.2 Methods

3.2.1 Construction of the Hallucination-Proneness Questionnaire (HQ)

The HQ was constructed by adapting questions from the Cardiff Anomalous Perceptions Scale (CAPS) (Bell et al., 2006) and the Launay-Slade Hallucinations Scale (LSHS) (Morrison et al., 2000; Morrison, Wells, & Nothard, 2002) because they focus on subtle perceptual distortions rather than on full-blown hallucinations, the latter not being commonly observed in the normal population. Furthermore, the purpose of the questionnaire is to observe the relationship between hallucination-

proneness in different modalities. Therefore, the questions asked in the HQ reflect a subjective evaluation, representing hallucination-proneness from visual, auditory and other modalities with approximately the same number of items included in each scale. In the final version of the HQ, three scales were developed, namely visual (9 items), auditory (10 items), and other sensory modality scale (10 items). The HQ items, by category, are attached in Appendix 4. Each item is presented with a statement requiring an answer ranging from 0 ("certainly does not apply to me") to 4 ("certainly applies to me"). However, in Chapter 2, the issue of measuring "realistic" and "pathological" experiences was raised (Giorgi, 2003). For the same reason, the constructed questionnaire allows the participants to clarify and give explanation for each numerical answer they chose.

Apart from proneness to hallucinatory experiences in the specific perceptual modality, the sum of all three scales presents the total HQ score.

3.2.2 Participants

An opportunity sample of 555 undergraduate students (384 females and 171 males) from Oxford Brookes University, with a mean age of 21.61 years (SD = 5.94; range from 17 to 29), completed the HQ (278 students completed it between May 2006 and October 2006 and 277 students in January 2008). Apart from age and gender, the following variables were collected in the present study: handedness, the presence/absence of dyslexia, vision and hearing problems, and the presence/absence of psychiatric or neurological disorders. All participants had normal or corrected-to-normal vision and hearing. Participants with a history of psychiatric or neurological disorders were excluded from the sample (2 cases). Questionnaires with one or more missing answers were excluded from the analysis (14 cases).

3.2.3 Procedure

Written permissions from lecturers of different disciplines were obtained before introducing the study at the beginning of the lectures. Questionnaires were distributed together with the information sheets (Appendix 5) in the class. At the end of the lecture, the questionnaires were collected. In order to avoid coercion, the exact percentage of returned questionnaires is unknown; however, it is estimated that between 40-70% of the students in each class completed the questionnaires. The students were informed that the study was anonymous, but for the purpose of the follow-up studies, the students were asked to leave their electronic contact details if they so wished.

The present and all the following studies with the normal individuals were approved by the University Research Ethics Committee (see Appendix 3).

3.2.4 Analysis

First, descriptive statistics were calculated for all three scales (visual, auditory and other modality scale) as well as for the total HQ sum. Correlation analysis was performed between all HQ scales to test if there is a link between the individual scales. One-way analysis of variance (ANOVA) was used to test the differences on the three HQ scales and the total HQ sum among different age groups, and the independent t-tests were used to test the differences on HQ among other dichotomous measures (i.e., gender, handedness, dyslexia, vision and hearing problems). A logistic regression analysis was performed to predict the outcome of the HQ on the basis of the independent variables (age, gender, vision and hearing problems, dyslexia and handedness). Finally, principal component analysis (PCA) was performed to test if 29 HQ items can be explained in terms of a much smaller number of factors. PCA reveals the internal structure of the data in a way which best explains the variance in the data, and the variances extracted by the factors are called the eigenvalues (Stevens, 1992). The number of retained factors was determined by the eigenvalues greater than 1 (also known as the Kaiser's criterion).

All analyses were performed with SPSS Version 15.0 (SPSS Inc., Chicago, IL).

3.3 Results

The reliability coefficient was high for all three scales and for all items of the HQ (Cronbach α for the auditory scale was .805, for visual scale .802, for other modalities .859 and for all items of the HQ .922). Descriptive statistics for all three scales and the HQ total sum are displayed in Table 3.1. The range was wide for all HQ scales: for the visual scale was from 0 to 30 (out of 36 maximum possible points), for the auditory scale from 0 to 31 (out of 40 maximum possible points), and for the other sensory modalities from 0 to 36 (out of 40 maximum possible points). Hallucination-proneness in other sensory modalities (taste, touch, olfaction, etc.) was twice as frequent as proneness to visual or auditory hallucinations. The results indicate a wide dispersion of hallucination-proneness in the normal population; however, low hallucination-proneness was more frequent than high hallucination-proneness, as indicated by the positively skewed distributions of all three scales and the final HQ score (see Table 3.1).

Table 3.1. Descriptive statistics for all HQ scales and the final HQ score.

	Visual	**Auditory**	**Other**	**HQ**
M (SD)	8.76 (6.86)	8.86 (7.12)	14.63 (8.68)	32.12 (19.97)
Skew (Std Error)	.779 (.104)	.856 (.104)	.249 (.104)	.483 (.105)
Kurtosis (Std Error)	-.102 (.207)	.180 (.208)	-.889 (.208)	-.603 (.209)

The results of the correlation are displayed in Table 3.2. All three scales and the final HQ score were significantly positively correlated.

Table 3.2. Correlation matrix.

	Visual	**Auditory**	**Other**	**HQ**
Visual	1			
Auditory	.692**	1		
Other	.704**	.614**	1	
HQ	.891**	.855**	.894**	1

** Correlation is significant at the 0.01 level.

Participants' responses were not statistically different depending on their gender, vision or hearing problems, handedness and dyslexia (see Table 3.3).

Table 3.3. T-test results for the HQ scales.

	Gender	**Handedness**	**Dyslexia**	**Vision problems**	**Hearing problems**
Visual	t=0.24, p=0.813	t=0.12, p=0.908	t=-1.22, p=0.225	t=1.55, p=0.121	t=-0.86, p=0.389
Auditory	t=-1.37, p=0.172	t=0.14, p=0.889	t=-1.04, p=0.300	t=0.42, p=0.674	t=-0.89, p=0.374
Other	t=1.08, p=0.283	t=-0.12, p=0.908	t=-0.56, p=0.579	t=1.93, p=0.064	t=0.96, p=0.335
HQ	t=0.11, p=0.91	t=0.05, p=0.959	t=-1.01, p=0.313	t=1.66, p=0.100	t=-0.22, p=0.824

The results indicate that hallucination-proneness in all modalities are more or less equally expressed in the normal population regardless of gender, other vision or hearing problems, handedness or dyslexia.

Correlation between age and the measures of HQ were calculated (see Table 3.4); there are no statistically significant correlations. However, it has to be stressed that the age range (see Section 3.2.2) of the student sample is limited (ranging from 17 to 29) and therefore any differences based on age are not likely to be observed.

Table 3.4. Pearson's correlations between age and all measures of HQ.

	HQ- visual scale	**HQ- auditory scale**	**HQ- other modalities scale**	**HQ - total**
Age	.024	-.037	-.035	-.016

Using a logistic regression analysis, no model could predict the HQ outcome or the outcome of the individual scales on the basis of the independent variables that were taken into account in the present study (i.e. gender, vision or hearing problems, handedness and dyslexia). The regression analysis results are presented in Tables 3.5 to 3.8.

Proportion of the variance of the visual scale of the HQ explained by the model is 13%. The ANOVA showed that the model is not a significant predictor of HQ-visual scale ($F = 1.179$, d.f. = 5/449, $p = 0.318$. Overall, the regression analysis is not significant and individual predictors are not significant either (for exact values of the independent variables see Table 3.5).

Table 3.5: Regression analysis for the visual scale of the HQ.

Model		Standardized Coefficients (Beta)	t	p
1	(Constant)		.730	.466
	Gender	-.028	-.592	.554
	Age	.024	.519	.604
	Vision Problems	-.071	-1.498	.135
	Hearing Problems	.026	.550	.583
	Dyslexia	.067	1.420	.156

Proportion of the variance of the auditory scale of the HQ explained by the model is 5%. The ANOVA shows that the model is not a significant predictor of HQ-auditory scale ($F = .478$, d.f. = 5/445, $p = 0.793$. Overall, the regression analysis is not significant and individual predictors are not significant either (for exact values of the independent variables see Table 3.6).

Table 3.6: Regression analysis for the auditory scale of the HQ.

Model		Standardized Coefficients (Beta)	t	p
1	(Constant)		.920	.358
	Gender	.046	.959	.338
	Age	-.013	-.283	.778
	Vision Problems	-.018	-.369	.712
	Hearing Problems	.020	.418	.676
	Dyslexia	.049	1.038	.300

Proportion of the variance of other sensory modality scale of the HQ explained by the model is 11%. The ANOVA shows that the model is not a significant predictor of HQ-other scale (F = 0.943, d.f. = 5/443, p = 0.453. Overall, the regression analysis is not significant and individual predictors are not significant either (for exact values of the independent variables see Table 3.7).

Table 3.7: Regression analysis for the other sensory modalities scale of the HQ.

Model		Standardized Coefficients (Beta)	t	p
1	(Constant)		.920	.358
	Gender	-.046	-.970	.333
	Age	-.021	-.432	.666
	Vision Problems	-.045	-.937	.349
	Hearing Problems	-.031	-.661	.509
	Dyslexia	.066	1.385	.167

Proportion of the variance of the HQ(total) explained by the model is 9%. The ANOVA shows that the model is not a significant predictor of HQ-other scale (F = 0.771, d.f. = 5/440, p = 0.571. Overall, the regression analysis is not significant and individual predictors are not significant either (for exact values of the independent variables see Table 3.8).

Table 3.8: Regression analysis for the HQ.

Model		Standardized Coefficients (Beta)	t	p
1	(Constant)		1.687	.092
	Gender	-.016	-.328	.743
	Age	.000	.000	1.000
	Vision Problems	-.055	-1.155	.249
	Hearing Problems	.002	.036	.971
	Dyslexia	.068	1.423	.156

Principal Component Analysis (PCA)

PCA revealed 6 factors, where the eigenvalue was higher than 1, which accounted for 55% of the variance (see Table 3.9). The first factor accounted for 32% of the variance and was defined as general hallucinatory tendency.

Table 3.9. Principal Component Analysis (PCA).

Component	**Eigenvalue**	**% of Variance**	**Cumulative %**
1	9.270	31.966	31.966
2	1.988	6.854	38.820
3	1.365	4.708	43.528
4	1.195	4.120	47.648
5	1.089	3.756	51.403
6	1.052	3.629	55.033

Next, absolute values of the individual items extracted with the PCA that were less than .40 were suppressed (Stevens, 1992). Even with the .40 suppression value, all 29 items of the HQ loaded on the first factor (see Appendix 6). Therefore, the factor analysis strongly supported the one-dimensional solution of the proneness to the hallucinatory experiences, which is in line with statistically significant positive correlations between the scales (see Table 3.2).

3.4 Discussion

The aim of the present study was to investigate how hallucination-proneness is expressed in the normal population, using a measure of hallucination-proneness in the visual, auditory and other sensory modalities. The results suggest that the HQ, which was constructed on the basis of other hallucination-proneness questionnaires and has a high internal reliability, elicits a wide range of answers, varying from low to high hallucination-proneness (see Table 3.1). This was true not only for the total HQ score, but also for all three scales (the visual, the auditory and the other modalities). The results therefore suggest that hallucinatory experiences are expressed in varying degrees in the normal population. These results are in line with several authors who proposed a continuum nature of the hallucinatory experiences (Crow, 1998; Lopez-Rodrigo et al., 1997; Slade & Bentall, 1988).

The results from the present study suggest that although the majority of participants experienced occasional occurrence of hallucinatory experiences, high incidence of hallucinatory-like experiences were rare (the distributions for all scales were positively skewed, see Table 3.1). Based on the results from the present study, hallucination-proneness is therefore likely to lie on a continuum, with the majority of people occasionally experiencing some anomalous perceptions either in the visual, auditory or other sensory modalities. Similar distribution was also suggested by both Aleman et al. (2001) and Bentall and Slade (1985), who used the LSHS (Morrison et al., 2000; Morrison, Wells, & Nothard, 2002).

Regarding hallucination-proneness in different modalities, the multi-dimensionality of the HQ was investigated with the principal component analysis. Although 6 factors were yielded, all 29 items of the HQ saturated on the first factor, with a higher explanatory variance than all the other 5 factors together. Therefore, the first factor can be described as a tendency towards hallucinatory experiences, and hallucination-proneness (as measured and defined in the present study) can be considered a one-dimensional construct. Further, the one-dimensional construct is based on strong correlations between the HQ items (see Table 3.2), and is additionally supported by the positive significant correlations between all HQ scales

and the final HQ score. High hallucination-proneness in the visual modality therefore implies high proneness to hallucinatory experiences in all the other modalities. This is an important finding because it gives evidence that hallucination-proneness in the normal population differs from hallucinations in PD patients who usually report hallucinations in the visual modality. As described in Section 1.2 and in the results of Chapter 2, hallucinations in modalities other than visual are rare in PD and imply a differential diagnosis, independent of PD (Bodis-Wollner, 2003; Fenelon et al., 2000; Inzelberg et al., 1998; Mosimann et al., 2006).

Finally, the scores on all three HQ scales and the final HQ score were not dependant on the participants' age, gender, dyslexia, handedness, and vision or hearing problems, confirmed by the ANOVA results (see Table 3.3). Similarly, the independent variables could not predict the final outcome of the HQ scales or the final HQ score using regression analysis. The results therefore suggest that the differences between the high and low-prone normal individuals may be related to the cognitive factors (see Section 1.5), rather than to the independent variables. The findings are in line with Lopez-Rodrigo et al. (1997), who suggested there are qualitative differences between individuals who are high and low-prone to have hallucinatory experiences. Similar to VHs in PD, the results from the present study suggest that there is a need for further exploration of the underlying cognitive risk factors that contribute to higher hallucination-proneness in individuals from the normal population.

3.4.1 Limitations

The main limitation of the current study is that the sample may not be wholly representative of the normal population, as the participants were an opportunistic sample of the undergraduate students. The aim of the study, however, was to develop an instrument which would be able to identify high and low-prone individuals from the continuum of the hallucinatory experiences. Although replication of the study is warranted on a sample from the general population, it is unlikely that the sample had an effect on the usefulness of the HQ to differentiate

high and low-prone individuals. Further, for future analyses of the cognitive risk factors involved in hallucination-proneness, matching the independent variables between high and low-prone individuals might be of a higher importance than a truly representative sampling from the general population.

Further, a specific limitation of the present study was a lack of control of those students who have experienced altered states of mind due to the use of drugs. Drug use is associated with several medical complications, both acute and long-lasting (Ricaurte & McCann, 2005); chronic use of recreational drugs may, for example, cause increased nervousness, irritability, and psychosis, an altered state of mind. Chronic abusers may become paranoid and may suffer auditory and VHs, as well as erratic and violent behaviour (Chiras, 2005). Furthermore, withdrawal from the drug can cause severe depression (ibid). Chronic exposure to drug use may permanently modify the nervous system. Therefore, the limitation of the present study is a lack of control for drug use and future studies should screen for it. In future years, research priorities include the possible role of previous drug use in the subsequent proneness to hallucinatory experiences or even a possible development of neuropsychiatric illness.

Finally, a limitation of the present study was that there was no attempt to assess either the reliability or the validity of the HQ. One possible approach to demonstrate validity is to ensure that the items within a measure are inter-related and therefore measure a single construct. Factor analysis is often used to demonstrate relationships among items. In the present study, the factor analysis showed one single factor, indicating the concept is unidimensional. Another approach to demonstrate validity is to simply test whether an instrument measures what is was supposed to measure. In the current study, for example, it would be useful to assess the validity by administering other hallucination-proneness questionnaires, such as the Cardiff Anomalous Perceptions Scale (CAPS) (Bell et al., 2006) and the Launay-Slade Hallucinations Scale (LSHS) (Morrison et al., 2000; Morrison, Wells, & Nothard, 2002). Similarly, although the Cronbach α reliability coefficient was high for all three scales and for all items of the HQ, an additional test-retest reliability analysis would be necessary to assess the reliability of the HQ. Test-retest reliability is an excellent

measure of score consistency because it allows the direct measurement of consistency from administration to administration. However, a possible shortcoming of the test-retest reliability is that this coefficient is not the easiest to do in practice because of its problems and limitations. One limitation related to the present study is that it requires two administrations of the same test with the same group of individuals. This can be expensive and demanding of people's time. In terms of the present study it would be difficult to ask 555 participants to fill out the same questionnaire after a period of time. Finally, if the time interval is short, participants may be overly consistent because they remember some of the questions and their responses. Despite all of these limitations, both reliability and validity are the crucial elements in quantitative research, especially when trying to establish a new measure. Therefore, the limitation of the present study is a lack of control to assess the test-retest reliability and validity to ascertain that the HQ really measures hallucination-proneness and that the degree of errors that are non-systematic and measures hallucination proneness consistently over time.

3.4.2 Conclusions

In order to investigate the nature of hallucination-predisposition in the healthy young population, the aim of the present study was two-fold: firstly, to construct a valid and reliable measure of subtle perceptual distortions (not only clear hallucinations) taking the equal representations of visual, auditory and other sensory modalities into consideration; and secondly, to investigate how hallucination-proneness is expressed in the normal population using the constructed hallucination-proneness questionnaire. The HQ is a useful tool for identifying individuals who are high and low-prone to have hallucinatory-like experiences. The results confirmed previous reports that hallucination-proneness is a concept that is expressed in different degrees in the normal population without any history of psychiatric disorders. Further, hallucination-proneness is a unitary concept, encompassing high proneness to anomalous perceptions in the visual, auditory and other sensory modalities. All three scales, as well as the final HQ score, could not

be predicted with the independent variables (age, gender, dyslexia, handedness, and vision or hearing problems), implying that specific cognitive risk factors may predispose high-prone individuals to hallucinatory experiences. Similar findings and therefore a hypothesis that cognitive, rather than demographic, factors are implemented in VHs were proposed in PD patients (Chapter 2). Possible risk factors (based on the ones described in Section 1.6) will be addressed in the following studies, namely the role of perceptual, imagery and executive functions, sleep patterns and meta-cognitive processes.

Summary of Part I

Part I examined the nature of VHs in PD and hallucination-proneness in the normal population. VHs in PD and hallucination-proneness in the normal population were not related to, or predicted by, any independent variables examined. The findings from the studies suggest that hallucinating PD patients and high-prone normal individuals differ from non-hallucinating PD patients and low-prone normal individuals in cognitive functioning, rather than in demographics. Several possible cognitive risk factors may have a role to play (see Section 1.6) and part II will investigate the following factors: visual memory and visual imagery (Chapter 4), early visual processing components (Chapter 5), executive functions (Chapter 6), meta-cognitive processes (Chapter 7) and sleep patterns (Chapter 8). Finally, Chapter 9 will address behavioural cognitive strategies that PD patients themselves develop to cope with their VHs. Comparing if the same risk factors are implicated in both hallucinating PD patients and in high-prone individuals will aid understanding as to whether hallucinations and hallucination-proneness are alleviated by the same cognitive factors, upon which a new model for VHs could be built.

Part II[14]

Chapter 4: Visual Memory and Visual Imagery in Hallucinating PD Patients and in High-Prone Normal Individuals

Chapter 5: Early Visual Processing Components in High-Prone Normal Individuals: an EEG Study

Chapter 6: Executive Functions in Hallucinating PD Patients and in High-Prone Normal Individuals

Chapter 7: Personality in Hallucinating PD Patients and in High-Prone Normal Individuals

Chapter 8: Sleep Patterns in Hallucinating PD Patients and in High-Prone Normal Individuals

Chapter 9: Behavioural Cognitive Coping Strategies in Hallucinating PD Patients

[14] The main findings from Chapters 4-8 have formed the basis of an article which has been accepted for publication (Maravic, in press), see Appendix 7.

Chapter 4: Visual Memory and Visual Imagery in Hallucinating PD Patients and in High-Prone Normal Individuals

4.1 Introduction

Following the detailed phenomenology of VH in PD in Chapter 2, it has been suggested that the functioning of the association visual cortex is affected in hallucinating PD patients. The visual system is based on dopaminergic pathways which are impoverished in PD. In addition, age-related vision problems, which are not in themselves sufficient for the generation of VHs in the general population, represent an additional risk factor in PD population. Several authors (Chapman et al., 1999; Diederich et al., 1998; Fenelon et al., 2000; Holroyd et al., 2001; Uc et al., 2005) have suggested that poor visual input affects the early stages of visual processing and the subsequent processing in the visual association cortex. This area has traditionally been associated with higher level processing of visual information and multi-sensory integration. Despite the growing evidence for impaired functioning of the association visual areas in hallucinating PD patients, the functioning of these areas remains poorly investigated.

Two studies have investigated the role of visuo-spatial functioning in hallucinating PD (Barnes et al., 2003; Ramirez-Ruiz, Junque et al., 2007). Both studies suggest dysfunctions of object recognition and visual memory for faces in hallucinating PD patients, which point to a degeneration of the association visual cortex. It can therefore be hypothesized that dysfunctions of the higher level visual processing are implicated in the occurrence of VHs in PD; the same hypothesis which was tentatively put forward in Chapter 2.

The aim of the current study is to further explore the role of a higher level perceptual processing in the generation of VHs in PD, using a well-known, reliable and valid neuropsychological battery. The Cambridge Neuropsychological Automated Testing Battery (CANTAB) is an accurate, sensitive, reliable and well-validated battery assessing a range of cognitive domains (22 tests altogether) such

as visual memory, executive functioning, attention, semantic/verbal memory and decision making and response control (CANTABeclipse, 2006). Importantly, the interpretation of results can be easily understood by a trained assistant. Apart from high measure characteristics, the CANTAB has the advantage of detecting early cognitive changes in different disorders: its tests are language independent and culturally blind, it provides normative data and the touch-screen technology delivers rapid and non-invasive cognitive assessment (ibid).

Visual memory tests from the CANTAB battery have yet to be tested in the PD group in relation to VHs. If hallucinating PD patients perform worse on the visual memory tasks than non-hallucinators, this would point to dysfunctions of such higher level perception processes in the occurrence of VHs in PD. In contrast, similar performance between the two PD groups on this task would support an explanatory model for VHs in PD without inclusion of these visual processing functions. In addition, the results from Chapter 2 suggest that VHs is PD reflect the functional specialization of the visual areas and specific brain areas are sensitive for specific visual memory tasks (see Section 4.2.2); therefore, possible dysfunctions in performance on different tasks of visual memory will contribute to our understanding of which underlying neural mechanisms are likely to be related to VHs in PD.

Another perceptual attribute related to VHs is visual imagery. It is defined as the degree of similarity of a mental image to actual perception; the more vivid the image, the closer the experience is to an actual perception of sensory input (Aleman et al., 1999). In contrast to higher level perceptual processing, visual imagery correlates with fMRI activity in the early visual cortex (Amedi, Malach, & Pascual-Leone, 2005; Cui, Jeter, Yang, Montague, & Eagleman, 2007) and frontal lobe (Ishai, Ungerleider, & Haxby, 2000). As discussed in Chapter 2, the high incidence of age-related visual abnormalities in an already compromised dopaminergic retinal system, could suggest that the visual input projection to the primary visual cortex is suboptimal and would manifest itself in a dysfunction of early visual processing (e.g., visual imagery). To date, only one study has addressed the issue of visual imagery in VHs in PD (Barnes & L Boubert, 2008), which found that hallucinating

and non-hallucinating PD patients did not differ in their imagery capabilities; however, hallucinating PD patients expressed a higher tendency to report imaged stimuli as percepts. Hence, the role of visual imagery in the generation of VHs remains unclear and future studies are warranted to address the role of visual imagery in their occurrence.

Stemming from the continuum hypothesis, the role of visual memory and visual imagery might not only be implicated in a well known neurological disorder, characterized by VHs, but also in the normal population who are high-prone to having hallucinatory-like experiences. Currently, no studies have addressed the role of visual memory in high-prone individuals; therefore, the present study will pioneer this research. Visual imagery studies from the normal population have detailed contradictory results: some authors report that visual imagery is related to the occurrence of VHs, and some find no relation between visual imagery and occurrence of hallucinations (Aleman et al., 1999; Aleman et al., 2000; Lopez-Rodrigo et al., 1997).

The aim of the present study is to examine whether VHs in PD and hallucination-proneness in the normal population arise from degradation of visual memory and/or altered visual imagery. The results will provide a line of evidence as to whether these visual functions can be considered as necessary factors in the hypothetical model of the occurrence of VHs in PD and hallucination-proneness in the normal population.

4.2 Methods

4.2.1 Participants

PD Group

10 PD patients with VHs and 20 PD patients without were recruited for the visual memory and visual imagery study. All patients were members of the PD societies in

the UK, with normal hearing and normal or corrected-to-normal vision. A criterion for eligibility was a clinical diagnosis of PD as assessed by their GPs, and the exclusion criterion were a moderate or severe stage of dementia, confirmed by the carers of the PD patients, and the loss of independent maintenance of daily living activities, also reported by the carers. The independent variables (as justified in Section 1.6) were the same as stated in Chapter 2 (Section 2.2.1): age, amount of daily levodopa medication and the use of any other medication, years since their diagnosis, side of the body more affected by PD, the presence/absence of migraine, the presence/absence of ocular pathology (not including correction glasses) and HY motor disability stage. As far as the assessment of vision is concerned, patients were asked if they are wearing glasses, and if so they were asked to use them during the testing. Further, and as described in Chapter 2, patients were asked if they have any additional ocular pathology or if they have ever consulted a doctor because of their vision problems (e.g., double vision, cataract, loss of focus, conjunctivitis, etc.). However, no formal assessment of patents' visual acuity was taken.

Demographics of hallucinating and non-hallucinating PD patients are summarised in Table 4.1. The criteria for grouping patients as hallucinating PD patients were recurrent VHs in the past month. 1 patient had VHs once a week, 7 had them 2-5 times a week, and 2 patients had VHs more than 5 times a week. 20 participants who have never experienced VHs were grouped as non-hallucinating PD patients.

Table 4.1. Participants' demographics.

	Hallucinating PD patients	**Non-hallucinating PD patients**	**Control group**	**Normals – high-prone**	**Normals - low-prone**
N	10 (6 male)	20 (15 male)	11 (4 male)	16 (4 male)	12 (4 male)
Age	67.1 (6.9)	71.4 (7.8)	70.3 (4.5)	21.1 (3.6)	21.6 (3.5)
Years since diagnosis	9.4 (5.4)	5.9 (5.8)	-	-	-
Levodopa (mg)	523.1 (278.1)	477.3 (286.3)	-	-	-
HY	2.1 (1.06)	2.1 (1.08)	-	-	-

Data (except number of participants) are presented as means (±standard deviations). HY refers to the Hoehn-Yahr disability scale (1967).

Control Group

For the visual imagery tasks, 11 age-matched control participants (see Table 4.1) were contacted on a snowball basis[15]. All participants had normal hearing and normal or corrected-to-normal vision. The exclusion criterion was a history of psychiatric or neurological disorders.

The CANTAB normative database was created with over 3000 control subjects (aged 4-90) who participated in various research studies, most being English-speaking UK residents (CANTABeclipse, 2006). Apart from age, the CANTAB battery also offers comparison depending on gender and the NART estimated IQ. The exact number of normative controls varies according to the CANTAB tasks, as well as on the age-range, and is presented in Table 4.2. The numbers of the normative database participants vary because they come from control data from a variety of studies, the total of could not really be expected to distribute evenly over the age groups. The numbers are different because new measures were added at different stages in the development of the battery. As it can be seen from Table 4.2, the number of normative database is extensive; for this reason it was utilised rather than collecting new data from age-matched participants. New collection would supply lower numbers than the CANTAB can provide, and it is therefore more reliable source of comparison than collecting new data.

Table 4.2. Number of normative controls extracted for the CANTAB analysis.

	Age-range		
	50-59	60-69	70-79
DMS	37-124	34-411	34-408
PAL	52-135	88-445	109-462
PRM	87-394	30-400	87-394
SRM	88-133	31-401	88-394
IED	38-96	60-158	53-171
SOC	80	179	187
SWM	80	63-183	66-190

[15] A technique, where the current study participants recruit future participants from among their acquaintances.

Results were compared as closely as possible to the participants' age range, namely 50-59, 60-69 and 70-79. Therefore, a performance of a 72 year old PD patient was compared to the database of healthy volunteers aged between 70 and 79.

Apart from age-range and gender, the normative database of CANTAB also offers the possibility of comparing the data from participants of the same IQ range (as assessed by the NART); however, this was not taken into account in the current studies. The implications of not including NART are discussed in the limitations section (see Section 4.4.1).

Performance of CANTAB tasks was presented as the standard z-score that compared each patient with the mean performance of healthy subjects matched by age and sex. The CANTAB program was used to calculate z-scores on the basis of the extensive normative database included in CANTAB. A positive value indicates better than average performance and a negative value indicates poorer than average performance.

High and Low-Prone Normal Individuals

12 individuals, low-prone to experience VHs (low-prone individuals) and 16 individuals, high-prone to experience VHs (high-prone individuals, see Table 4.1) were recruited for the study (see Appendix 8). They were all undergraduate students at Oxford Brookes University with normal hearing and normal or corrected-to-normal vision. Exclusion criterion was a history of psychiatric or neurological disorder. As in Chapter 3 (see Section 3.2.1), the following independent variables were collected in the present study: age, gender, handedness and the presence/absence of dyslexia. The students received a compensation for their participation. There were no drop outs.

4.2.2 Assessments

CANTAB Visual Memory Tests[16]

The CANTAB was originally devised to assess cognitive function in elderly and patients with dementia (Robbins et al., 1994), but quickly began to be used in the analysis of cognitive function in a range of adult neuropsychiatric syndromes, following drug treatments in healthy volunteers, and also in a neurodevelopmental context (Lee, Owen, Rogers, Sahakian, & Robbins, 2000). Two main guiding principles have been to use some tests that can be related to the extensive neuropsychological literature in animals and human participants and to employ tests that can be broken down into their discrete cognitive components in order to define more readily which functions are impaired and which are spared, and thus the overall specificity of any deficits (ibid).

Visual memory tasks of the CANTAB battery include the following four tasks: Delayed Matching to Sample task (DMS), Paired Associated Learning (PAL), Pattern Recognition Memory (PRM) and Spatial Recognition Memory (SRM).

Delayed Matching to Sample (DMS)

DSM is a test of immediate and delayed perceptual matching. In this task, a participant is presented with a stimulus. Next, four stimuli (of which one is the same as the original stimulus and three are distractors) appear, either simultaneously with the original stimulus or with a delay of 4 or 12 seconds (Figure 4.1). The participants are instructed to indicate when they recognise the target stimulus among the distractors as quickly and accurately as possible. Administration time is approximately 10 minutes. This test is primarily sensitive to damage in the medial temporal lobe area, with some input from the frontal lobes (CANTABeclipse, 2006). The DMS test of visual recognition memory is derived

[16] The CANTAB battery and advice on its administration and analysis were provided by Dr Zola Mannie and Dr Catherine Harper, Department of Psychiatry, University of Oxford.

from an analogue paradigm used with monkeys (Mishkin, 1982; Passingham, 1985) and the results showed that the prefrontal lesions in monkeys impair performance both at short delays and in a simultaneous condition. The neural substrates include lesions to different regions of the temporal lobes, the midline thalamic nuclei, and the ventromedial prefrontal cortex (Murray, 1992; Owen, Sahakian, Semple, Polkey, & Robbins, 1995). Sahakian et al. (Sahakian et al., 1988) found deficits of delayed matching in patients with Alzheimer's Disease, whereas PD patients showed deficits in both simultaneous and delayed condition.

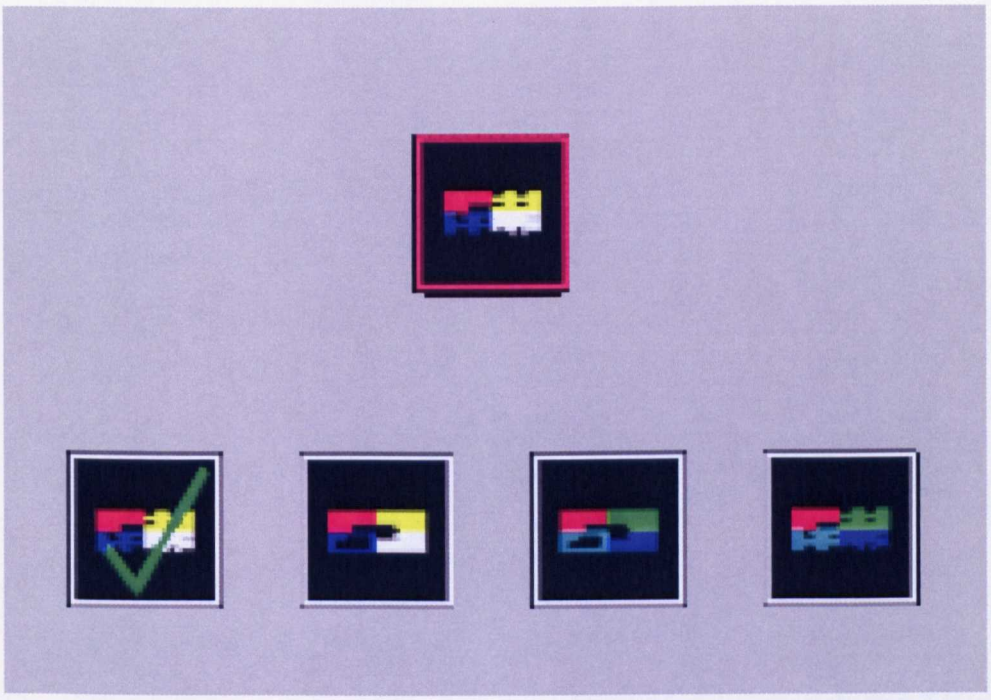


Figure 4.1. An example of the DMS task.

DMS has the following outcome measures:

a) Percent of correct simultaneous answers: This measure reports, as a percentage, the number of occasions in which the participant selected the correct stimulus in trials when the stimulus was left in view whilst the target stimulus and the three distractors were simultaneously presented.

b) Percent of all correct answers: This measure reports, as a percentage, the number of occasions in which the participant selected the correct stimulus in trials

when the target stimulus and the three distractors had been hidden, with delays of 0, 4 and 12 seconds. The percentage of correct solutions for all delay conditions gives a good overall impression of visual memory ability, when compared with the percentage of correct solutions for the simultaneous condition. The discrepancy between percent correct (simultaneous) and percent correct (all delays) indicates the increased memory load of delay conditions.

c) Probability of making a double error: This measure reports the probability of a double error - an error occurring when the previous trial was responded to incorrectly. Mitchell and Dalrymple-Alford (2006) suggested that larger thalamic lesions would have a temporary effect on spatial working memory, and only in terms of double errors. Higher amount of double errors in hallucinating PD patients and/or in high-prone normal individuals would therefore reveal poorer performance on spatial working memory and more extensive thalamic lesions in these groups.

Paired Associates Learning (PAL)

PAL assesses episodic visual memory and new learning. In this task, a participant is presented with six or eight boxes, which are opened (and then closed) in a randomized order. One or more of the boxes contain a pattern. The patterns shown in the boxes are then displayed in the middle of the screen, one at a time, and the participant must touch the box where the pattern was originally located. If the participant makes an error, the boxes are opened again to remind the participant of their locations. When the participant gets all the locations correct, they proceed to the next stage. There are five stages with a different number of patterns (one, two, three, six or eight). The stages always start with the easiest one (a stage with only one pattern) and then progress in difficulty. If the participant cannot complete a stage correctly, the test terminates. Administration time is approximately 10 minutes. This test is primarily sensitive to changes in medial temporal lobe functioning (CANTABeclipse, 2006).

PAL has the following outcome measures:

a) Total number of errors: This measure reports the total number of errors, with an adjustment for each stage not attempted due to previous failure. This adjustment is calculated by summing the number of patterns not attempted and subtracting the number of patterns divided by the number of boxes from it. This result is then multiplied by the number of trials allowed for the stage (ten in the clinical mode). For aborted runs, the adjustment is based on the stages, trials and responses not attempted due to the abort, with each missed response giving rise to an adjustment of 1 – 1 / number of boxes.

b) Average trials for a successful solution: This is calculated by calculating the total number of trials required (maximum score = 10 trials per stage) to locate all the patterns correctly in all stages attempted, and dividing the result by the number of successfully completed stages.

c) Average number of completed stages: This is a key indicator of the participant's overall success, recording how many stages were successfully completed. When analysing other outcome measures from PAL it is crucial that analyses are conducted with reference to the number of stages completed. Clearly, a participant that fails prior to the successful completion of the 8-pattern stage will have had less opportunity to make errors than a participant who completes the test.

Pattern Recognition Memory (PRM)

PRM is a test of visual pattern recognition memory in a 2-choice forced discrimination paradigm. In this task, a participant is presented with a series of 12 patterns, one at a time, in the centre of the screen. These patterns are designed so that they cannot easily be given verbal labels. In the recognition phase, the participant is required to choose between a pattern they have already seen and a novel pattern. In this phase, the test patterns are presented in reverse order to the original order of presentation. Administration time is approximately 10 minutes. This test is sensitive to dysfunction in medial temporal areas of the brain and relatively insensitive to dysfunction in the frontal lobe (CANTABeclipse, 2006).

The following outcome PRM measure was taken:

Percent of correct answers: This is the number of correct responses, expressed as a percentage. This is a good indicator of overall performance on a test of visual short-term recognition memory, which is impaired in disorders such as mild to moderate Alzheimer's disease (Swainson et al., 2001).

Spatial Recognition Memory (SRM)

SRM is a test of spatial recognition memory in a forced-choice paradigm. In the presentation phase, a white square is shown on the screen in five different locations. Each appearance of a square marks a location on the screen, which the participant must later remember. In the recognition phase, the square reappears in the same five locations as in the presentation phase, in the reverse order to the original order of presentation. On each appearance, it is paired with an identical distractor square in a location not used in the presentation phase. The participant must touch the square in the location that has appeared before, whilst ignoring the distractor. This test is primarily sensitive to dysfunction in the frontal lobe, and relatively insensitive to temporal lobe damage (CANTABeclipse, 2006). Increased activation in right parahippocampal gyrus during the PAL task have been shown in neuroimaging studies in healthy volunteers (Maguire et al., 1998; Owen, Doyon, Petrides, & Evans, 1996). Furthermore, animals (Miyashita, Kameyama, Hasegawa, & Fukushima, 1998) and humans (M. L. Smith & Milner, 1981) with temporal lobe lesions show impairments on the PAL task. The PAL task therefore requires intact medial temporal lobe, and more specifically, hippocampi (Wood et al., 2002). Administration time is approximately 10 minutes.

The following outcome SRM measure was taken:

Percent of correct answers: This is the number of correct responses, expressed as a percentage.

Visual Imagery

The Vividness of Visual Imagery Questionnaire (VVIQ) (Marks, 1973) is a subjective measure of the vividness of visual imagery (see Appendix 9). It is an extension of the visual subscale of the Betts scale (Richardson, 1969). VVIQ consists of 16 descriptions that are rated on a 5-point Likert-scale:

The image aroused by an item might be:

1- "Perfectly clear and as vivid as normal vision",

2 – "Clear and reasonably vivid",

3 – "Moderately clear and vivid",

4 – "Vague and dim", or

5 – "No image at all, you only 'know' that you are thinking of an object".

Four questions refer to imagining a (familiar) person, and twelve refer to imagining a scene (a rising sun, a familiar shop, a country scene). Participants imagine the scene with their eyes open, and then rate the items. Next, they try to imagine the same scene, but this time with their eyes closed. Participants again rate the vividness of the imagined scene. The questionnaire is scored by summing the ratings. Lower scores indicate more vivid imagery. Cui et al. (2007) demonstrated that subjective vividness (measured by the VVIQ) is correlated with the early visual cortex activity, as measured by the fMRI.

4.2.3 Procedure

PD Group

The study was introduced verbally and information sheets were given out at the monthly meetings in various PD societies throughout the UK between April and May 2008. Potential participants were encouraged to participate regardless of whether they had vision/perception problems and VHs or not. Those who decided to take part contacted the researcher at the end of the meeting. Patients individually

agreed on a convenient meeting time with the researcher either in their own homes or at the society meeting venue. After a brief description of the aim of the study, the methodology and the debriefing preference, participants were encouraged to ask further questions before starting the experiment. Participants were reminded to notify the researcher if they felt tired during the testing. This is important because when dopaminergic medications start wearing off (the "off-phase") PD patients get stiff muscles, which makes their movement slow and tiresome (see Section 1.1). The PD patients were also asked how they felt before the beginning of each task and, when necessary, testing was temporarily stopped so they could take their prescribed medication (2 cases). The visual memory tasks from the CANTAB battery and the visual imagery questionnaire were then administered and completed in a single session lasting approximately one hour. All participants completed every stage of the research. Debriefing took place at the end of the study at the PD society meetings, patients' homes or, if preferred, sent by post.

Control Group

The VVIQs were distributed to the age-matched control group. All participants were given a stamped envelope to send it back to the experimenter once they filled in the questionnaires. Debriefing was carried out either in person, by phone, or post depending on the participant's preference.

High and Low-Prone Normal Individuals

277 students without any history of neurological or psychiatric illness filled in the Hallucination-Proneness Questionnaire (HQ, see Section 3.2.1). The top 5% (i.e., the high-prone individuals who scored 17 points and above) and the bottom 5% of the visual scale distribution of the HQ (i.e., the low-prone individuals who scored 4 points and below) were invited to participate in a perception and visual imagery study. 12 low-prone and 16 high-prone normal individuals agreed to participate in the study. After a brief description of the aim of the study, the methodology, and the

debriefing options, participants were encouraged to ask further questions and were reminded to notify the researcher if they needed a break during the testing for any reason. Normal individuals from the present and all subsequent studies were then asked to read and sign the informed consent form (Appendix 10) in accordance with the university research ethics. The visual memory tasks from the CANTAB battery and the visual imagery questionnaires were then administered, and completed in a single session lasting approximately one hour. All testing was completed in February 2008. A debriefing sheet was sent to the participants who expressed a wish to receive it.

4.2.4 Statistical Analysis

Statistical analysis was performed using SPSS for Windows version 15.0 (SPSS Inc., Chicago, IL). Descriptive statistics were used to describe the profile of hallucinating and non-hallucinating PD patients and of high and low-prone normal individuals. The demographics and the CANTAB features of hallucinating and non-hallucinating PD patients and of high and low-prone normal individuals were compared using t-tests for independent samples. The CANTAB tasks are provided with a normative database; the standardised scores were therefore used as a comparison for both PD groups.

4.3 Results

4.3.1 Demographics

Independent sample t-tests showed no difference between hallucinating and non-hallucinating PD patients on any of the following independent variables: age, gender, daily dopamine dosage, HY disability stage, years since diagnosis, side of

body more affected by PD, migraine, and any other concurrent illness (all p-values > .182). Further, there was no interaction between the presence of VHs and ocular pathology (F=1.212, df=1,20, p=.284). The two PD groups only differed in the presence of VHs in the hallucinating group (see Table 4.1).

Likewise, using the independent t-test, there was no difference between high and low-prone participants in age, gender, vision and hearing problems, dyslexia or handedness (all p-values > .397).

4.3.2 CANTAB Visual Memory Task

The results from the CANTAB Visual Memory tasks and the statistical differences between hallucinating, non-hallucinating and the control group are summarised in Table 4.3. Hallucinating PD patients significantly differed from non-hallucinating PD patients on some measures of the DMS task (percent of correct delayed answers and probability of a double error) in the absence of differences between the two PD groups on other measures (see Table 4.3).

Table 4.3. Visual memory results: Means, SDs, and t-tests results.

CANTAB Visual Memory Test	**Hallucinators PD patients**	**Non-hallucinating PD patients**	**t**	**df**	**p**
DSM					
Percent of correct delayed answers - *absolute values*	48.25 (19.157)	74.85 (15.009)	-3.036	17	**.007**
- *standardized value*	-2.87 (1.764)	-0.43 (1.380)			
Percent of correct simultaneous answers					
- *absolute values*	76.43 (25.935)	90.00 (10.954)	-1.246	17	.230
- *standardized value*	-1.78 (2.734)	-.34 (1.155)			
Probability of a double error					
- *absolute values*	.41 (.212)	.19 (.135)	2.538	17	**.028**
- *standardized value*	-2.07 (1.516)	-.49 (.963)			
PAL					
Total number of errors					
- *absolute values*	81.57 (91.782)	74.15 (69.389)	.065	19	.949
- *standardized value*	.60 (.531)	.10 (.500)			
Average trials for a successful solution					
- *absolute values*	2.91 (2.380)	2.16 (.583)	1.171	19	.256
- *standardized value*	.62 (.628)	.26 (.474)			
Average number of completed stages					
- *absolute values*	6.00 (2.887)	6.69 (1.652)	-.462	19	.649
- *standardized value*	.27 (.040)	.14 (.540)			
PRM					
Percent of correct answers					
- *absolute values*	75.00 (15.591)	76.79 (17.428)	-.317	20	.755
- *standardized value*	-.88 (1.427)	-.72 (1.594)			
SRM					
Percent of correct answers					
- *absolute values*	71.88 (12.230)	70.83 (10.408)	.174	19	.864
- *standardized value*	-.60 (1.087)	-.70 (.923)			

Data are presented as means (±standard deviations). CG = control group

Table 4.4. Interaction between the presence of VHs and ocular pathology for all visual memory tasks.

CANTAB Visual Memory Test	Mean Square	df	F	Sig.
DSM				
Percent of correct delayed answers	1.818	1	1.110	.315
Percent of correct simultaneous answers	1.312	1	.333	.576
Probability of a double error	.133	1	.107	.750
PAL				
Total number of errors	.207	1	.767	.431
Average trials for a successful solution	.206	1	.799	.422
Average number of completed stages	.059	1	.134	.733
PRM				
Percent of correct answers	.396	1	.166	.691
SRM				
Percent of correct answers	1.046	1	1.133	.312

Table 4.4 shows there is no interaction between the presence of VHs and ocular pathology on none of the visual memory tasks between hallucinating and non-hallucinating PD patients.

Table 4.5. Analysis of Variance between Group and Condition.

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	7246.452[a]	3	2415.484	7.755	.000
Intercept	201796.079	1	201796.079	647.860	.000
Group	2756.532	1	2756.532	8.850	.005
Condition	4393.439	1	4393.439	14.105	.001
Group x Condition	406.629	1	406.629	1.305	.261
Error	10590.349	34	311.481		
Total	232501.277	38			
Corrected Total	17836.801	37			

"Group" refers to hallucinators and non-hallucinators and "condition" refers to simultaneous and delayed condition (0, 4 or 12 ms delay).

Further, a 2 x 2 (hallucinators/non-hallucinators x simultaneous/delayed condition) between subjects factorial ANOVA was conducted on the test of delayed matching to sample (DMS) (see Table 4.5). There was a significant main effect for group (hallucinators/non-hallucinators), $F(1, 34) = 8.85$, $p = .005$. Non-hallucinators ($M = 82.42$, $SD = 14.985$) performed overall better than hallucinators ($M = 65.17$, $SD = 26.286$). There was also a significant main effect for condition (simultaneous/delayed), $F(1, 34) = 14.105$, $p = .001$. Participants solved the simultaneous condition ($M = 85.52$, $SD = 18.626$) significantly better than the delayed condition ($M = 64.79$, $SD = 20.424$). There was, however, no significant interaction between group and condition, $F(1, 34) = 1.305$, $p = .261$. Hallucinators performed consistently better on the simultaneous condition ($M = 76.43$, $SD = 25.935$) than the delayed condition ($M = 48.25$, $SD = 19.157$). Likewise, non-hallucinators performed consistently better on the simultaneous condition ($M = 90.00$, $SD = 10.954$) than the delayed condition ($M = 74.85$, $SD = 15.009$) (see also Table 4.3).

Finally, no statistically significant differences in visual memory were found between high and low prone normal individuals on any of the CANTAB Visual Memory tasks (all p-values > .209, see Table 4.6).

Table 4.6. Visual memory results: Means, SDs, and t-tests results.

CANTAB Visual Memory Test	**High-prone Individuals**	**Low-Prone Individuals**	**t**	**df**	**p**
DSM					
Correct delayed answers	.11 (.11)	.09 (.08)	-.481	26	.634
Correct simultaneous answers	.06 (.25)	.08 (.29)	.204	26	.840
Probability of a double error	.03 (.07)	.06 (.12)	.739	26	.467
PAL					
Total number of errors	4.88 (3.88)	7.83 (5.42)	1.69	26	.104
Average trials for a successful solution	10.31 (1.40)	10.15 (3.43)	-.172	26	.865
Average number of completed stages	8.00 (.00)	8.00 (.00)	a	a	a
PRM					
Correct answers	20.75 (3.73)	19.17 (2.69)	-1.244	26	.224
SRM					
Correct answers	16.31 (2.09)	15.67 (2.90)	-.686	26	.499

a = t-test could not be computed because the standard deviations of both groups are 0.

4.3.3 Visual Imagery

Table 4.7 illustrates the descriptive statistics for the VVIQ for the PD, control and student groups. When hallucinating and non-hallucinating PD groups and the control group were compared on the vividness of visual imagery task, there were no significant differences between the groups on any measures of the task (all p-values > .480). Similarly, no statistically significant differences on visual imagery were found between high and low-prone normal individuals (all p-values > .231).

Table 4.7. Visual imagery results: Means and SDs.

Group	M (SD)
Hallucinating PD	2.35 (.814)
Non-hallucinating PD	2.26 (.762)
Control group	1.87 (.697)
Normals - high-prone	2.11 (.912)
Normals - low-prone	2.30 (1.027)

4.4 Discussion

The aim of the study was to examine whether VHs in PD and proneness to VHs in the normal population arise from degradation of visual memory and impaired visual imagery, and in so doing, expand the current theoretical understanding of the occurrence of VHs in PD and proneness to VHs in the normal population. To this end, visual memory tests from the CANTAB battery and the vividness of visual imagery questionnaire were used in both PD and the normal groups.

Hallucinating and non-hallucinating PD patients did not differ in a number of independent variables that were taken into account, such as age, gender, daily levodopa dose, years since diagnosis, side of body more affected by PD, migraine, vision problems or any other concurrent illness (see Table 4.1). Similarly, high and low-prone normal individuals were similar in terms of age, gender, handedness, dyslexia, and vision and hearing problems. Therefore, given the homogeneity of the demographic characteristics of both PD patients and the normal individuals, any

perceptual and imagery differences between the groups on the CANTAB tasks were hypothesised to be related to VHs or to the proneness to VHs in the hallucinating PD group and in the high-prone normal group, respectively. Apart from the homogeneity of the demographic characteristics, both PD and the normal groups were recruited within the same sample group; hallucinating and non-hallucinating PD groups were recruited from the same PD societies and high and low-prone groups were recruited from the healthy young student population. Importantly, none of the PD patients was diagnosed with dementia; therefore, possible differences in cognitive functioning in the hallucinating PD group could not be attributed to it. Further, the mean HY score (Hoehn & Yahr, 1967) in both PD groups was 2.10 (SD=1.0), indicating a relatively early (motor) stage of PD (see Table 4.1). An intact cognitive performance was therefore expected in both PD and normal groups, and all differences in CANTAB performance could be attributed to VHs in the PD hallucinating group or to the proneness to VHs in the high-prone normal group.

Examination of the differences between hallucinating and non-hallucinating PD patients and the age-matched control group (as indicated by the standardised scores; see Table 4.3) revealed inconsistent results between the four visual memory tasks. As reported by several other studies (Owen et al., 1993; Owen et al., 1995; Sahakian et al., 1988), PD patients show impaired performance on some measures of the visual memory tasks. On three visual memory tasks (PAL, PRM and SRM), there was no statistically significant difference in performance between the three groups. Further, hallucinating PD patients scored significantly lower on the DMS task than the non-hallucinating counterparts or control group. These disparate findings suggest that visual memory comprises of functionally and neurologically different elements and is not a unitary concept.

Further, while the PAL and the PRM are sensitive to dysfunction in medial temporal lobe, and the SRM to dysfunction in the frontal lobe (CANTABeclipse, 2006), the DMS combines simultaneous sensitivity for temporal and frontal lobe dysfunctions (CANTABeclipse, 2006; Eskandar, Optican, & Richmond, 1992; Miller & Desimone, 1994). Hallucinating PD patients displayed significantly lower on the DMS compared with non-hallucinating patients and the control group in the

absence of differences on the PAL and the PRM. It could thus be hypothesised that a combined effect of temporal and frontal dysfunction is more pronounced than temporal or frontal dysfunction alone in hallucinating PD patients. The hypothesis that the temporofrontal dysfunction is implicated in hallucinating PD patients is consistent with evidence from an autopsy (Harding et al., 2002) and an fMRI study (Stebbins et al., 2004). Harding et al. (2002) found a higher density of Lewy bodies in both the temporal and frontal regions in the hallucinating PD patients. The only fMRI study to date that combines the role of both temporal and frontal lobe in occurrence of VHs in PD (Stebbins et al., 2004) has suggested that a pattern of relative hyperactivity of the frontal cortex in conjunction with decreased cortical activation in the posterior occipoparietal areas may play a role in the pathophysiology of VHs. The present study is the first to provide behavioural evidence of involvement of both systems simultaneously, as a specific dysfunction of the visual memory. There is therefore a need to further investigate the role of frontal lobe functioning in VHs in PD, both through the executive functioning and personality components, which will be addressed in Chapters 6 and 7, respectively.

Finally, hallucinating PD patients showed significantly poorer performance than non-hallucinating patients on the simultaneous as well as the delayed matching to sample task (measures of the DMS; please refer to Table 4.3). In addition, there was no interaction between group (hallucinating and non-hallucinating PD patients) and the condition (simultaneous and delayed) (see Table 4.5). Non-hallucinating PD patients consistently performed better than their hallucinating counterparts, and both groups consistently performed better on the simultaneous condition. Several authors (Chapman et al., 1999; Diederich et al., 1998; Fenelon et al., 2000; Holroyd et al., 2001; Uc et al., 2005) suggested that the poorer performance in the hallucinating PD patients might be related to perceptual deficits, as hallucinating PD patients in their studies suffered from poorer visual acuity than their non-hallucinating counterparts. However, the results from the present study (see Tables 4.4 and 4.5) show that both groups performed better on the simultaneous condition. These results would suggest that the significantly poorer performance in delayed condition reflects a failure in the visual memory, rather than perceptual

dysfunctions. However, the hallucinating PD patients performed significantly worse than their non-hallucinating counterparts, therefore, it is important to acknowledge that the results do not invalidate the possibility that perceptual problems might also be implicated in the hallucinating PD patients. The limitation of the present study, however, is that visual acuity has not been assessed systematically, and the impact of visual acuity could not be addressed satisfactorily. In order to establish the extend to which perceptual problems could potentially affect the performance of the hallucinating PD patients, future studies need to take a multidisciplinary approach, addressing the role of ocular pathology with appropriate ophthalmologic measures.

In line with the continuum hypothesis, stating that hallucinations are expressed in different degrees in the general population, the aim of the present study was to explore the performance on the CANTAB visual memory tasks in hallucinating PD patients and high-prone individuals. In contrast to the PD patients, no differences in performance on any visual memory tasks were observed between high and low-prone individuals (see Table 4.6). The results of the present study therefore give evidence that higher level perception processing is intact in high-prone individuals and can therefore not be implicated in the hypothetical model of proneness to VHs in the normal population. These results are therefore not in agreement with the continuum hypothesis, as dysfunction in visual memory has been showed in hallucinating PD patients, but not in the high-prone normal individuals.

However, it can be argued that the CANTAB battery shows impaired performance of a well extended pathology (such as PD), and that pathology in high-prone normal individuals is too subtle to be observed by the use of behavioural methodology. Therefore, a study investigating underlying neural mechanisms using a neurophysiologic methodology is warranted and will be addressed in the following chapter (see Chapter 5).

Apart from investigating visual memory, the study also aimed to explore how (if at all) visual imagery relates to VHs in PD and in high-prone individuals. The present study found no differences between the groups on any measures of the visual imagery (for faces and objects/scenes, and with open and closed eyes; see

Table 4.7). These results are consistent with the study of Barnes et al. (2003) and suggest that the visual imagery of hallucinating PD patients and high-prone individuals is intact, and probably not involved in the occurrence of VHs.

Despite non-significant findings in the visual imagery task, the hypothesis that top-down processing, especially rich fantasy and vivid imagination, may be connected to the generation of VHs in PD and to higher hallucination-proneness in the normal population is not called into question, as Stebbins et al. (2004) suggest that VHs are indeed evoked by internally driven frontal lobe functioning. Therefore, chapters 6 and 7 will explore whether executive and personality factors could be potential attributes for VHs in PD and hallucination-proneness in the normal population.

4.4.1 Limitations

Robbins et al. (2007) acknowledge that the main caution regarding the CANTAB battery is not to assume there is a one way relationship between a deficit on any CANTAB test and brain damage to an anatomically defined region. They emphasise that many brain regions are interconnected in neural networks networks, meaning that performance on any task may be impaired due to lesions in widely distributed brain structures. The challenge in the light of the present study is to understand which distinct types of information processing are implicated in those PD patients who experience VHs. Such studies would aid the current understanding of what are the underlying mechanisms for the occurrence of VHs in PD.

Further, although hallucinating PD patients had normal or corrected-to-normal vision and claimed they saw the patterns well, they scored significantly lower than their non-hallucinating counterparts and the control group on the DMS task of the CANTAB. The results from the present study suggest that the poorer performance in the hallucinating PD patients is more likely to be due to the memory, rather than perceptual, impairments (see Tables 4.4 and 4.5). However, given the crude assessment of visual acuity in the present study, it cannot be entirely ruled out that visual acuity in hallucinating PD patients is impaired and, consequently, the poorer

performance of the hallucinating PD patients arises from lower visual acuity. However, if hallucinating PD patients really have reduced visual acuity, it remains unclear why the performance would be worse only on one, but not the other visual memory tasks. Therefore, future studies are warranted to match the hallucinating and non-hallucinating sample according to their visual acuity, using a more precise ophthalmologic measure of visual acuity. A multidisciplinary approach including an optometrist would be therefore highly useful in future studies on hallucinations in PD when the emphasis is based on the functioning of the visual system, such as in the present study where visual memory and visual imagery were assessed.

4.4.2 Conclusions

In summary, DMS was the only visual memory test where hallucinating PD patients differentiated from their non-hallucinating counterparts. The finding points to the simultaneous aberrant functioning of both visual and frontal areas in hallucinating PD patients, and is supported by the neuroimaging study. Thus, these areas must play a role in the occurrence of VHs in PD. However, no such differences were found between high and low-prone normal individuals, and the results are therefore not in agreement with the continuum hypothesis, as there is a specific dysfunction present in hallucinating PD patients, but not in the high-prone normal individuals. However, although no difference in visual memory was found between high and low-prone individuals, the results could reflect intact behavioural, but not necessarily intact neural, functioning. An electrophysiological study investigating the role of the visual system will be carried out (see Chapter 5). The results from the present study also suggest that dysfunctions of higher level perceptual processing may be related to the frontal lobe functioning. Similar to what was proposed in Chapter 2, top-down processing may be triggered in the system due to the impoverished visual processing, and hence there is a higher chance of hallucinations occurring. VHs in PD and hallucination-proneness in the normal population will be examined in relation to frontal functioning, namely executive functions and personality factors (Chapters 6 and 7, respectively).

Chapter 5: Early Visual Processing Components in High-Prone Normal Individuals: an EEG Study [17]

5.1 Introduction

The results from the perception study (see Chapter 4) showed evidence that specific disruptions in visual memory are related to VHs in PD, but no such link was found in the high-prone individuals from the normal population. Nonetheless, it has been suggested that proneness to VHs might possibly occur due to impairments in the visual system which are so subtle in nature that they cannot be observed by behavioural testing. Therefore, an electrophysiological or psychophysical testing could serve as a solution to uncover the possible link between proneness to VHs and the visual processing in the high-prone normal individuals.

Numerous studies have found disruptions of early electrophysiological brain responses to external stimuli (also known as event-related potentials or ERPs) in a wide range of psychiatric and neurological conditions, such as schizophrenia (Butler et al., 2008; Campanella, Montedoro, Streel, Verbanck, & Rosier, 2006a; 2004), PD (Kida, Tachibana, Takeda, Yoshikawa, & Okita, 2007), Williams Syndrome and autism (Grice et al., 2001). Since these disorders are frequently accompanied by VHs, it may be the case that the observed modulations of early visual components are expressions by a visual dysfunction, which may in turn facilitate the occurrence of VHs in the patients.

ERPs that have been most commonly linked to face processing are the P1, the N170, and the P2. ERP components are referred to by a preceding letter indicating

[17] The study presented in the current chapter was conducted in collaboration with David Schwartzman (Oxford Brookes University) and Dr Cornelia Kranciocziocz (University of Portsmouth). The results have formed the basis of a joint publication (see Schwartzman, Maravic, Kranczioch, & Barnes, 2008, see Appendix 11). Ksenija Maravič ran the data collection, while David Schwartman analyzed the EEG data and produced the figures. Ksenija Maravič analyzed the behavioural data and assisted in both the statistical analysis of the EEG data and in writing the publication.

polarity followed by the typical latency in milliseconds (Luck, 2005). Thus, the P1 and P2 ERPs components are described as a positive voltage deflection occurring approximately 100 and 200 milliseconds after stimulus onset, respectively, whereas the N170 component describes a negative voltage deflection 170 milliseconds after stimulus onset. In the context of the face perception paradigm, P1 is assumed to reflect the extraction of fine/local information from face stimuli (Herrmann, Ehlis, Ellgring, & Fallgatter, 2005; Liu, Harris, & Kanwisher, 2002), N170 is assumed to reflect face-specific structural encoding (Eimer, 2000), and P2 deeper processing, which is required when ambiguous face stimuli need to be categorized (Latinus & Taylor, 2006).

Following from these studies, VHs are associated with altered visual processing components; if VHs lie on a continuum of severity, then differences in early visual processing components might be evident between high and low hallucination-prone participants. Therefore, the aim of the present study is to investigate the differences in local feature based processing (faces) and holistic processing (Mooney) between high and low-prone individuals using a classic face perception experimental design, which is known to reliably elicit early ERPs (Eimer, 2000; Herrmann, Ehlis, Ellgring, & Fallgatter, 2005). The results will provide evidence if early visual processing components differ in the high and low-prone normal individuals. If that is the case, the disruptions in early processing may serve as a bottom-up process, facilitating the proneness to frequent occurrence of hallucination-like experiences. However, if the disruptions of early processing are not recorded, hallucination-proneness in the normal population is probably attributable to personality related top-down processes.

5.2 Methods

5.2.1 Participants

According to their score on the HQ (see Section 3.2.1), 11 high-prone (8 female, two left-handed, mean age 23.6 years, SD=9.1) and 11 low-prone normal individuals (7 female, one left-handed, mean age 23.4 years, SD=5.0) were recruited in the study. As described in Section 3.2.1, a high total score of the visual scale of the HQ indicates frequent experiences of visual misperception, for example distorted images of people and environment, especially in relation to distortions in lighting, patterns and shapes. High scores do not indicate frank hallucinations. Furthermore, high proneness to visual experiences should not be confused with high ability for visual imagery as there were no significant differences between high and low-prone participants (t=1.079 p=0.309, see Chapter 4) on the Vividness of Visual Imagery Questionnaire (Marks, 1973). All participants were undergraduate students from Oxford Brookes University with normal or corrected-to-normal vision. The exclusion criterion was a history of psychiatric disorder. All students received compensation for their participation.

5.2.2 Stimuli

Stimuli were photographs of faces, Mooney faces[18], and scrambled Mooney faces. Mooney faces are high-contrast pictures of human faces, and scrambled Mooney faces are Mooney faces modified in the Photoshop software until the faces are not recognisable any more (see Figure 5.1). Faces and Mooney faces were presented in either an upright or inverted orientation (see Figure 5.1).

[18] Mooney pictures were kindly provided by Aaron Schurger from Princeton University.

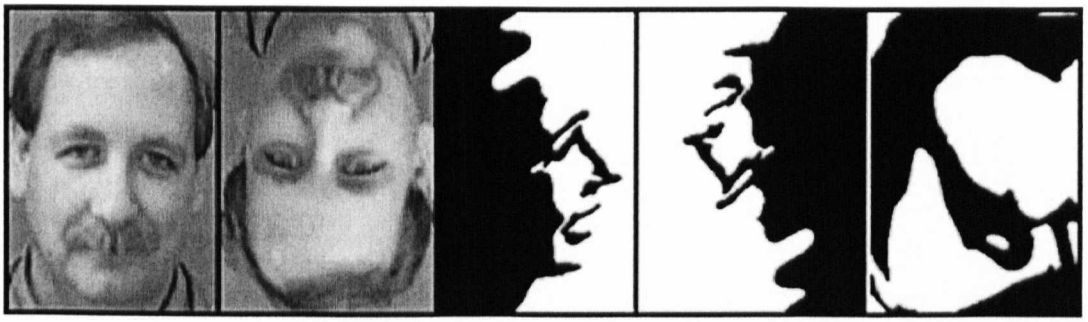


Figure 5.1. Examples of stimuli. L to R: face, face inverted, Mooney, Mooney inverted, and scrambled Mooney face.

The experiment was programmed in the E-Prime experimental operating system software (Psychological software tools, Inc., Pittsburgh, Pennsylvania, USA). All face photographs were matched for luminance and presented in frontal view, with the eyes placed at the centre of the screen. All stimuli where adjusted to maintain identical size (400 x 400 pixels), and occupied approximately 3° × 4.5° of visual angle.

5.2.3 Electroencephalogram (EEG)

Electroencephalography is a technique that records the electrical activity of the brain. Signals are picked up by electrodes placed to the scalp, and are then amplified and filtered, before finally recording on a computer. The EEG does not give information about the structure of the brain (the spatial resolution is low, because the electrical waves are attenuated and distorted by passing through the skull). However, EEG offers excellent information about specific time locked cognitive events (the temporal resolution is high, because it detects changes in electrical activity in the brain on a millisecond time scale).

5.2.4 Recording and Data Analysis

Electrical activity was recorded using an electrical Geodesic Sensor Net with 128 electrodes (Electrical Geodesic inc.) (Tucker, Liotti, Potts, Russell, & Posner, 1994) and was digitized at a rate of 250 Hz. The recording was done with a hardware

band-pass filter of 0.01 Hz to 100 Hz. Before each recording, impedance of all 128 electrodes was kept below 50 kΩ (Ferree, Luu, Russell, & Tucker, 2001). Unsegmented (raw) data were digitally filtered offline using a band-pass of 0.01-30Hz.

For all conditions, target locked epochs (epochs of activity in a time sequence shortly before and after the target is presented) were created for conditions in which participants reported perceiving a face. Each epoch started 100 ms before onset of the target and ended 1000 ms afterwards. The segments were highlighted if they contained eye blinks or movements, as defined by eye channel activity greater than 50 μv. Two data sets (one from a high and one from a low-prone group) were excluded from the final ERPs data analysis due to excessive artefacts. The data were then processed by an ocular artefact reduction technique to correct the eye blinks and eye movements (Gratton, Coles, & Donchin, 1983). If noise occurred in more than 20% of trials on any channel, that channel was excluded from further analysis. Segments were then average-rereferenced (referenced against the mean of all the other channels) and epochs were baseline corrected for the first 100 ms before the onset of the stimulus.

Conditions (face, inverted face, Mooney face, inverted Mooney face, and scrambled Mooney face) were compared between high and low-prone groups by producing t-tests for every 4 ms sample between the two waveforms for the entire epoch. All statistics were processed using the MATLAB software version 7.1. Scripts were adapted from Astle et al. (2006). Two waveforms were considered to be significantly different if the significance was maintained for a minimum of 10 consecutive samples (40 ms). However, two significant points in time were considered to be a continuation of the same difference in amplitude if the gap between the two points was smaller than 10 samples (Astle et al., 2006; Rugg, Doyle, & Melan, 1993).

The following time windows were selected for further analysis over electrode 52 (corresponding to the parietal-temporal junction electrode P3 from the international 10/20 system): 80-130 ms for the P1 component (Herrmann, Ehlis, Ellgring, & Fallgatter, 2005; Liu et al., 2002), 140-170 ms for the N170

(Campanella, Montedoro, Streel, Verbanck, & Rosier, 2006b; Eimer, 2000; Herrmann, Ehlis, Ellgring, & Fallgatter, 2005; Herrmann, Ellgring, & Fallgatter, 2004; Liu et al., 2002) and 200-260 ms for the P2 component (Latinus & Taylor, 2006; Sugase, Yamane, Ueno, & Kawano, 1999). Electrode P3 was selected because it exhibited the maximum significance across all conditions. The peak (maximum value) can occur anywhere within these time windows. Therefore, the adaptive mean algorithm (which finds a peak within a specified time window, and redefines the time window around this peak) needed to be performed. Finally, the mean voltage can be calculated from the new time windows.

The mean adaptive means were used to perform the between group t-tests. Only significant differences are reported.

Latency - The onsets of the P1, N170 and P2 were calculated from the peak amplitude defined by the adaptive mean time window.

5.2.5 Procedure

281 Oxford Brookes University undergraduate students, none of whom had any neurological or neuropsychiatric disorder, completed the HQ. 13 participants with high and 13 participants with low visual scale score of the HQ were invited to participate in the study. There were 4 drop outs; therefore, 11 high and 11 low-prone normal individuals participated in the study.

After a brief description of the aim of the study, the methodology and their task, all participants were encouraged to ask questions and were reminded to notify the researcher if they felt tired or needed to take a break during the testing. After the EEG electrodes were placed on the participants' scalps, participants were seated in an electromagnetically protected cubicle in a dark room, with a computer screen placed approximately 120 cm in front of them. Participants were asked to hold the response box in their both hands.

The participants' task was to first look at the presented image and then indicate whether they perceived the image to be a face or not by pressing the left or right button of the response box, using their left and right index finger. Response

buttons were randomized for each participant. Participants were asked to press the response button as quickly as possible. They were also asked to maintain central eye fixation and to avoid blinking during the picture presentation. However, they could blink when the pictures were not presented.

For each category of stimuli there were one hundred images presented in a random order in 10 blocks of fifty trials (500 stimuli altogether). First, a stimulus was presented for 200 ms. Next, a black screen appeared for 1000 ms. Finally, a response window occurred, lasting up to 5000 ms, in which the participants were asked to press a button indicating whether they perceived the image as a face or not. There was a 1000 ms blank screen before the next trial started.

All testing was completed in November 2006 and lasted approximately one hour.

5.4 Results

5.4.1 Behavioural Results

In 99% of trials for face and inverted face stimuli, both high and low-prone individuals correctly reported seeing a face. Similarly, both groups correctly recognized an image of a face in the Mooney face condition in 92% of the trials. Not surprisingly, the correct identification was much lower in the inverted Mooney face condition, with 58% of trials perceiving an image as a face in low-prone, and 60% of trials in the high-prone group. In the scrambled Mooney condition, low-prone participants reported seeing a face in 20% of trials, and high-prone participants in 26% of trials. None of the behavioural differences between high and low-prone individuals was statistically significant.

5.4.2 Latency Effects

There were no statistically significant differences in the latency effects between high and low-prone individuals for P1, N170 or P2 in any condition.

5.4.3 Amplitude Effects

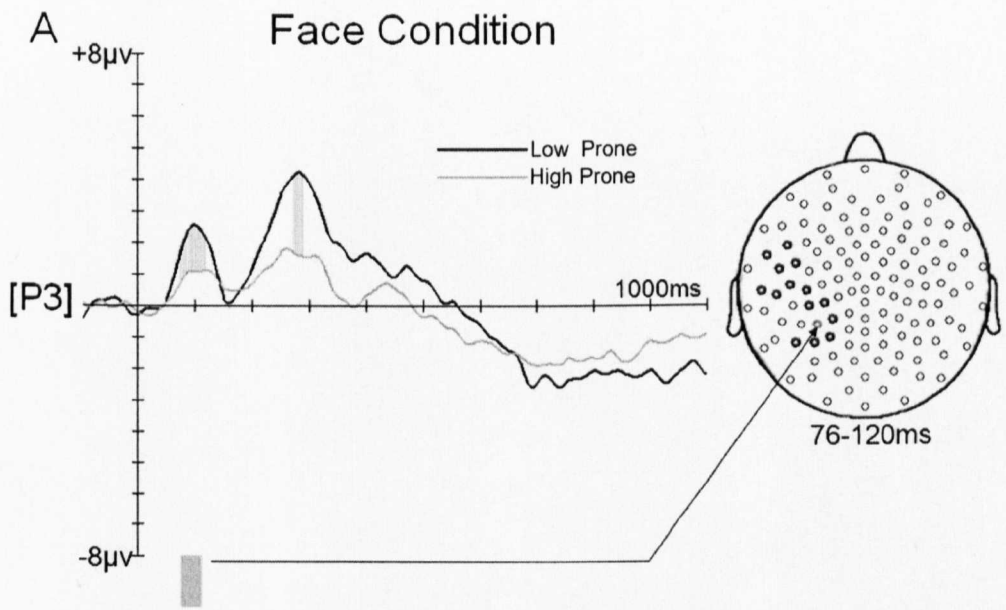
P1 Effects

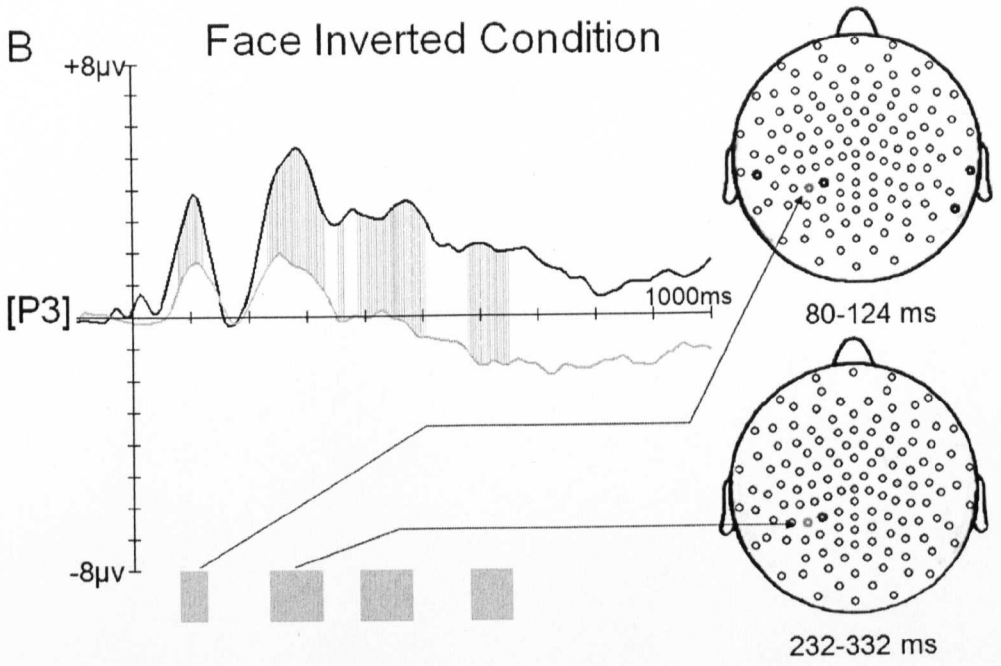
In the face condition, P1 (located in the parieto-temporal regions) amplitude was statistically smaller ($t(18) = 3.012$, $p = .007$) in high-prone ($M = 1.06\ \mu V$, $SD = .97$) compared to low-prone individuals ($M = 2.35\ \mu V$, $SD = .94$) between 76-120 ms after stimulus presentation (see Figure 5.2, A). Similarly, in face inverted condition, P1 amplitude was statistically smaller ($t(18) = 2.34$, $p = .031$) in high-prone ($M = 1.47\ \mu V$, $SD = 1.09$) compared to low-prone participants ($M = 3.34\ \mu V$, $SD = 2.27$) between 80-124 ms after stimulus presentation (see Figure 5.2, B). In inverted Mooney stimuli condition, P1 amplitude was statistically smaller ($t(18) = 2.76$, $p = .013$) in high-prone ($M = .89\ \mu V$, $SD = 1.01$) compared to low-prone participants ($M = 2.65\ \mu V$, $SD = 1.75$) between 52-100 ms after stimulus presentation (see Figure 5.2, D). Additionally, topographic plots indicated that this condition was also associated with fronto-central activity (see Figure 5.2, D). No statistical significance was found in the Mooney faces and scrambled Mooney condition between high and low-prone individuals (see Figure 5.2, C and E).

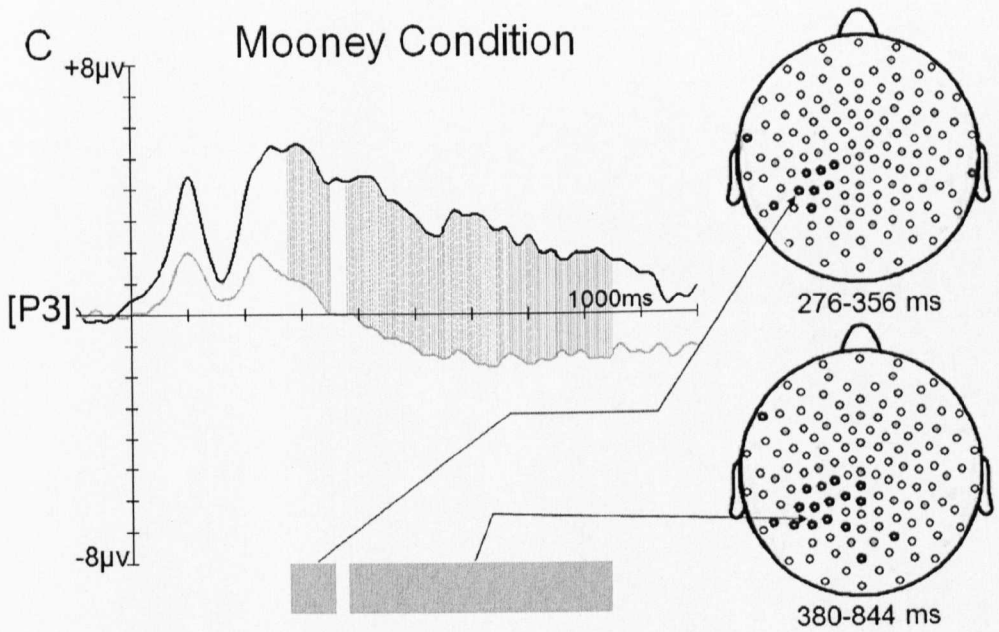
N170 Effects

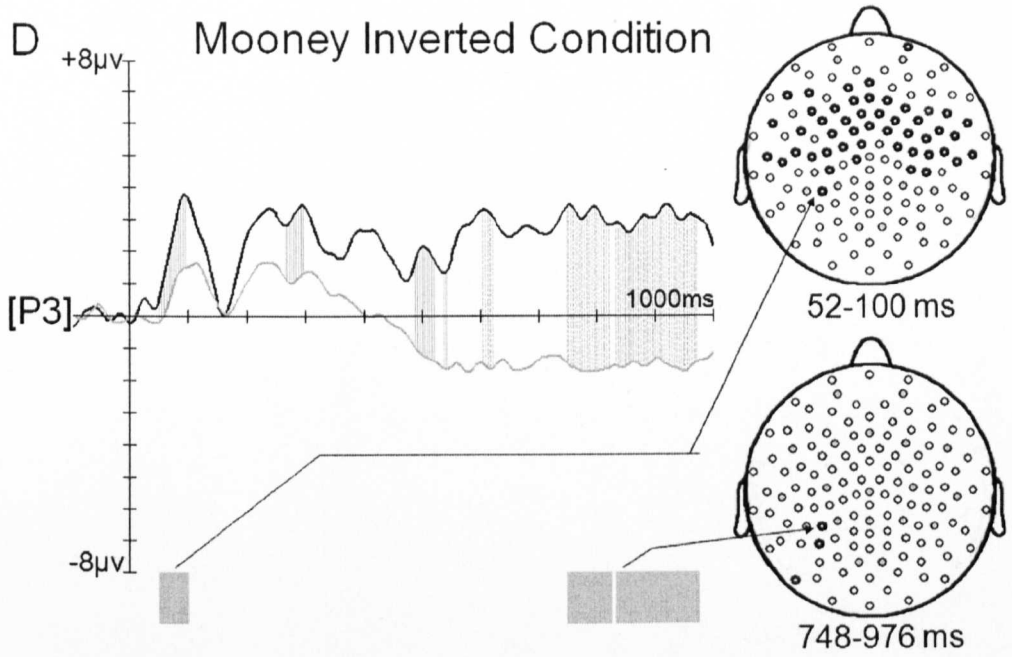
In all conditions, clear N170 components were observed over posterior electrodes. However, for this time window no consecutive significances were observed in the mean amplitudes between high and low-prone individuals for all conditions (see Figure 5.2).

In the inverted face condition, parieto-temporal P2 mean amplitude was statistically smaller ($t(18) = 2.39$, $p = .028$) in high-prone ($M = 1.50$ μV, $SD = 2.43$) compared to low-prone individuals ($M = 4.56$ μV, $SD = 3.23$) between 232-340 ms after stimulus presentation (see Figure 5.2, B). In the Mooney faces condition, mean amplitude was statistically smaller ($t(18) = 2.37$, $p = .029$) in high-prone ($M = .65$ μV, $SD = 2.28$) compared to low-prone participants ($M = 4.93$ μV, $SD = 5.233$) between 276-356 ms after stimulus presentation (see Figure 5.2, C). No statistical significance was found in the faces, Mooney faces and scrambled Mooney condition between high and low-prone individuals (see Figure 5.2, A, D and E).




B
Face Inverted Condition
+8μv
[P3]
1000ms
-8μv
80-124 ms
232-332 ms


C
Mooney Condition
+8μv
[P3]
1000ms
-8μv
276-356 ms
380-844 ms



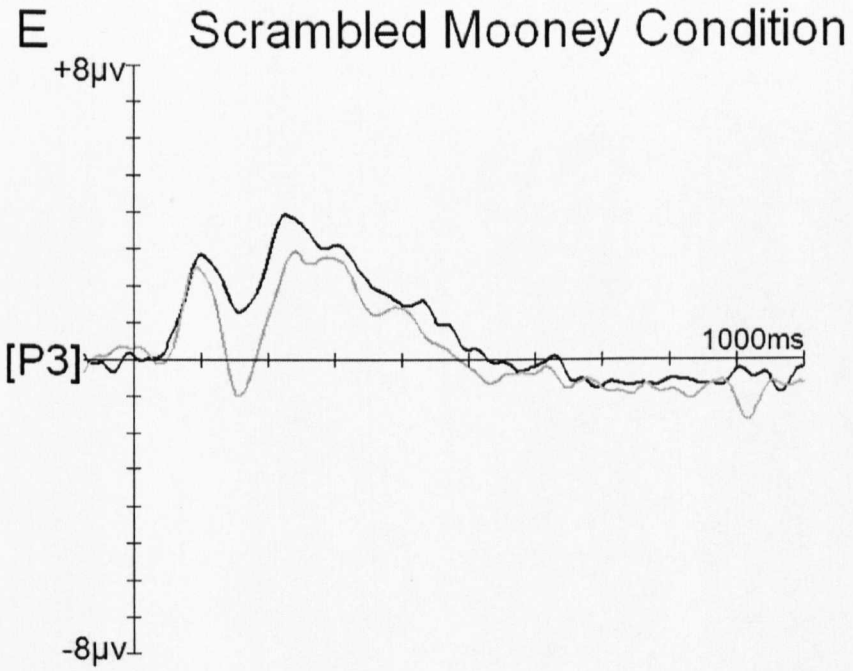


Figure 5.2, A-E. Parietal-temporal P1 and P2 time locked to target-onset at 0 ms. Waveforms are taken from electrode 52 and topographic plots apply to time periods of consecutive significance at electrode P3. In the topographical plots, dark circles designate significantly greater positivity for low-prone compared to high-prone individuals. Arrows indicate the electrode where the waveforms were recorded.

5.5 Discussion

The behavioural results from the present study show that both high and low-prone normal individuals perceived the images as faces in approximately the same percentages of trials across all conditions. This is in line with the results from Chapter 4, where deficits in visual functioning in high-prone normal individuals were not observed using the traditional neuropsychological behavioural assessments. Therefore, the aim of this study was to observe the early visual components using a classic face perception paradigm, using the EEG. The present study is the first to explore the neurophysiologic basis in face processing in high-prone normal individuals.

The results from the present study show that amplitude means in both early and late ERPs components are statistically lower in high-prone compared to the low-prone normal individuals. Moreover, these lower amplitudes were observed as early as 100 ms after stimuli of faces and inverted faces were presented, mainly over the temporal-parietal regions. The P1 is a face selective component correlated with face categorization processes that extract fine/local information (Herrmann, Ehlis, Ellgring, & Fallgatter, 2005; Liu et al., 2002; Sugase et al., 1999). The observed differences in P1 between high and low-prone individuals might therefore suggest that the process of extraction of fine information is somewhat disrupted in the high-prone group. This distortion might not be extensive enough for full-blown hallucinations to occur, but can nonetheless serve as a basis for proneness to misinterpreting visual information, resulting in higher proneness to hallucinatory-like experiences.

Similarly, reduced mean amplitudes were observed in high-prone individuals in the Mooney faces condition; however, they lacked consecutive significance (see Figure 5.2, C). One possible explanation why no consecutive significance was observed is that the faces presented were altered and do not display all the criterion characteristics of a face (Latinus & Taylor, 2005), and that is why no significant differences were observed in the Mooney condition. Therefore, the task being performed is altering. The lack of all standard features of the face might result in

the associated P1 to be less susceptible to the differences in fine processing. For this reason, it was surprising to find statistical differences in the mean amplitude between high and low-prone individuals in the inverted Mooney condition. Inverted Mooney faces were recognized as faces in only 60% of the trials in both groups. In contrast to the expected posterior distribution in the other face conditions, frontal central topography was observed in the inverted Mooney condition (see Figure 5.2, D). The distinct frontal distribution probably reflects additional, probably holistic processing that is required when stimuli of this type are presented. The role of frontal lobe functioning in occurrence of VHs has been already raised in Chapter 4 and will be addressed in detail in Chapters 6 and 7.

Further, no periods of consecutive significance were found for the N170 component between high and low-prone individuals in any of the conditions (see Figure 5.2). Lack of significant differences are difficult to interpret and possible explanations are often a matter of speculation (Luck, 2005). The N170 component has been shown to reflect the structural encoding of faces (Eimer, 2000; Herrmann, Ehlis, Ellgring, & Fallgatter, 2005). The results from the present study might therefore indicate that both high and low-prone individuals are equally able to extract information about configuration of faces. However, in order to avoid the beta error type[19], future studies need to address the issue of structural encoding and employ a perception task that includes structural modifications of faces (Bentin, Golland, Flevaris, Robertson, & Moscovitch, 2006). However, based on the context of the present study no significant differences in N170 components between high and low-prone individuals were found.

Finally, the reduced amplitudes were observed for the posterior P2 components in the high-prone individuals in the inverted faces and Mooney faces conditions (see Figure 5.2, B and C). A similar pattern of reduced amplitudes was also found for the inverted Mooney faces condition in the high-prone individuals (see Figure 5.2, D), but the differences lacked consecutive significance. It has been suggested that the P2 component (in particular the left-lateralized) reflects a more

[19] Beta error refers to a type of statistical error concluding there is no difference between the groups when there really is one.

extensive and deeper processing of indistinct face stimuli which allows the categorization of these stimuli (Latinus & Taylor, 2006). The results from the present study therefore propose that this later processing is altered in the high-prone group. Two possibilities for this impairment arise; either the lower P2 amplitudes result from earlier P1 aberrations of the extraction of fine/local information, or they are independent from the previous P1 effects and simply reflect a lack of later processing stages once a face has been identified in high-prone individuals.

The results from the study are important in understanding the factors that contribute to hallucination-proneness in the normal population and also in VHs in clinical populations such as PD. Electrophysiological responses of high-prone individuals were objectively different, yet apparently not a sufficient element for generating VHs. The findings from this study therefore give evidence that modulations of early evoked visual responses are not a sufficient factor for developing VHs in the normal population. However, further issues have been raised by the study, namely if there is a specific threshold that is reached in clinical populations with full-blown hallucinations, but not in the high-prone normal individuals. Since the EEG study was only carried out on the normal population, and not with the PD group, it is not possible to conclude whether or not the same modifications are present in the hallucinating PD population. It was therefore not possible to infer as to whether or not the continuum hypothesis is supported; that is, if hallucinating PD patients show the same patterns of EEG response to the high-prone normal individuals. In order to ascertain this claim, future studies need to be carried out on hallucinating and non-hallucinating PD patients.

In summary, the present study provides a novel method of studying subtle neurophysiological differences between high and low-prone normal individuals. It is the first study to provide evidence that high-prone individuals display disruption of early visual processing components in the face perception paradigm, as early as 100 ms after the stimulus is presented. This finding could reflect that subtle differences, not extensive enough for the development of VHs, may in turn result in higher frequency of experiencing hallucinatory-like images in the high-prone individuals. The results from the study therefore provide evidence for inclusion of

the bottom-up neurophysiological components in the model accounting for hallucination-proneness in the normal population, and open a new path of researching the underlying pathology associated with VHs in clinical populations.

5.5.1 Limitations and Further Studies

Apart from the hypothesis that VHs are related to a specific electrophysiological response threshold, several other issues were raised when interpreting the results from the present study and need to be addressed in the future studies. First, the results show evidence that early visual processing components in the face perception paradigm are different in high and low-prone individuals, possibly predisposing the high-prone group to a higher incidence of hallucinatory-like experiences. Whether or not high-prone individuals are at higher risk for developing full-blown hallucinations in later years is impossible to conclude; only a longitudinal study could explore that possibility.

Second, the aim of the study was to observe the early visual processing components in high-prone individuals. However, apart from significant differences between high and low-prone individuals in the P1 and P2 components, several statistical differences have been found in later visual components. The effect is either due to the disruption of earlier components, as seen between high and low-prone individuals in face, inverted face and inverted Mooney faces, or an indicator of a higher cognitive processing of non-conventional face stimuli. The latter hypothesis is in line with aberrant frontal activation in the high contrast Mooney faces condition, probably reflecting an involvement of top-down processes. Investigation of top-down processes in proneness to VH in the normal population is therefore warranted and will be addressed in Chapters 6 and 7.

Third, the highly ambiguous scrambled Mooney stimuli may be processed differently in high and low-prone group (Latinus & Taylor, 2005); however, no differences have been found between the two groups. In the scrambled Mooney condition, the only analysed trials were the ones that participants responded they

saw a face, which happened in 20% of the trials in low and 26% of the trials in high-prone individuals. Low number of trials could have contributed to a higher chance for beta error. Therefore, the study of the later visual processing components in the scrambled faces conditions is warranted in sufficient number of trials.

Finally, an important point to note when interpreting ERP components is that a given ERP component that is elicited by differing experimental tasks is likely to reflect activity from different neural structures and also different psychological processes. A well documented example of this phenomenon is provided by Luck (2005), who demonstrates that modulation of the N2 which is elicited by an attentional bias in social categorization tasks is not the same N2 generated by tasks involving conflict or inhibition of responses and is therefore not reflecting identical neural sources. Therefore, within the context of this study, care should be taken when making conclusions about the functional significance of each component of interest. From Collerton et al.'s (2005) PAD model there is the possibility that any differences between the electrophysiological responses of low and high-prone individuals seen in this study could potentially be due to attentional differences, or to some degree, a mix of both attentional and visual processing impairments in high-prone individuals. Within the context of ERP face perception paradigms, the P100 (located at lateral occipital electrodes with a latency of 80-110 ms) has been correlated with facial processing (Herrmann et al., 2004; Liu et al., 2002). Itier & Taylor (2004) found that the P100 was earlier and significantly larger for faces in either normal or inverted orientations compared to control stimuli. Their findings are consistent with intracranial recordings from macaque monkeys showing that global information about faces is processed by 110 msec (Sugase et al., 1999). Furthermore, Herrmann et al.(2004) found increased P100 amplitudes to faces compared to buildings which they interpreted as being related to early categorization processes. Additionally, in a magnetoencephalography (MEG) study, Liu et al. (2002) found a significant response component to faces located over occipitotemporal areas at a latency of approximately 100 msec (M100) compared to control stimuli which they related to face categorization. Their data suggests that different features are extracted from the faces at ~100ms fine/local information vs.

~170ms coarse/global information. Therefore, it seems likely that in the current study the main differences observed between high and low-prone individuals in the P100 component reflect differences in visual processing, relating to the extraction of fine/local information rather than attentional processes.

As presented in Figure 5.2, (B-D) later differences (300ms) between the two groups showed high levels of significance. These findings may be explained by Campanella et al. (2006b), who found a reduction in the amplitude of the N170 component in patients with flourishing schizophrenia which they attributed to a reduction in P100 amplitude. This suggested that schizophrenics' impairments in face processing may be due to earlier disruption of general visual processing. The differences seen in the P300 and later components reported in this study may well be caused by a dysfunction in the early visual processing stages of the face stimuli. It is possible that normal functioning of attentional and resource allocation components is reliant on earlier successful processing of stimuli. Impairments in these earlier components, such as the P100, may underlie the divergence observed in later components (P300) between high and low prone individuals.

5.5.2 Conclusions

Significantly lower P1 and P2 amplitudes were found in the high-prone compared to the low-prone normal individuals. Deficiencies in early visual processing components (seemingly independent of face recognition processes) might in turn affect the visual processing of high-prone individuals. This may not be extensive enough to manifest in VHs, but enough for a frequent occurrence of hallucinatory-like experiences. Apart from posterior areas, the results showed lower activation in frontal areas in cognitively challenging situations (i.e., inverted Mooney faces), suggesting that frontal top-down functioning is implicated in hallucination-proneness in the normal population. This is an important finding and will be addressed in Chapters 6 and 7.

Chapter 6: Executive Functions in Hallucinating PD Patients and in High-Prone Normal Individuals

6.1 Introduction

The results from both previous studies (see Chapters 4 and 5) highlighted the frontal dysfunctions as a potential explanatory candidate in understanding VHs in PD and hallucination-proneness in the normal population. Two areas of investigation were proposed to explore the role of the frontal functioning: executive functions and personality factors. The present study will address the role of executive functioning in relation to VHs in PD and hallucination-proneness in the normal population. Chapter 7 will investigate the role of top-down personality processes in VHs in PD and in the hallucination-prone normal population.

The executive functions are defined as a set of brain processes, such as planning, abstract thinking, rule acquisition, initiating appropriate responses and inhibiting inappropriate responses (as defined by, for example, Miller & Cohen, 2001; Norman & Shallice, 2000; Posner & Petersen, 1990). A major difficulty is the heterogeneity of frontal lobe impairments and executive forms; however, the following tests have been argued to reflect some of these processes: Wisconsin Card Sorting Test, Tower of London test, source memory tasks, working memory and memory retrieval, tests of fluency and spatial working memory tests, Raven's Coloured Progressive Matrices and the executive functioning subtests of the Cambridge Cognition Neuropsychological Test (Foster, Black, Buck, & Bronskill, 2007; Gazzaniga, 2002; Golden, Espe-Pfeifer, & Wachsler-Felden, 2000; Leeds, Meara, Woods, & Hobson, 2001; Phillips, 2007; Rabbitt, 2007; Robbins et al., 2007; Roth et al., 1986). In addition, the Frontal Assessment Battery (FAS) (Dubois, Slachevsky, Litvan, & Pillon, 2000; Iavarone et al., 2004) is a brief screening battery for frontal dysfunction that includes six executive tasks, namely similarities task, phonological fluency, motor series, conflicting instructions, go-no go task and prehension behavior (environmental autonomy).

Many studies have reported a decline of specific executive functions in hallucinating PD patients, such as memory and abstract thinking (Athey et al., 2005), inhibitory disability (Barnes & Boubert, 2008; Santangelo et al., 2007), the go/no-go FAB subtest, verbal learning-immediate recall task and semantic and phonological fluency tasks (Grossi et al., 2005; Santangelo et al., 2007), and a general decline in executive functioning (Imamura, Wada-Isoe, Kitayama, & Nakashima, 2008). Greater activation and frontal hypermetabolism were also evidenced in some neuroimaging studies (Nagano-Saito et al., 2004; Stebbins et al., 2004).

However, the majority of these authors report intact functioning on several executive domains, including most of the Executive Functioning subtests of the CAMCOG (Athey et al., 2005), delayed free recall and Raven's Coloured Progressive Matrices score (Grossi et al., 2005), fluency (Barnes et al., 2003), and delayed verbal recall (Santangelo et al., 2007). In accordance with the findings, several neuroimaging studies found no frontal lobe alterations in hallucinating PD patients as compared to non-hallucinating PD patients (Matsui, Nishinaka et al., 2006a, 2006b; Oishi et al., 2005; Ramirez-Ruiz, Marti et al., 2007). Furthermore, Capitani and colleagues (2007) believe that a severe cognitive deficit is not sufficient by itself to invariably cause hallucinations, because VHs do not exceed the 25% incidence rate even in extremely advanced cases of dementia (Capitani et al., 2007).

The studies have therefore offered inconsistent results, and the link between VHs and executive functions is uncertain. Furthermore, it remains unclear whether VHs are a predisposing or a resulting factor of executive dysfunctions, or if VHs and executive functions are elevated by unrelated underlying mechanisms. Thus, one possibility is that executive functions may be an important substrate for the development of VHs even when the signs of dementia are not yet apparent. This notion is in line with two longitudinal studies where VHs were recognized as a risk factor for a later development of dementia (Aarsland et al., 2003; Santangelo et al., 2007). However, other studies suggest that the executive dysfunctions cause, or at least precede, VHs (Barnes & Boubert, 2008; Grossi et al., 2005; Meco et al., 1990;

Sanchez-Ramos et al., 1996). As a third position, Fenelon et al. (2000) suggested that PD patients with impaired cognition are not so self-conscious and for that reason report experiencing VHs more often; therefore, VHs and a decline in executive functioning are independent, but can masquerade as dependant variables. Resolving this issue is especially desirable for setting up the diagnostic criteria of VHs and executive functions in the course of the neurodegenerative disorders.

In the normal population, a specific executive dysfunction has been identified to relate to hallucination-proneness: a source memory deficit. This is a dysfunction of distinguishing the real from the imaginary (also known as a reality monitoring or reality discrimination deficit, see Johnson & Raye, 1981). A dysfunction of source memory offers one of the most straight-forward explanations for predisposition to VHs: a failure in reality monitoring leads to confusion between self-generated mental images and perception, resulting in hallucinations. Although source memory has been proposed as the main contributing factor for the development of hallucinations in the normal population and in patients with schizophrenia (Aleman et al., 2000; Bocker et al., 2000; Lopez-Rodrigo et al., 1997; Rankin & O'Carroll, 1995), the link between hallucination-proneness and source monitoring is far from confirmed (Keefe, Arnold, Bayen, & Harvey, 1999). Apart from the different patient group that the studies stem from (i.e., schizophrenia), this link has only been proposed for hallucinations in the auditory, and not visual, modality. The only source memory study in PD patients with VHs (Barnes et al., 2003) showed that hallucinating PD patients made more source memory errors than their non-hallucinating counterparts. However, the authors were unable to conclude which factor is more critical for the genesis of VHs because the patients from their study also showed deficits in perception.

In summary, executive functions have been poorly investigated in PD patients with VHs and in high-prone normal individuals. Therefore, the aim of the present study is to explore the differences in executive functioning between hallucinating and non-hallucinating PD patients; and between high and low-prone normal individuals. In particular, further investigations are required to verify the usefulness of simple executive tasks in identifying non-demented PD patients at risk for the

development of hallucinations, while taking independent factors into consideration (e.g., age, years of diagnosis, disease severity, levodopa dose, etc). Comparing if executive functions are implicated in both hallucinating PD patients and in high-prone individuals will be an aid to current understanding as to whether hallucinations and hallucination-proneness are alleviated by the same cognitive factor, and will therefore serve as evidence to explain the occurrence of VHs in PD and proneness to VHs in the normal population.

6.2 Methods

6.2.1 Participants

PD Group

9 PD patients with, and 17 PD patients without, VHs were recruited for the executive functioning study. All patients were members of the PD societies in the UK, with normal hearing and normal or corrected-to-normal vision. A criterion for eligibility was a clinical diagnosis of PD as assessed by their GPs, and excluding criteria was a moderate or severe stage of dementia, confirmed by the carers of the PD patients, and the loss of independent maintenance of daily living activities, also reported by the carers. The independent variables were the same as stated in the previous studies of this research: age, amount of daily levodopa medication and the use of any other medication, years since their diagnosis, side of the body more affected by PD, the presence/absence of migraine, the presence/absence of ocular pathology (not including correction glasses) and HY motor disability stage.

Participants' demographics are summarized in Table 6.1. The criteria for grouping patients as PD hallucinators were recurrent VHs in the past month. 2 patients had VHs once a week, 5 had them 2-5 times a week, and 2 patients had VHs more than 5 times a week. 17 participants who have never experienced VHs were grouped as PD non-hallucinators.

Table 6.1. Participants' demographics.

	Hallucinating PD patients	**Non-hallucinating PD patients**	**High-prone normals**	**Low-prone normals**
N	9 (6 male)	17 (12 male)	16 (4 male)	12 (4 male)
Age	68.5 (7.2)	71.7 (6.8)	21.1 (3.6)	21.6 (3.5)
Years since diagnosis	7.8 (6.3)	6.1 (5.6)	-	-
Levodopa, daily dose	513.6 (266.3)	482.5 (269.1)	-	-
HY	2.3 (1.23)	2.0 (1.36)	-	-

Data (except the number of participants) are presented as means (±standard deviation). HY refers to the Hoehn-Yahr disability scale (1967).

Control Group

The CANTAB Executive functions tasks are supplied with a normative database from approximately 1000 elderly normal participants, which serves as a comparison age-matched control group. Instead of comparing the raw scores, CANTAB expresses the results as standardized scores.

High and Low-Prone Normal Individuals

The same student sample from the visual memory and visual imagery study (Chapter 4) participated in the executive functioning study. Therefore, 12 low-prone and 16 high-prone individuals were recruited for the executive functioning and source memory study (see Table 6.1). They were all undergraduate students from Oxford Brookes University with normal hearing and normal or corrected-to-normal vision. The exclusion criterion was a history of psychiatric disorder. The students received compensation for their participation. All participants completed all stages of the study.

6.2.2 Assessments

CANTAB: Executive function, working memory and planning tests

It is desirable that any cognitive examination should be a relatively brief and straightforward assessment. Executive function, working memory and planning tests of the CANTAB battery (CANTAB Eclipse 3.0, Cambridge Cognition) (Sahakian & Owen, 1992) include five tasks, assessing different aspects of executive functions, working memory and planning. All five measures are primarily sensitive to changes of the fronto-striatal areas of the brain and are standardised and widely used measures of executive functioning (CANTABeclipse, 2006). However, in order to prevent the effects of tiredness, stiffness or tremor from prolonged testing condition in the PD group, the testing was scheduled to last no longer than 45 minutes. This time limit allowed no more than 3 tests to be carried out. Therefore, despite the fact that all 5 executive tasks of the CANTAB are widely used and standardised tasks of executive functioning, the present study employed only three tasks in order to insure the best performance of both PD and the normal population group and to avoid the effects of tiredness.

All participants completed the following three executive functioning tasks: Intra/Extra Dimensional Set Shift (IED), Stockings of Cambridge (SOC) and Spatial Working Memory (SWM). As described in more details in the next section, IED and SOC are modifications of widely used neuropsychological assessments of executive functioning, namely the "Wisconsin Card Sorting Test" (Berg, 1948) and the "Tower of London" task (Culbertson & Zillmer, 1998), respectively. As such, they are widely accepted and used tasks, so it makes sense to contribute to knowledge by employing well-known tasks in one of the first studies which look at the differences in executive functioning between hallucinating and non-hallucinating PD patients. Furthermore, it has been shown in recent studies that the SWM impairments may be present at the early stages of the development of psychosis (Bartok, Berecz, Glaub, & Degrell, 2005). As discussed in Chapter 1, VHs in PD are thought to lead to the development of malign signs of psychosis

(Goetz et al., 2001); therefore, a SWM as a potential indicator between psychotic and non-psychotic states, was used in the present study. The tests have been shown to be particularly sensitive to frontostriatal syndromes ranging from neurosurgical excisions for tumors or epilepsy (Owen, Downes, Sahakian, Polkey, & Robbins, 1990) to Parkinson's (Owen et al., 1992) and Huntington's diseases (Lawrence et al., 1996).

Due to the obvious motor dysfunction in the PD group (especially during the "off" state, when the medications start wearing off), all latency measures were omitted in the analysis.

Intra/Extra Dimensional Set Shift (IED)

IED is a test of rule acquisition and attentional set shifting. It features visual discrimination and attentional set formation, maintenance, shifting and flexibility of attention. IED is a modification of the "Wisconsin Card Sorting Test" (Berg, 1948). In this task, two artificial dimensions are used: colour-filled shapes and white lines. Simple stimuli are made up of just one of these dimensions, whereas compound stimuli are made up of both, namely white lines overlying colour-filled shapes (see Figure 6.1). In the first block, the participant must learn which of the two colour-filled shapes is correct by touching it, and continue doing so until the criterion is reached (6 consecutive correct responses). In the next block, the contingencies are reversed, so that now the previously incorrect stimulus is correct. In the next stages, the second dimension (white lines) is introduced. If at any stage the participant fails to reach the criterion after 50 trials, the test terminates. Administration time is approximately 7 minutes. The test is primarily sensitive to changes of the fronto-striatal areas of the brain (CANTABeclipse, 2006). The deficits in the IED performance have been observed following orbitofrontal and lateral prefrontal damage (Dias, Robbins, & Roberts, 1996). Clark et al. (2004) suggest that topographical connections exist between the ventral parts of the prefrontal cortex and ventral parts of the striatum. Support for this claim is offered by a number of studies

where lesions to the ventral striatum disrupts reversal learning, leading to preservative response tendency (Annett, McGregor, & Robbins, 1989; Stern & Passingham, 1995).

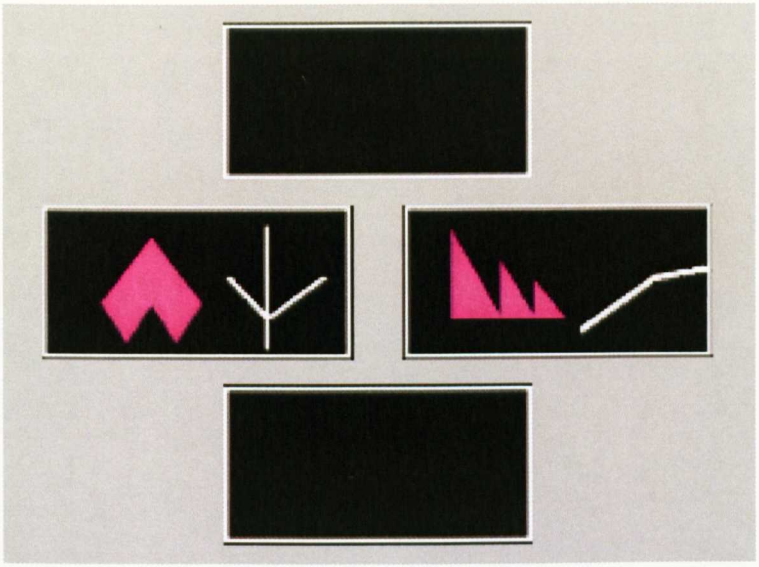


Figure 6.1. An example of the IED task.

IED has the following outcome measures:

a) ID errors: This is the total number of errors taken to successfully complete an intra-dimensional (ID) shift (the shift of attention to a novel exemplar within a previously relevant perceptual dimension).

b) ED errors: This is the total number of errors taken to successfully complete an extra-dimensional (ED) shift (the shift of attention to a novel exemplar of a previously unrewarded perceptual dimension).

c) Total errors (raw): ID and ED errors taken together, these two measures can give a relative measure of attentional "flexibility". Performance at this stage is sensitive to cognitive deficits in PD (Downes et al., 1989) but can also be sensitive to pharmacological manipulation of dopamine function by, for example, sulpiride (Mehta, Sahakian, McKenna, & Robbins, 1999).

d) Total errors (adjusted): This is a measure of the participant's efficiency in attempting the test. Thus, whilst a participant may pass all nine stages, a substantial

number of errors may be made in doing so. It is crucial to note that participants failing at any stage of the test by definition have had less opportunity to make errors. Therefore, this adjusted score is calculated by adding 25 for each stage not attempting due to failure. This value of 25 is used since participants must complete 50 trials to fail a stage and half of these could be correct by chance alone.

e) Stages completed: This is the total number of stages the participant completed successfully. There are nine stages to be completed in this task in the clinical mode. Participant completing all stages are deemed to have "passed the test".

f) Completed stage trials: This is the number of trials undertaken on all successfully completed stages.

g) Total trials (adjusted): This is the number of trials completed on all attempted stages with an adjustment for any stages not reached. The adjustment adds 50 for each stage not completed due to failure at an earlier stage.

Stockings of Cambridge (SOC)

SOC is a test of spatial planning, spatial working memory and motor control which gives a measure of frontal lobe function (CANTABeclipse, 2006). SOC is a modification of the "Tower of London" task (Culbertson & Zillmer, 1998). In this task, the participant is shown two displays (upper and lower), both containing three coloured balls. The displays are presented in such a way that they can easily be perceived as stacks of coloured balls held in stockings or socks suspended from a beam. The participant's task is to use the balls in the lower display to copy the pattern shown in the upper display. The balls may be moved one at a time by touching the required ball, then touching the position to which it should be moved. At first it is only necessary to move one ball, the number being increased in steps to five moves. If the participant makes more than double the number of moves necessary for the simplest solution, the problem is terminated. If the computer terminates three problems in a row, the entire test ends. There is no time limit. The researcher demonstrates the first problem. After that, participants must make all the

moves themselves. The test has been found to be sensitive to frontal lobe damage in several neuroimaging studies, especially in the left mid-dorsolateral frontal cortex (Owen et al., 1990; Owen et al., 1996). However, the result that only the left prefrontal activation reached significance does not necessarily indicate that the process of planning is strongly lateralized to the left hemisphere, but is more likely to have been an artifact of the substraction technique employed (Owen, 1997). This is supported by Owen et al's study (1996) where significant right dorsolateral prefrontal cortex activation was observed compared with a resting condition in the difficult planning condition prior to the subtraction of the specific task control condition. Therefore, planning deficits are evident in patients with either right or left prefrontal cortical damage (Owen et al., 1990; Owen et al., 1995; Shallice, 1982). Administration time is approximately 10 minutes.

The following SOC measure was used:

SOC Problems solved in minimum moves: This is a fundamental measure, recording the number of occasions upon which the participant has successfully completed a test problem in the minimum possible number of moves. For the clinical mode, this is scored out of a possible 12 problems, since eight practice problems are excluded from the calculation (the first six problems in the first block and the first two problems in the second block). This measure is a succinct expression of overall planning accuracy in SOC (Robbins et al., 1998).

Spatial Working Memory (SWM)

SWM is a test of the participant's ability to retain spatial information and to manipulate remembered items in a working memory. It is a self-ordered task, which also assesses heuristic strategy. This test is a sensitive measure of frontal lobe and "executive" dysfunction (CANTABeclipse, 2006). The test begins with a number of coloured squares (boxes) being shown on the screen. The participant must touch each box in turn until one opens with a blue "token" inside (a search). When a blue token has been found, the participant has to place it in the right column ("home") by touching the right-hand side of the screen. The participant must then begin a new

search for the next blue token. It may be found in any of the boxes that so far have been empty. This is repeated, until a blue token has been found in every box on the current screen. Touching any box in which a blue token has already been found is an error. The number of boxes is gradually increased from three to eight boxes. The colour and position of the boxes used are changed from trial to trial to discourage the use of the stereotyped search strategies. The participant decides the order in which the boxes are searched. The computer determines the number of empty boxes that must be visited (discounting errors). Performance at the harder levels of this task is enhanced by the use of the heuristic search strategy. The task has been related to the activity of the frontal lobe, as shown in a number of lesion and electrophysiological studies in nonhuman primates (Goldman-Rakic, 1987), neuropsychological studies of patients with frontal lobe damage (Owen et al., 1990; Owen et al., 1996; Owen et al., 1995) and functional neuroimaging studies in humans (Owen, 1997). Owen et al. (1990) showed that impaired performance on this task in neurosurgical patients with frontal lobe excisions may be related to the inefficient use of a particular search strategy associated with superior performance in normal participants. Furthermore, Owen et al. (1998) showed that during the SWM task, an increased activity was evident in the ventrolateral and premotor regions of the right frontal lobe in patients with PD.

Administration time is approximately 8 minutes.

The following outcome SWM measures were taken:

a) Within errors: Within errors are defined as the number of errors made within a search, i.e. the number of times a participant revisits a box already found to be empty during the same search. This is calculated for trials of four or more tokens only.

b) Between errors: Between errors are defined as times the participant revisits a box in which a token has previously been found. This is calculated for trials of four or more tokens only.

c) Double errors: These are occasions where the participant has committed an error that can be categorised as both a within and between error. This is calculated for trials of four or more tokens only.

d) Total errors: This is the number of times a box is selected that is certain not to contain a blue token and therefore should not have been visited by the participant, i.e. between errors + within errors – double errors.

e) Strategy: Owen et al. (1990) have suggested that an efficient strategy for completing this task is to follow a predetermined sequence by beginning with a specific box and then, once a blue token has been found, to return to that box to start the new search sequence. An estimate of the use of this strategy is obtained by counting the number of times the participant begins a new search with a different box for 6- and 8-box problems only. A high score represents poor use of this strategy and a low score equates to effective use.

Source Memory Task

Source memory is thought of as memory for the characteristics of the specific conditions or context under which a memory is acquired (Drag, Bieliauskas, Kaszniak, Bohnen, & Glisky, 2009). It has been suggested that source memory abilities are related to the integrity of the frontal lobes, more specifically the dorsolateral prefrontal cortex, as has been demonstrated by studies using lesion evidence, neuropsychological data, and neuroimaging (Craik, Morris, Morris, & Loewen, 1990; Dobbins, Simons, & Schacter, 2004; Glisky, Rubin, & Davidson, 2001; Nolde, Johnson, & D'Esposito, 1998; Trott, Friedman, Ritter, Fabiani, & Snodgrass, 1999). Craik et al. (1990) demonstrated that source memory correlated with measures of verbal fluency and the Wisconsin Card Sorting Test (WCST).

In this computerized task, designed by SuperLab Version 2 (Cedrus Corporation, San Pedro, California, USA), participants were presented with a series of objects which were shown in either the form of a contoured picture ("picture", see Figure 6.2), a word ("word") or a spoken word ("sound"). 24 objects were presented for each category. The objects were taken from the Snodgrass and Vanderward (1980) set of standardized 2-D jpeg images. All pictures were of the same size (400 x 400 pixels). At the encoding stage, 72 objects were presented on a computer screen (24 pictures, 24 words and 24 sounds). Each picture and written

word was displayed for 2 seconds, and a white screen which lasted for 2 seconds was displayed between the presentations of the stimuli. A description of how a study was carried out is offered in section 6.2.3.

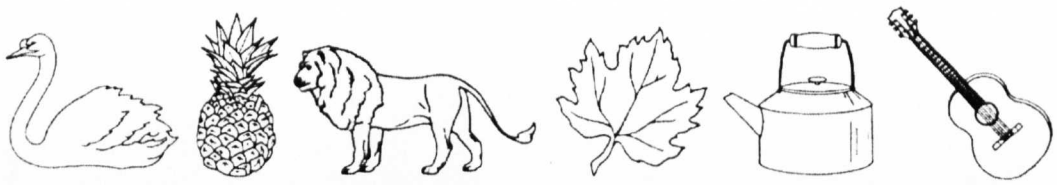


Figure 6.2. Examples of the "picture" stimuli.

The following source memory outcome measures were taken:

a) Same picture: Same picture is defined as the number of correct answers made in the test stage when participants recognise the picture which was previously shown in a picture format. The maximum number of correct answers is 8 (8 same pictures are presented in the first and test stage).

b) Same sound: Same sound is defined as the number of correct answers made in the test stage when participants recognise the sound which was previously heard in the same format. The maximum number of correct answers is 8 (8 same sounds are presented in the first and test stage).

c) Same word: Same word is defined as the number of correct answers made in the test stage when participants recognise the word which was previously presented in the same format. The maximum number of correct answers is 8 (8 same words are presented in the first and test stage).

d) Percent same: Percent same is defined as the percent of all correct answers made in the test stage when participants recognise that the stimuli has been presented in the same format (picture, sound, or word). 100 percent corresponds to the maximum number of correct answers, which is for this condition 24 (24 same stimuli are presented in the first and test stage).

e) Different picture: Different picture is defined as the number of correct answers made in the test stage when participants recognise the picture which

was previously shown in a *different* format (either word or sound). The maximum number of correct answers is 8 (8 different pictures are presented in the first and test stage).

f) Different sound: Different sound is defined as the number of correct answers made in the test stage when participants recognise the sound which was previously heard in a *different* format (either picture or word). The maximum number of correct answers is 8 (8 different sounds are presented in the first and test stage).

g) Different word: Different word is defined as the number of correct answers made in the test stage when participants recognise the word which was previously presented in a *different* format (either picture or sound). The maximum number of correct answers is 8 (8 different words are presented in the first and test stage).

h) Percent different: Percent different is defined as the percent of all correct answers made in the test stage when participants recognise that the stimuli have been previously presented in a *different* format. 100 percent corresponds to the maximum number of correct answers, which is for this condition 24 (24 different stimuli are presented in the first and test stage).

i) New picture: New picture is defined as the number of correct answers made in the test stage when participants recognise the picture which was not presented before. The maximum number of correct answers is 8 (8 new pictures are presented in the test stage).

j) New sound: New sound is defined as the number of correct answers made in the test stage when participants recognise the sound which was not presented earlier. The maximum number of correct answers is 8 (8 new sounds are presented in the test stage).

k) New word: New word is defined as the number of correct answers made in the test stage when participants recognise the word which was not previously presented. The maximum number of correct answers is 8 (8 new words are presented in the test stage).

l) Percent new: Percent new is defined as the percent of all correct answers made in the test stage when participants recognise that the stimuli has been presented in a new format (picture, sound, or word). 100 percent corresponds to the maximum number of correct answers, which is for this condition 24 (24 new stimuli are presented in the first and test stage).

m) Percent correct (total): Percent correct (total) is defined as the percent of all correct answers made in the test stage when participants correctly recognise a stimuli as the same, different or new. 100 percent corresponds to the maximum number of correct answers, which is for this condition 72 (24 for each condition, namely same, new and different).

6.2.3. Procedure

PD Group

The study was introduced verbally and information sheets were given out at the monthly meetings in various PD societies throughout the UK between May and June 2008. Potential participants were encouraged to take part regardless of whether they had VHs or not. Those who decided to take part contacted the researcher at the end of the meeting. Patients individually agreed on a convenient meeting time either in their own homes or at the society meeting venue. After a brief description of the aim of the study, the methodology, and the debriefing preference, participants were encouraged to ask further questions before starting the experiment. All participants were reminded to notify the researcher if they felt tired during the testing.

All participants filled in a short questionnaire of the demographic variables and, where applicable, the nature of their VHs. In accordance with the university research ethics, filling in the questionnaire was taken as a written informed consent. Next, the participants were seated approximately 50 cm away from a screen (close enough to touch the screen). The executive functioning tasks from the CANTAB battery (CANTAB Eclipse 3.0, Cambridge Cognition) were administered, and

completed in a single session lasting approximately one hour. Debriefing took place at the end of the study at the PD society meetings or, if preferred, was sent by post.

High and Low-Prone Normal Individuals

The same student sample from the visual memory and visual imagery study (Chapter 4) participated in the executive functioning study. The recruitment was therefore the same as in the previous study (see Chapter 4). After completing the visual imagery and visual imagery task, the source memory (part I) was administered, in which 72 trials (24 picture, 24 words and 24 sounds) were presented in a randomized order. Each picture and written word was displayed for 2 seconds, and a white screen which lasted for 2 seconds was displayed between the presentations of the stimuli. Participants were instructed to simply watch and listen as the objects were presented. No further instructions were given. Next, the executive tests from the CANTAB battery and the source memory task were administered, and completed in a single session lasting approximately half an hour. After the CANTAB executive functioning tasks, a "surprise" source memory test (part II) was presented, in which a series of 96 cards was presented: 32 objects from all three categories (picture, word, sound) where 8 from each category were presented in the same format, 16 in a different format and 8 distractor (new) pictures. In this retrieval phase, participants were asked to indicate whether each item had been seen previously as a percept (same), or was same object presented in a different form/category (different), or was completely new (new). Source discrimination errors were calculated, which consisted of the number of errors made in the identification of an item's original source. All testing were completed in January 2008. A debriefing sheet was sent to the participants who expressed a wish to receive it.

6.2.4 Statistical Analysis

Statistical analysis was performed using SPSS for Windows version 15.0 (SPSS Inc., Chicago, IL). Descriptive statistics were used to describe the profile of both PD groups and high and low-prone normal individuals. The demographic features and the measures of the CANTAB executive tasks of hallucinating and non-hallucinating PD patients and of the high and low-prone normal individuals were compared using independent sample t-test and ANOVAs. All CANTAB tasks are provided with a normative database; therefore, the standardized scores were used as a comparison for both PD groups. Independent t-tests were run to compare high and low-prone normal participants on the source memory task.

6.3 Results

6.3.1 Demographics

Independent sample t-tests showed no difference between hallucinating and non-hallucinating PD patients on any of the following independent variables: age, gender, daily dopamine dosage, HY disability stage, years since diagnosis, side of body more affected by PD, migraine, or vision problems, and any other concurrent illness (all p-values > .188). The two PD groups only differed in the presence of VHs in the hallucinating group (see Table 6.1).

Likewise, using the independent t-test, there was no difference between high and low-prone participants in age, gender, vision and hearing problems, dyslexia or handedness (all p-values > .397).

6.3.2 CANTAB Executive Functioning and the Source Memory Task

PD Group

The standardized results of hallucinating and non-hallucinating PD patients across different measures of the IED, SOC and SWM are displayed in Table 6.2.

Table 6.2. Standardized results of the executive functioning tasks: Means and SDs.

	Non-hallucinating PD patients	Hallucinating PD patients	t	df	p
IED					
- *total errors (adjusted)*	-.08 (.691)	-.60 (1.562)	1.099	21	.284
- *total errors (raw)*	-.24 (.882)	-.57 (1.057)	-.713	21	.484
- *completed stage error*	.50 (.733)	-.08 (1.590)	-1.124	21	.274
- *completed stage trials*	.55 (.814)	.15 (1.524)	-.583	21	.566
- *ED errors*	-.86 (1.072)	-.56 (1.201)	-.624	21	.539
- *ID errors*	.59 (.242)	.08 (1.250)	1.508	21	.146
- *stages completed*	-.26 (.779)	-.63 (1.490)	.790	21	.439
- *total trials*	-.03 (.622)	-.20 (1.078)	.489	21	.630
- *total trials (adjusted)*	-.16 (.761)	-.65 (1.437)	1.072	21	.296
SOC					
- *problems solved in minimum moves*	-.17 (1.268)	-.72 (1.685)	.884	21	.387
SWM					
- *between errors*	.09 (.816)	-.03 (.987)	.305	18	.764
- *double errors*	.29 (1.007)	.48 (.376)	-.501	18	.622
- *strategy*	-.31 (.689)	-.37 (.624)	.180	18	.859
- *total errors*	-.21 (.879)	-.36 (1.058)	.335	18	.741
- *within errors*	.33 (.971)	.49 (.404)	-.426	18	.675

A standard score chart for a measure shows the number of standard deviations that the participant's performance lays from the peer group means. IED = Intra/Extra Dimensional Set Shift; SOC = Stockings of Cambridge; SWM = Spatial Working Memory.

The standardized values show that hallucinating PD patients scored similarly to non-hallucinating patients and the age-matched control group. The independent sample t-tests showed no statistically significant differences between PD groups across all the CANTAB executive functioning measures. There were large individual differences, especially within the hallucinating PD group (see Table 6.2).

High and Low-Prone Normal Individuals

Similar to the PD groups, there were no significant differences between high and low-prone normal individuals on any measure of CANTAB and the source memory task (see Table 6.3).

Table 6.3: Source memory and the CANTAB tasks results for high and low-prone groups: Means, SDs, and p-values.

	Low-prone Individuals	**High-prone Individuals**	*t*	*df*	*p*
Source Memory Task					
Same picture	6.25 (1.76)	5.44 (.16)	1.277	26	.213
Same sound	5.50 (.90)	5.38 (1.02)	.335	26	.740
Same word	3.58 (1.83)	3.25 (1.95)	.459	26	.650
Percent same	63.89 (10.41)	58.59 (12.12)	1.214	26	.236
Different picture	9.17 (2.59)	9.19 (2.17)	-.023	26	.982
Different sound	8.92 (1.88)	9.50 (3.01)	-.589	26	.561
Different word	8.08 (2.81)	9.62 (3.14)	-1.344	26	.191
Percent different	54.52 (8.13)	58.59 (12.41)	-.930	26	.361
New picture	5.92 (1.62)	5.19 (1.76)	1.122	26	.272
New sound	5.75 (1.42)	4.50 (2.25)	1.794	26	.085
New word	4.33 (2.15)	4.56 (2.03)	-.288	26	.775
Percent new	66.67 (15.99)	59.37 (20.44)	1.022	26	.316
Percent correct (total)	59.89 (5.70)	58.92 (11.65)	.266	26	.793
CANTAB Tasks					
IED					
- stages completed	7.92 (1.00)	8.5 (.89)	-1.627	26	.116
- total errors	28.75 (15.64)	18.94 (10.71)	1.972	26	.059
- total trials	96.83 (26.95)	84.06 (15.66)	1.579	26	.126
SOC					
- problems solved in minimum moves	8.00 (1.76)	7.44 (2.00)	.775	26	.445
SWM					
- between errors	14.50 (10.97)	22.31 (18.42)	-1.302	26	.204
- double errors	.92 (1.73)	.94 (1.84)	-.030	26	.976
- strategy	32.08 (4.19)	32.69 (4.56)	-.359	26	.722
- within errors	1.25 (1.82)	1.44 (3.10)	-.187	26	.853

6.4 Discussion

Deficits in executive functions in PD patients without dementia are relatively well documented, but their assessment is not straightforward. The present study is the

first to investigate the differences in executive functioning between hallucinating and non-hallucinating PD patients using the highly reliable and valid neuropsychological assessment. Moreover, the administration procedure in the present study showed that the executive functioning tasks of the CANTAB battery are a viable tool to apply in the PD population.

No standardized measures of the executive tasks (IED, SOC and SWM) were statistically different between PD hallucinators, PD non-hallucinators and the control group (see Table 6.2), although PD patients in general performed worse than the control group (see Table 6.4) as reported by several authors before (Morris et al., 1988; Owen et al., 1992; Owen et al., 1995). Similarly, high and low-prone normal individuals did not differ in any of the behavioural measures of the executive functioning tests of the CANTAB battery. The comparable executive functioning between the PD group and control group is not surprising given the patients' demographic characteristics (see Table 6.1). The mean Hoehn and Yahr score (1967) in PD hallucinating groups was 2.30 (SD=1.23) and 2.0 (SD=1.36) in PD non-hallucinating group, indicating a relatively early (motor) stages of PD. Furthermore, all patients reported relative or complete independent care for themselves, and there was therefore a higher expectancy of the intact executive functioning. The first finding of the present study is that when hallucinating and non-hallucinating PD patients were matched for age, years since diagnosis, HY disability scale, side of body more affected by PD, any ocular pathology and the levodopa daily intake dosage, the executive functioning in both groups was intact and comparable with the age-matched control group.

As described in Section 1.6.3, the consensus has not been reached about how, if at all, VHs are linked to the executive functions. The results from the present study suggest that VHs occur in the absence of executive dysfunctions; therefore, executive dysfunctions do not precede the development of VHs. In a study of Capitani and colleagues (2007) VHs in PD did not exceed the 25% incidence rate even in the extremely advanced cases of dementia. Their results suggest that a severe cognitive deficit is not sufficient by itself to invariably cause VHs.

More likely, the results of the present study support the idea that VHs precede cognitive decline. This is in line with the eight-year longitudinal study (Aarsland et al., 2003) where hallucinating PD patients were three times more likely to develop dementia than their non-hallucinating counterparts. Santangelo et al. (2007) also support the idea that development of VHs precedes the decline in executive functioning. Consequently, the frontal functioning (as measured by the executive functioning tasks) is not the first area of interest in relation to VHs (although it can become dysfunctional in the later stages of the illness). Therefore, if there is a common underlying mechanism for both VHs and executive dysfunction, the dysfunction first manifests in the development of VHs, when the level of pathology is not yet extensive enough for the executive dysfunction to be unvaryingly evident.

An alternative explanation, however, is that executive functions are implicated in VHs in PD, acting as a top-down process on an impoverished functioning of the association visual cortex. However, these differences were not observed due to a number of reasons such as the specificity of the executive tasks used in the present study, the number of participants, etc. Non-hallucinating PD patients might be protected by as yet unknown executive functions whereas the hallucinating PD patients, where this functioning is affected, are not. One possibility could be the anterior cingulate (Stebbins et al., 2004; Whitty & Lewin, 1957).

Given that no deficits in executive functioning were found in the hallucinating PD group, it is not surprising there were no differences in performance on the executive tasks between high and low-prone normal individuals. Additionally, no behavioural differences were found between high and low-prone groups on the source memory tasks. Therefore, the present study was unable to provide evidence whether proneness to VHs in the normal population arises as a result of misinterpreting internally generated mental images as externally based perceptions (source memory generated errors). The results from the study suggest that the executive functions are probably not the factors contributing to the proneness to VHs in the normal population and are not a viable candidate in constructing the hallucination-proneness model. In the continuum hypothesis, similar dysfunctions should be expressed in both hallucinating PD patients and high-prone normal

individuals; however, as both groups performed equally well as non-hallucinating PD patients and low-prone individuals respectively, it seems that executive functions, as measured in the present study, are not likely candidates as risk factors on a hallucination continuum.

6.4.1 Limitations

Some caution needs to be taken when interpreting the results from the present study. There were large individual differences in the hallucinating PD group (Table 6.2). These differences could blur the effect between the groups and result in making a beta error. This type of error is especially common in experiments with a limited amount of data due to the relative rarity of VHs in PD and the specific care that needs to be taken when working with this fragile population (the duration of tasks, medication variations throughout the day, etc.). With the exception of Fenelon et al.'s (2000) study comprising of a sample of 86 hallucinating PD patients, the studies usually operate with data of up to 30 participants. Therefore, a possible explanation is that there are differences in the executive functioning between hallucinating and non-hallucinating groups, but they were not observed due to the limited amount of participants.

In light of the earlier discussion about the limitations of the CANTAB battery (see Chapter 4), it is imperative to acknowledge that the performance on the CANTAB tests may be impaired due to the lesions to widely distributed brain structures. Robbins et al. (2007) argue that this is especially true of the prefrontal cortex which has major reciprocal projections to posterior cortical areas, as well as to subcortical areas such as the hypothalamus and the striatum (Goldman-Rakic, 1987). Furthermore, Owen et al. (1998) found that PD patients showed decreased activity in the globus pallidus during the SWM task, whereas the age matched control group showed increased activity in the same area. From these results, it was suggested that striatal dopamine depletion in PD patients disrupts the normal pattern of basal ganglia outflow, which, in turn, disrupts the various cognitive functions of the frontal lobe by interrupting normal transmission of information through

frontostriatal circuitry (Lee et al., 2000). In the light of the results from the present study, it could be expected that PD patients might show some impairments of the prefrontal cortex not due to the lesions in the prefrontal cortex, but possibly due to the suboptimal activity in the posterior areas which may then, according to Robbins et al. (2007) and Lee et al. (2000) project to the prefrontal cortex. Finally, Robbins et al. (2007) suggest that the interconnection between prefrontal cortex and other brain regions makes it an ideal candidate for mediating many aspects of executive function.

6.4.2 Further Studies

Although PD patients are a notoriously heterogeneous group, the individual differences were much more pronounced in the hallucinating than in the non-hallucinating PD group. The large set of independent variables (age, years since diagnosis, HY disability scale, side of body more affected by PD, any ocular pathology and the levodopa daily intake dosage) are therefore most likely not a final set of factors that are necessary to be taken into consideration when planning an experiment with this particular patient group.

Graham and colleagues (1997), for example, investigated the homogeneity of a population of patients with idiopathic PD and hallucinosis and found two subgroups of hallucinating PD patients. In patients with disease duration of five years or less, VHs were associated with rapid progression of the motor component of the disease, but not with cognitive impairment. However, in patients with PD of longer than five years duration, VHs were associated with postural instability and global cognitive impairment. Although the PD hallucinating group (M=7.8 years, SD=6.3) was diagnosed slightly longer than the non-hallucinating PD group (M=6.1 years, SD=5.6), the difference in years of diagnosis was not significant (p=0.188). If Graham's conclusions are correct, the difference between PD groups in our sample should not be noticeable due to the heterogeneity of years since diagnosis in the PD groups. However, the small number of patients in both groups prevented further analysis in comparing PD hallucinators according to their years since

diagnosis. Similarly, Owen and colleagues (1993) claimed that multiple memory deficits in PD may differentially depend on the severity of the motor disability. Again, there was no difference in the HY scale between the PD samples in the present study, so no significant difference in cognitive performance was expected in the two groups according to their severity stage. Furthermore, the mean HY disability score was 2.3 in the hallucinating and 2.0 in the non-hallucinating group, indicating relatively early stages of PD, and therefore a higher expectancy of intact cognitive performance. In summary, although there is a notable difficulty in recruitment of this vulnerable patient group, further studies need to address the issue of years since diagnosis and severity of disability as decisive dividing factors for development of VHs with a sufficient number of participants.

Finally, the results from the previous studies (Chapters 4 and 5) brought attention to the possible dysfunctions of the frontal lobe in the hallucinating PD patients during a specific visual memory task (DMS, sensitive to temporal and frontal lobe damage; but not the SRM which is sensitive to frontal lobe functioning alone), and in the high-prone normal individuals during the face perception task; however, the results from the present study do not show evidence for the involvement of the executive functions in relation to VHs in PD. Based on the results from the present study it was suggested that VHs are independent of executive functioning. It is suggested that the reason why more PD patients with dementia also experience VHs is because they are often older, have been diagnosed longer, and have consequently more advanced neurodegeneration lesions than their non-hallucinating counterparts.

Despite the non-significant results, the executive functions as measured in the present study, are likely to have an important protective function, associated with preserving an insight into the hallucinatory nature of the images that PD patients perceive. When the executive functions start wearing off (as in case of dementia), patients lose that insight, consequently the patients are less self-conscious and are less inhibited to report their hallucinations frequently. Some evidence behind this reasoning is offered in cases where patients with dementia report a higher frequency of VHs than the patients without dementia (Capitani et al., 2007; Hobson & Meara,

1999; Janvin, Aarsland, & Larsen, 2005; O'Brien et al., 2005), but it is important to differentiate that frequent reports about hallucinations are a side-effect of executive dysfunction and there may be no immediate causal effect.

Two possible paths of investigation are therefore proposed. First, there may be an underlying executive dysfunction involved in the generation of VHs which is not extensive enough to be observed by behavioural tasks. An investigation of executive functioning using neuroimaging studies which explore neural differences at a micro level, similar to the study in Chapter 5, would offer new insights. The other possibility, as justified in Chapters 4 and 5, is that internally-driven personality factors play an important role, which will be addressed in the following chapter.

6.4.3 Conclusions

Based on the previous studies, it was expected that compared to non-hallucinating PD patients, patients with VHs would perform worse on the tests of executive functioning. However, this was not demonstrated in the present study where a performance on the executive functioning in hallucinating and non-hallucinating groups was comparable to the control group. Similarly, no differences were found between high and low-prone individuals from the normal population on any measures of executive functioning or the source memory task. The results suggest that if VHs and executive dysfunctions are linked by the same underlying mechanism, VHs are the first to be expressed and precede the development of executive dysfunctions. These results do not explain the involvement of the executive functioning in the genesis of VHs or hallucination-proneness and therefore call for further investigation into the link between VHs and the frontal lobe functioning. The results suggest that hallucination-proneness in the normal population and VHs in PD may be related to internally driven personality processes. These processes will be explored in Chapter 7.

Chapter 7: Personality in Hallucinating PD Patients and in High-Prone Normal Individuals

7.1 Introduction

The results from Chapters 4 and 5 give evidence that some form of frontal dysfunction might possibly be implicated in the generation of VHs in PD, and hallucination-proneness in the normal population. Two lines of research were proposed to investigate the importance of the frontal functioning in the occurrence of VHs and hallucination-proneness: via executive functioning and via personality factors. However, the results from the executive study (see Chapter 6) show that executive functioning was intact in both hallucinating and non-hallucinating PD patients as well as in high and low-prone individuals. Therefore, the aim of the present study is to determine whether specific personality processes are implicated in VHs in PD and, following the continuum hypothesis, in hallucination-proneness in the normal population.

PD patients have often been associated with specific personality type, the so-called "Parkinsonian personality". The term has been linked with the following characteristics: compulsive, industrious, introverted, morally and sociably rigid, suspicious, self-protective, punctual, serious, stoic, quiet, emotionally and attitudinally inflexible, lacking of novelty seeking and affect, predisposing to depressive illness, introspective, over-controlled, anhedonic with suppressed aggression, avoiding harm (Cloninger, 1987; McNamara, Durso, & Harris, 2007; Todes & Lees, 1985)[20]. Moreover, other studies propose that PD patients were over-controlled, depressed, introverted and inflexible before the diagnosis of PD (Heberlein, Ludin, Scholz, & Vieregge, 1998; Poewe, Karamat, Kemmler, & Gerstenbrand, 1990)[21]; however, it remains unclear to what extent does the neuropathology of PD link to premorbid vulnerabilities (Bodis-Wollner, 2003).

[20] See also Evans et al., 2006; Hubble & Koller, 1995; Kaasinen et al., 2001; Menza, Golbe, Cody, & Forman, 1993.

[21] See also Hubble, Venkatesh, Hassanein, Gray, & Koller, 1993; Menza, Forman, Goldstein, & Golbe, 1990; Ward et al., 1984, Gerstenbrand & Karamat, 1999.

Further, authors (Heberlein et al., 1998; Poewe et al., 1990) recognise the limitation of retrospective and highly subjective reports from patients and their carers. It remains unclear, therefore, whether or not the "Parkinsonian personality" is premorbid or merely a reactive consequence of having PD.

McNamara et al. (2007) suggested that PD patients with frontal impairment are especially susceptible to personality changes, and that the frontal lobes are required for maintenance of prosocial personality traits. However, the link between VHs and frontal impairment, which can be manifested in a range of personality changes, has not been explored in detail. Meco et al. (1990) and Glantz et al. (1987) both using the Minnesota Multiphasic Personality Inventory (MMPI) (Butcher, Dahlstrom, Graham, Tellegen, & Kaemmer, 1989) reported a higher score on schizophrenia scale in hallucinating PD patients, indicating a higher level of social alienation, bizarre feelings and general dissatisfaction. However, none of these studies provide an explanation of how these personality factors affect the occurrence of VHs. Thus, the aim of the present study is to investigate the role of personality factors in hallucinating PD patients: if hallucinating patients exhibit specific personality traits as compared to non-hallucinating patients, that could provide evidence for involvement of top-down processing of information in the generation of VHs in PD. Unlike other studies (such as Glantz et al., 1987; Meco et al., 1990), the present study is the first study to observe the differences in a range of personality traits using a more generalized, yet highly reliable and standardized personality factors questionnaire 16PF (Cattell, 1956).

Specific personality traits have also been implicated in hallucination-proneness in the normal population, namely fantasy proneness and meta-cognitive beliefs. Fantasy proneness refers to a non-pathological trait defined by a profound involvement in fantasy and imagination (Lynn & Rhue, 1986), characterized by having vivid fantasies with hallucinatory intensities, reporting vivid childhood memories, experiencing strong bodily concomitants of fantasies, having out-of-body and other paranormal (e.g. telepathic) experiences, and having intense religious experiences. However, individuals scoring high on fantasy proneness, as a rule, do not have genuine, life-like hallucinations (Van de Ven & Merckelbach,

2003) and in fact, adopt lax criteria when classifying internal experiences as hallucinations (Lynn & Rhue, 1986).

Wells et al. (2000; 1994) proposed that intrusive mental experiences are subject to interpretation that relies on meta-cognitive beliefs (beliefs that are linked to the interpretation, selection and execution of particular thought processes). Thus, meta-cognitions are relevant to the study of VHs and a number of studies have found evidence of association between meta-cognitive beliefs (Laroi & Van der Linden, 2005) and the presence of hallucinations in both clinical and nonclinical samples (Jones & Fernyhough, 2006; Laroi, Collignon, & Van der Linden, 2005; Laroi, Van der Linden, & Marczewski, 2004). More specifically, all measures of meta-cognitive beliefs have been more pronounced in high-prone individuals, namely intrusive thoughts, negative beliefs about the uncontrollability and danger of thoughts, loss of cognitive confidence, thought control through worry and positive beliefs about worry (Cangas et al., 2006; Garcia-Montes, Cangas, Perez-Alvarez, Fidalgo, & Gutierrez, 2006; Laroi & Van der Linden, 2005). Morrison et al. (1995) proposed that meta-cognitive beliefs influence how intrusive thoughts are dealt with when they occur. They suggest that an internal thought is attributed to external source in situations when the thought is not consonant with general meta-cognitive beliefs (and are therefore considered intrusive). As investigated by Wells et al. (2000; 1994), meta-cognitive beliefs are an executive function of excessive self-focused attention and reflective processes. Therefore, it is likely that meta-cognitive processes are linked to the proneness of VHs.

Although no relationship was found between executive functioning or visual imagery and VHs in either PD patients or normal individuals (see Chapters 4 and 6), the idea of vivid fantasy or imagination remains, and needs to be addressed in further studies. To date, no study has investigated the role of fantasy proneness in hallucinating PD patients or in high-prone individuals from the normal population. Similarly, no study has addressed the role of meta-cognitive beliefs in hallucinating PD patients. Therefore, the aim of the present study is to examine personality traits, fantasy proneness and meta-cognitive beliefs in hallucinating PD patients and, in

line of the continuum hypothesis, in high-prone individuals from the normal population.

7.2 Methods

7.2.1 Participants

PD Group

11 PD patients with, and 20 PD patients without, VHs were recruited for the personality study. All patients were members of the PD societies in the UK, with normal hearing and normal or corrected-to-normal vision. A criterion for eligibility was a clinical diagnosis of PD as assessed by their GPs, and excluding criteria was a moderate or severe stage of dementia, confirmed by the carers of the PD patients, and the loss of independent maintenance of daily living activities, also reported by the carers. The independent variables were the same as stated in the previous studies of this research: age, amount of daily levodopa medication, years since their diagnosis, side of the body more affected by PD, the presence/absence of migraine, the presence/absence of ocular pathology (not including correction glasses) and HY motor disability stage.

Participants' demographics are summarized in Table 7.1. The criteria for grouping patients as PD hallucinators were recurrent VHs in the past month. 3 patients had VHs once a week, 5 had them 2-5 times a week, and 3 patients had VHs more than 5 times a week. 20 participants who have never experienced VHs were grouped as PD non-hallucinators.

Table 7.1. Participants' demographics.

	Hallucinating PD patients	**Non-hallucinating PD patients**	**Control group**	**High-prone normals**	**Low-prone normals**
N	11 (6 male)	20 (14 male)	12 (4 male)	16 (4 male)	12 (4 male)
Age	65.91 (5.974)	69.85 (6.604)	71.42 (4.889)	21.1 (3.6)	21.6 (3.5)
Years since diagnosis	14.0 (7.76)	9.2 (7.22)	-	-	-
Levodopa, daily dosage	560.1 (291.9)	502.1 (276.7)	-	-	-
H-Y	2.07 (1.058)	1.71 (.906)	-	-	-

Data (except the number of participants) are presented as means (±standard deviation). HY refers to the Hoehn-Yahr disability scale (1967).

Control Group

12 age-matched participants were recruited for the personality study (see Table 7.1). They were contacted on a snowball principle. All participants had normal hearing and normal or corrected-to-normal vision. The exclusion criterion was a history of psychiatric or neurological disorders. The control group did not fill in the 16PF personality questionnaire (Cattell, 1956), as it is provided with a normative age-matched database.

High and Low-Prone Normal Individuals

The same student sample participated in the perception, executive functions and personality study. Therefore, 12 low-prone and 16 high-prone individuals were recruited for the study (see Table 7.1). They were all undergraduate students from Oxford Brookes University with normal hearing and normal or corrected-to-normal vision. An exclusion criterion was a history of psychiatric disorder. The students received compensation for their participation. All participants completed all stages of the research.

7.2.2 Assessments

The Sixteen Personality Factor Questionnaire (16PF)

16PF (Cattell, 1956) is an objective self-report personality test, which includes measurements of 16 dimensions (Table 7.2).

Grounded in the data itself, the questionnaire was developed. The data itself determined the factors, while the other personality questionnaires were developed based on methods that forced their factors to be uncorrelated, and as a result shaped their definitions[22] (Cattell & Schuerger, 2003). The development of so called Big Five theories (proposing there are five broad factors or dimensions of personality) (Costa & McCrae, 1985) was heavily influenced by the use of 16PF. Further, Cattell (1946) found that the 16 primary factors gave rise to five global traits, which are to some extent comparable to the Big Five factors (Byravan & Ramanaiah, 1995). However, the 16PF are the only Big Five scales developed without their definitions' being constricted by methods of statistical convenience (Cattell & Schuerger, 2003). Further, the five global scales of 16PF give an outline of personality traits at a broad level, but the more specific 16 primary factors offer a comprehensive understanding of the individual's distinctive personality at various levels of organization and help to understand individual's deeper motivations (Cattell & Schuerger, 2003; Chamorro-Premuzic & Furnham, 2003; Rothstein, Paunonen, Rush, & King, 1994). Finally, the 16PF primary factors have been proven to be powerful predictors of actual behaviour, which is what makes the 16PF one of the most frequently used personality tests (Cattell & Schuerger, 2003).

Internal consistency reliabilities average .76 (ranging from .68 to .87 over the 16 factors) in the normative sample of 10,261 individuals (Cattell & Schuerger, 2003). High construct and applied validity were also reported. Importantly, Goldberg (in press) compared several personality questionnaires in their ability to predict six clusters of behavioural criteria and found that the 16PF dimensions had the highest predictive validity.

10 to 13 items are provided for each of the 16 dimensions (185 questions in total). Three alternative answers are provided for each of the questions, usually true, unsure, and false. 16PF generally requires about 45-60 minutes for administration. Simple and clear instructions are printed for participants on the cover page of the test booklet (see Appendix 12). Participants are asked to give their first, natural

[22] Technically, the 16PF scales emerged in a factor analysis that allowed oblique rotations; in contrast, the other systems used orthogonal rotations, despite the fact that these systems have repeatedly been found to be significantly correlated (Cattell & Schuerger, 2003).

answer and to answer as honestly as possible. They are encouraged to answer every question and to avoid mainly selecting the middle, "uncertain" answer. All answers are made on a separate answer sheet.

The answers are scored by hand or by machine; the raw scores are converted to the "sten" scores by the standardization tables. Sten scores are distributed over 10 equal-interval standard score points (assuming normal distribution), from 1 through 10. The population average (or mean) for a sten distribution is fixed at 5.5 and the standard deviation is 2.0 sten scores. The exact limits of sten 5 and 6 (4.5 – 6.5) extend, respectively, a half standard deviation below and above the mean, constituting the solid centre of the population, while the outer limits for stens 1 and 10 are 2.5 standard deviations below and above the mean. Sten scores of 4 through 7 are usually considered to be average, since they fall within one standard deviation of the population mean and therefore represent approximately two-thirds of all the obtained scores. Sten scores 1, 2, 3, and 8, 9, 10 are generally considered to be of greater importance for profile interpretation as they are more extreme and occur far less frequently in a normal population (IPAT, 1991).

Meta-cognitions Questionnaire (MCQ)

MCQ (Cartwright-Hatton & Wells, 1997) assesses individual differences in positive and negative beliefs about worry and intrusive thoughts, meta-cognitive monitoring and judgments of cognitive efficiency (see Appendix 13). The 65 MCQ items are scored from 1 to 4, where 1 = 'do not agree', 2 = 'agree slightly', 3 = 'agree moderately' and 4 = 'agree very much'. Total scores can range from 30 to 120. Factor analysis of MCQ items reveals that the MCQ consists of five relatively distinct subscales (Lees, Blackburn, & Campbell, 1988).

- The first subscale, "Positive beliefs about worry", consists of items relating to beliefs that worry helps one to solve problems and avoid unpleasant situations.
- The second subscale, "Negative beliefs about the uncontrollability of thoughts and corresponding danger" includes items relating to beliefs that worry is

uncontrollable, that one must control one's worrying, and that worrying is dangerous.

- The third scale, "Cognitive confidence", includes items relating to concerns about one's cognitive efficiency.
- The fourth subscale, "Negative beliefs about thoughts in general" (in particular relating to superstition, punishment and responsibility), includes items relating to fears of outcomes that might result from having certain thoughts, and the acceptance of responsibility for having such thoughts.
- Finally, the fifth subscale, "Cognitive self-consciousness", includes items related to the tendency to monitor and focus on one's thinking processes.

The questionnaire takes approximately 10 minutes to complete. Initial validation studies found that the MCQ has good psychometric properties (Cartwright-Hatton & Wells, 1997).

Fantasy Proneness Questionnaire (CEQ)

The "Creative Experiences Questionnaire" (CEQ) (Cronbach's alpha=0.77) is a 25-item true-false index of fantasy proneness (see Appendix 14). Sample items are "As a child, I had my own make believe friend or animal" and "When I think of something cold, I actually get cold". True answers are summed to obtain a total score, with a higher total score implying a higher level of fantasy proneness (Van de Ven & Merckelbach, 2003). Substantial correlations have been found between the CEQ and standard measures of absorption, schizotypy, and dissociation (Merckelbach & van de Ven, 2001). The questionnaire takes approximately 5 minutes to complete.

Fantasy proneness levels are significantly associated with endorsement of atypical symptoms listed by malingering instruments (Merckelbach & Smith, 2003) and Silva and Kirsch (1992) report that participants who score high on a fantasy proneness tasks seem to be more eager to endorse odd items when confronted with suggestive task instructions. Likewise, Wilson and Barber (1983) reported fantasy proneness is a important factor related to hypnotic susceptibility. Fantasy proneness

overlaps with positive schizotypy (Merckelbach, Rassin, & Muris, 2000) and may also be involved in reports of hallucinatory experiences (Merckelbach & van de Ven, 2001).

7.2.3 Procedure

PD Group

The study was introduced verbally and information sheets were given out at the monthly meetings in various PD societies throughout the UK between March and July 2008. Potential participants were encouraged to take part regardless of whether they had VHs or not. Those who decided to take part contacted the researcher at the end of the meeting. They were given an envelope with the personality questionnaires, which they took back home, and filled them over the period of two weeks. Participants then sent the questionnaires back to the experimenter. Apart from the personality questionnaires, all participants filled in a short questionnaire of the demographic variables and, when applicable, the nature of their VHs. In accordance with the university research ethics, filling in the questionnaire was taken as a written informed consent. Debriefing took place at the end of the study in the same PD societies' meetings or, if preferred, was sent by post.

Control Group

Personality questionnaires were distributed to the age-matched control group. All participants were given a stamped envelope to send it back to the experimenter once they filled in the questionnaires. Debriefing was done either in person, by phone or post (depending on the participant's preference).

The same student sample participated in the personality, visual memory and the executive functions study. The recruitment is therefore the same as in the previous studies (see Chapters 4 and 6). After finishing the CANTAB studies, participants were asked to fill in the personality questionnaires, which lasted approximately half an hour. Testing was completed in January 2008. A debriefing sheet was sent to the participants who expressed a wish to receive it.

7.2.4 Statistical Analysis

Statistical analysis was performed using SPSS for Windows version 15.0 (SPSS Inc., Chicago, IL). Descriptive statistics were used to describe the profile of both PD groups and high and low-prone normal individuals. The demographic features and the measures of the personality tests of hallucinating and non-hallucinating PD patients and of the high and low-prone normal individuals were compared using t-tests for independent samples. 16PF questionnaire is provided with a normative database; therefore, the standardized scores were used as an age-matched comparison for both PD groups.

7.3 Results

7.3.1 Demographics

Using the independent t-test, there was no difference between hallucinating and non-hallucinating PD patients on none of the following independent variables: age, gender, daily dopamine dosage, HY disability stage, years since diagnosis, any other concurrent illness, or side more affected by tremor. The two PD groups only differed in the presence of VHs.

Likewise, using the independent t-test there was no difference between high and low-prone normal participants in age, gender, vision and hearing problems, dyslexia or handedness.

7.3.2 Personality Tests - PD Group

There were no statistically significant differences between PD hallucinators, PD non-hallucinators and age-matched control group on CEQ, MCQ or any factor of the 16PF questionnaire. The sten scores for both PD groups across all factors of the 16PF are displayed in Table 7.3. Except for the non-hallucinating PD patients on Factor A, the mean values of no other factor were below or above the cut-off line (3 and 7, respectively).

Table 7.3. Means, SDs and t-test results of the 16 PF sten scores.

16PF	Hallucinating PD patients	Non-hallucinating PD patients	t	df	p
Factor A	4.70 (1.946)	7.24 (2.705)	-1.589	25	.160
Factor B	5.90 (1.595)	5.65 (1.966)	.345	25	.733
Factor C	5.20 (2.251)	5.24 (1.393)	-.051	25	.960
Factor E	3.60 (1.955)	4.82 (1.468)	-1.850	25	.076
Factor F	3.60 (1.897)	4.47 (1.940)	-1.135	25	.267
Factor G	6.00 (1.700)	6.24 (1.715)	-.345	25	.733
Factor H	3.80 (1.619)	5.35 (2.422)	-1.798	25	.084
Factor I	4.50 (2.173)	4.35 (1.967)	.181	25	.858
Factor L	4.50 (2.068)	5.00 (2.031)	-.614	25	.545
Factor M	4.30 (2.452)	4.59 (2.320)	-.305	25	.763
Factor N	5.60 (1.350)	5.71 (1.724)	-.166	25	.869
Factor O	5.20 (2.394)	4.94 (1.819)	.318	25	.753
Factor Q1	5.50 (2.321)	4.35 (2.234)	1.270	25	.216
Factor Q2	5.00 (2.261)	5.47 (1.972)	-.568	25	.575
Factor Q3	6.80 (2.201)	6.41 (1.372)	.567	25	.576
Factor Q4	5.40 (1.430)	5.65 (1.579)	-.406	25	.688

7.3.3 Personality Tests - High and Low-Prone Normal Individuals

Very different to the results from the PD groups, high and low-prone individuals statistically significantly differed on several 16PF, MCQ and CEQ measures (see Table 7.4):

Table 7.4. Means, SDs and p-values for the personality questionnaires.

	Low-prone normals	High-prone normals	t	df	p
16PF					
Factor A	4.92 (1.31)	6.69 (2.24)	-2.618	26	**.015**
Factor B	2.33 (1.37)	3.19 (1.47)	-1.565	26	.130
Factor C	3.67 (1.67)	4.81 (1.87)	-1.678	26	.105
Factor E	5.58 (1.88)	6.19 (1.97)	-.818	26	.421
Factor F	4.83 (2.17)	7.19 (1.72)	-3.206	26	**.004**
Factor G	6.00 (1.48)	6.12 (1.36)	-.232	26	.818
Factor H	5.00 (1.70)	6.62 (1.96)	-2.290	26	**.030**
Factor I	5.67 (1.15)	5.69 (1.40)	-.042	26	.967
Factor L	6.08 (1.50)	6.38 (2.03)	-.418	26	.679
Factor M	5.50 (1.73)	4.12 (1.15)	2.528	26	**.018**
Factor N	6.17 (1.95)	5.38 (1.78)	1.118	26	.274
Factor O	6.00 (2.22)	7.19 (1.33)	-1.648	26	.118
Factor Q1	5.58 (1.73)	4.81 (1.72)	1.170	26	.253
Factor Q2	5.67 (1.72)	4.00 (2.25)	1.838	26	.070
Factor Q3	6.17 (1.53)	5.31 (1.92)	1.266	26	.217
Factor Q4	6.67 (1.23)	6.25 (1.95)	.691	26	.496
MCQ					
Factor 1	38. 58 (9.95)	36.62 (10.79)	.491	26	.628
Factor 2	32.58 (7.868)	40.31 (8.761)	-2.411	26	**.023**
Factor 3	18.17 (5.34)	21.62 (8.70)	-1.213	26	.236
Factor 4	21.17 (4.407)	27.19 (4.708)	-3.440	26	**.002**
Factor 5	18.67 (3.822)	22.12 (3.792)	-2.380	26	**.025**
CEQ					
CEQ	6.67 (3.626)	11.33 (4.923)	-2.738	26	**.011**

Further, a table of intercorrelations of all the 16 factors has been produced, in order to clarify the differences found between the high and low-prone individuals.

Table 7.5. Inter-correlations of all the 16 factors.

Factors	A	B	C	E	F	G	H	I	L	M	N	O	Q1	Q2	Q3
A	1														
B	.081	1													
C	.306	-.074	1												
E	-.029	.324	-.191	1											
F	.444*	-.126	.507**	-.178	1										
G	-.205	.334	-.270	.141	.032	1									
H	.419*	.185	.378*	.317	.577**	.015	1								
I	-.065	-.190	.328	-.040	.099	.013	-.067	1							
L	.045	.046	-.482**	.434*	-.104	-.216	.139	-.206	1						
M	-.419*	-.120	-.057	.153	-.219	-.024	-.285	.212	.013	1					
N	-.313	.157	-.080	-.316	-.353	.008	-.364	-.211	-.166	.162	1				
O	.170	-.133	-.100	-.049	.324	.331	.085	-.062	-.087	-.267	-.300	1			
Q1	-.327	-.048	-.073	.380*	-.160	.011	-.008	.021	.083	.262	.128	-.417*	1		
Q2	-.398*	.148	-.254	.322	-.514**	.146	-.229	.087	.258	.486**	.327	-.307	.526**	1	
Q3	-.267	.020	-.226	-.277	-.153	.354	-.401*	.164	-.124	-.141	-.084	.024	.087	.129	1
Q4	.063	.366	-.360	.276	.009	.243	.154	-.368	.247	-.037	-.031	.144	-.188	-.050	-.064

* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).

Several statistically significant inter-correlations emerged between the 16PF factors, indicating that the 16 factors are not independent. Further, high and low-prone individuals in the present study differed on 4 factors, namely A, F, H and M; however, the correlation matrix shows that factors A, F and H are statistically significantly correlated and are therefore not entirely separate and independent factors.

7.4. Discussion

The aim of the present study was to investigate how, if at all, specific personality factors link to proneness to VHs in the normal and in PD population. Similarly to the previous studies of this research, hallucinating and non-hallucinating PD patients did not differ in any demographic characteristic; the only difference between the groups was in the presence of VHs. Apart from bottom-up processing, the generation of VHs in PD was also suggested to be linked to specific, personality-related, processing. The results from the present study, however, found no association between any personality factors and the occurrence of VHs in PD (see Table 7.3).

Quite on the contrary, compared to the low-prone individuals, high-prone individuals reported significantly higher scores on factors A, F and H, and significantly lower on factor M (see Table 7.4). The factors describe a good-natured, easygoing, emotionally expressive, soft-hearted and adaptable person (factor A; for factor descriptions see Table 7.2). Similarly, a high-prone individual is described as cheerful, active, talkative, expressive, carefree person (factor F), who is sociable, bold, ready to try new things, and spontaneous and abundant in emotional response (factor H).

The development of so called Big Five theories (proposing there are five broad factors or dimensions of personality) (Costa & McCrae, 1985) was heavily influenced by the use of 16PF. Cattell (1946) found that the 16 primary factors gave rise to five global traits, which are to some extent comparable to the Big Five factors (Byravan & Ramanaiah, 1995). Krug and Johns (1986) completed a large sample second-order factor analysis and provided a set of weights to use in calculating the second-order scales. According to them, a second-order factor 'extraversion' can be calculated on the basis of factors A, F, H and Q2. All factors but Q2 (with a borderline p-value of .070, see Table 7.4) are more highly expressed in the high-prone group. The hypothesis that these factors might underlie the same trait is further confirmed by the correlational matrix (see Table 7.5) where the four factors correlate significantly with each other (not all, but several correlations).

Therefore, it seems that a global trait, rather than specific personality traits, is related to hallucination-proneness in the normal population. In order to confirm the hypothesis that extraversion is related to hallucination-proneness, future studies need to employ a questionnaire measuring extraversion (e.g., EPQ; Eysenck & Eysenck, 1991). Such study would offer a more comprehensive understanding of hallucination-proneness.

Furthermore, low scorers on factor M tend to be anxious to do the right things, conscientious of practical matters, attentive over details and are sometimes unimaginative. The latter is especially surprising, since it is intuitively expected that people who are high-prone to hallucinatory experiences are also more imaginative, absorbed in thought and absent-minded (a high, rather than a low, expression of factor M). The results from the present study suggest that compared to low-prone individuals, high-prone normal individuals are open, sociable, practical and sometimes unimaginative.

Furthermore, the results from the meta-cognitive beliefs questionnaire describes the high-prone individuals as highly self-conscious individuals, who think worrying is dangerous and needs to be controlled, and also fearful of the outcomes that might results from having worrying thoughts. The results are in accordance with other studies that found a strong positive correlation between meta-cognitive beliefs and hallucination-proneness in both the normal population and in patients with schizophrenia (Baker & Morrison, 1998; Laroi et al., 2004; Morrison et al., 2000), advocating the influence of top-down processes in the occurrence of VHs.

Finally, high-prone individuals from the present study often described vivid memories and frequent fantasizing in childhood. It could be hypothesized that high-prone individuals are predisposed by high fantasy proneness in childhood and social compliance in adulthood. They are socially well adjusted and are afraid of worrying thoughts, thus becoming more self-conscious about the monitoring of their thoughts. The results from the study support the idea that high fantasy proneness, extraverted personality and strict thought monitoring are related to higher proneness to hallucinatory experiences in the otherwise healthy young population.

Stemming from the continuum hypothesis, it was suggested that VHs in PD might be related to similar risk factors as high hallucination-proneness in the normal population. The results from the previous studies have supported the hypothesis that VHs in PD and hallucination-proneness in the normal population are related to some cognitive functions (e.g., perception functioning), and unrelated to others (e.g., executive functioning). However, comparing the results of PD patients with full-blown VHs and high-prone normal individuals in the present study revealed that VHs might not be a continuation of the hallucination-proneness, as full-blown VHs do not seem to be mediated by, or dependant on, any personality-related factors. On the other hand, high-prone individuals have specific personality traits in common, which might make them more susceptible for rich visual perception, resulting in higher vulnerability to hallucinatory experiences. The results from the present study therefore do not support the continuum hypothesis, as one risk factor (personality characteristics) are importantly implicated in hallucination proneness in the normal population but not in hallucinations in PD. More likely, two separate models would explain the phenomena better than a unitary model: one model should therefore be proposed for hallucination-proneness in the normal population and the other for VHs in PD, where some of the risk factors may overlap, but some are specific for each of the phenomena and are unique.

The findings from the present study have important theoretical implications for the current understanding of the role of personality has to play in VHs in PD and hallucination-proneness in the normal population. The theoretical question that remains to be answered in future studies is to what extent top-down processing modulates the functioning of the bottom-up processing in the generation of VHs in PD and in hallucination-proneness in the normal population, and vice versa. The results from the present study offer a novel account that while personality-related top-down functioning affects visual perception in high-prone normal individuals (also suggested in research with highly-susceptible hypnotised individuals and patients with schizophrenia, see Lawrie et al., 2002; Spiegel, 2003), impoverished functioning of the association visual cortex might with time modulate some specific

personality traits in PD. However, the present study is the first to address this issue and it remains to be seen whether PD patients with a long history of VHs start accepting more bizarre experiences, and therefore change their personality traits over the years of experiencing hallucinations.

7.4.1 Conclusions

High-prone normal individuals are characterized by specific top-down processes, namely vivid fantasy proneness, emphasized meta-cognitive beliefs, extraverted personality traits which possibly reflect a general response bias to endorse bizarre items, and result in higher proneness to VHs. On the other hand, hallucinating and non-hallucinating PD patients did not differ on any personality measures, possibly reflecting the nature of VHs, which is independent of personality factors. Therefore, VHs in PD are probably not a continuation of hallucination-proneness in the normal population, as personality traits are implicated in proneness to VHs in the normal population, but are not a risk factor in full-blown VHs in PD.

Chapter 8: Sleep Patterns in Hallucinating PD Patients and in High-Prone Normal Individuals[23]

8.1 Introduction

The dopaminergic mesolimbic system, which is dysfunctional in PD, has extensive connections with the brainstem regions involved in the generation and maintenance of the REM sleep[24], which in turn result in nocturnal and daytime sleep disturbances in PD (Chaudhuri, Healy et al., 2006; Gugger & Wagner, 2007; Hilker et al., 2006; Manford & Andermann, 1998; Sei & Morita, 1999). Sleep disorders are frequently worse in PD patients with hallucinations (Chaudhuri, Martinez-Martin et al., 2006; Gupta et al., 2004). For example, Pappert et al. (1999) reported that 82% of hallucinating PD patients from their study experienced some form of sleep disorder. Similarly, Pacchetti et al. (2005) and Nomura et al. (2003) suggested that REM sleep behavioural disorder (RBD)[25] is associated with increased risk of developing VHs. Furthermore, both Iranzo et al. (2006) and Schenck et al. (1996) noted that RBD antedates the development of a neurodegenerative disorder in 45% - 65% of initially idiopathic RBD diagnosed patients. Compared to PD non-hallucinators, hallucinating PD patients have been reported to have reduced total sleep time and efficiency, reduced nocturnal REM sleep (5% in non-hallucinating versus 20% in a hallucinating group) and daytime non-REM[26] sleep, increased motor activity during REM sleep and fragmented sleep (Comella et al., 1993; Fenelon et al., 2000; Manni et al., 2002; Pappert et al., 1999). Antipsychotic drugs, which are effective in treatment of VHs and nocturnal sleep disorders in

[23] The study presented in the current chapter was conducted in collaboration with Dr Wiggs (Oxford Brookes University). The results have formed the basis of a publication (see Maravic, Wiggs, Connelly, & Barnes, 2007, see Appendix 15).

[24] Rapid eye movement sleep, also known as REM sleep, is a normal sleep stage characterized by loss of muscle tone and rapid movements of the eyes.

[25] REM sleep behavioural disorder (RBD) is a parasomnia defined by irregular loss of atonia (muscle paralysis) during the REM sleep, resulting in complex, aggressive and potentially harmful behaviours, such as kicking, punching, and screaming.

[26] Non rapid eye movement sleep (NREM) is a collective term for sleep stages 1, 2 (indicating light sleep), 3 and 4 (deep sleep). Unlike REM sleep, there is little or no eye movement during this stage.

hallucinating PD patients, conversely cause sedation and EDS (Friedman & Chou, 2004; Olanow, Watts, & Koller, 2001). These studies suggest a strong link between sleep abnormalities and the development of VHs in PD.

Few explanations have been proposed to explain a high incidence of sleep disturbances in PD patients with VHs. Some authors (Comella et al., 1993; Garcia-Borreguero, Larrosa, & Bravo, 2003) suggested that dopaminergic medication causes intrusions of REM sleep into wakefulness, experienced as VHs. They suggested that psychiatric symptoms start with sleep fragmentation (short nocturnal awakenings), following by vivid dreams, and finally frank hallucinations. This hypothesis was tested by Pappert et al. (1999) who found a strong interaction between sleep fragmentation and altered dream phenomena (vivid dreams, nightmares, RBD or night terrors) and between VHs and altered dream phenomena. However, because no interaction was evident between VHs and sleep fragmentation, the authors concluded that the three phenomena are independent but often overlapping behaviours. Further support for independence of VHs and vivid dreams was proposed by Diederich et al. (2005) who noted there is no strict parallelism between emotionally intense and bizarre, but frequently forgotten, dreams on one hand and easily recalled stereotyped VHs with retained insight on the other. Finally, Kulisevsky & Roldan (2004) proposed that the key behaviour may be altered dream phenomena, which can evolve into either sleep fragmentation or VHs; however, this claim remains inconclusive.

In summary, several studies give evidence for a link between VHs and sleep disorders. Although no comprehensive theory has been proposed, the link provides new areas of interest in understanding the generation of VHs in PD, shifting attention from traditional dopaminergic midbrain areas to the sleep-controlling brainstem areas. However, the exact mechanisms of the link between sleep patterns and VHs are not fully understood, and future studies need to address this issue. Specifically, the advent of new objective measures of sleep patterns promises a more elegant approach to sleep research, avoiding the disadvantages of the laboratory-based polysomnographic settings. Therefore, the aim of the present study

is to carefully examine a number of sleep patterns in relation to VHs in PD, using a new objective measure of sleep patterns: actigraphy.

In line of continuum hypothesis, the aim of this research is to investigate whether the same risk factors implicated in the generation of VHs in PD also predispose normal individuals to high hallucination-proneness. Normal individuals without any history of psychiatric disorders can experience VHs when sleep deprived (Babkoff et al., 1989; Kollar et al., 1969) or during sleep paralysis[27] (Cheyne & Girard, 2007; Girard & Cheyne, 2006; Solomonova et al., 2007). Healthy people can also experience prolonged hypnagogic (occurring at the transition from wakefulness to sleep) and hypnopompic hallucinations (occurring at the transition from sleep to wakefulness) (Manford & Andermann, 1998). Exceeding every expectation, a UK based telephone survey (Ohayon et al., 1996) revealed that 37% and 12.5% of the sample (5,000 people aged 15 to 100) experienced hypnagogic and hypnopompic hallucinations, respectively. These hallucinations are usually vivid and may be bizarre, but not disturbing, with preserved insight (Ohayon, 2000); strikingly similar descriptions have been reported by the hallucinating PD patients (see Chapter 2). VHs are therefore common in both the normal population and PD patients in the states of low arousal.

No studies to date, however, have examined the role of specific sleep patterns in individuals that are high-prone to have hallucinatory-like experiences. If specific sleep disruptions are a key element in high-prone normal population, they would expand our understanding about the functional structure of hallucination-proneness. Continued research is needed to further elucidate the generation of hallucinations and sleep disorders in PD and the normal population, and the link between them. Therefore, the aim of the present study is to carefully examine the link between sleep patterns in PD hallucinators and high-prone normal individuals, using a reliable, objective sleep methodology. The study is the first study to observe the differences in hallucinating PD patients and in high-prone normal individuals, using actigraphy, a non-invasive wristwatch-like methodology monitoring rest/activity

[27] Sleep paralysis (type of parasomnia) is a frightening state of temporary paralysis of the body when waking up or before falling asleep.

cycles. The findings will contribute to the understanding of the risk factors, which are implicated in the development of VHs not only in PD population, but also much earlier, in a population without any psychiatric history. Finally, a possible link between specific sleep patterns and VHs can have implications for future treatment regimes; because sleep disorders are potentially treatable, determining and treating specific sleep patterns that are related to VHs could in turn result in simultaneous cessation of VHs.

8.2 Methods

8.2.1 Participants

PD Group

12 PD patients with, and 16 PD patients without VHs, were recruited for the sleep study. All patients were members of the PD societies in the UK, with normal hearing and normal or corrected-to-normal vision. A criterion for eligibility was a clinical diagnosis of PD as assessed by their GPs, and excluding criteria was a moderate or severe stage of dementia based, confirmed by the carers of the PD patients, and the loss of independent maintenance of daily living activities, also reported by the carers. The independent variables were the same as reported in the previous studies of this research: age, amount of daily levodopa medication, years since their diagnosis, side of the body more affected by PD, the presence/absence of migraine, the presence/absence of ocular pathology and HY motor disability stage.

Participants' demographics are summarized in Table 8.1. The criteria for grouping patients as PD hallucinators were recurrent VHs in the past month. 5 patients had VHs once a week, 5 had them 2-5 times a week, and 2 patients had VHs more than 5 times a week. 16 participants who have never experienced VHs were grouped as PD non-hallucinators.

Table 8.1. Participants' demographics.

	Hallucinating PD patients	**Non-hallucinating PD patients**	**Control group**	**High-prone normals**	**Low-prone normals**
N	12 (11 male)	16 (13 male)	17 (9 male)	11 (4 male)	11 (5 male)
Age	68.2 (8.8)	65.1 (7.4)	71.8 (9.5)	23.1 (5.0)	23.0 (4.8)
Years since diagnosis	7.4 (4.1)	5.0 (3.8)	-		
Levodopa daily intake	581.2(247.5)	423.3 (309.3)	-		
HY	2.1 (.90)	1.6 (.63)	-		

Data (except the number of participants) are presented as means (±standard deviation).

Control Group

17 age-matched control group participants were recruited for the sleep study (see Table 8.1). All participants had normal hearing and normal or corrected-to-normal vision. The exclusion criterion was a history of psychiatric or neurological disorders.

High and Low-Prone Normal Individuals

11 high-prone and 11 low-prone individuals were recruited for the sleep study (see Table 8.1). They were all undergraduate students from Oxford Brookes University with normal hearing and normal or corrected-to-normal vision. An exclusion criterion was a history of psychiatric disorder. All participants completed all stages of the research. The students received compensation for their participation.

8.2.2 Assessments

Questionnaires

All participants were asked to fill-in the following self-rating sleep questionnaires:

(a) The Epworth Sleepiness Scale (ESS, see Appendix 16), a measure of daytime drowsiness where 10 points is considered to be the cut-off point for having daytime sleepiness problems (Johns, 1991);

(b) The Berlin Sleep Apnoea Questionnaire (BSAQ, see Appendix 17), a questionnaire for identifying individuals with sleep apnoea (5 points being the cut-off point) (Netzer, Stoohs, Netzer, Clark, & Strohl, 1999) and

(c) The Pittsburgh Sleep Quality Index (PSQI, see Appendix 18) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989), which assesses sleep quality and disturbances over a 1-month time interval (a cut-off point of 5 yields a good diagnostic sensitivity and specificity in distinguishing good and poor sleepers). Factor 1 refers to subjective sleep quality, factor 2 to sleep latency, factor 3 to sleep duration, factor 4 to habitual sleep efficiency, factor 5 to sleep disturbances, factor 6 to sleep medication and factor 7 to daytime functioning. Global PSQI is a sum of the 7 factors of the questionnaire.

(d) Participants were also asked to rate the frequency of other sleep-related behaviours typical of PD (Chaudhuri, Martinez-Martin et al., 2006), which are not assessed in the standardized questionnaire (restlessness of legs and arms, fidgeting, numbness or tingling of arms and legs, nocturnal hallucinations, painful muscle cramps, painful posture, and tremor, all causing disruption of sleep) on a scale of "Not during the past month", "Less than once a week", "Once or twice a week", or "Three or more times a week".

Actigraphy

An actigraphy is a small wrist-watch sized movement sensor, which objectively measures daytime and nocturnal activity. Actigraph monitors are the most reliable and accurate means of measuring activity levels and energy expenditure outside of a clinical setting. A recently published independent accelerometer evaluation (Plasqui & Westerterp, 2007) concluded that the ActiGraph is the only commercially available device of its kind that shows positive correlation with the doubly labelled water (DLW) technique of measuring energy expenditure. It is accepted as the most practical method for obtaining objective, quantitative, sleep-wake cycle data over extended periods of time (Ancoli-Israel et al., 2003; Sadeh & Acebo, 2002).

The actigraphs used in the present study were 1-3/8" diameter waterproof Mini-Motionloggers® (AW-64, Mini Motionlogger, Ambulatory Ambulatory Monitoring Inc., Ardsley, NY) weighing 0.9 oz. encased in a plastic enclosure. It contains 32K non-volatile memory, 16 Hz sample rate and 2-3 Hz bandwidth. The Mini Motionloggers offer applications that include basic sleep estimation, high resolution analog data collection, simultaneous environmental data collection, and comprehensive sleep scoring and sleep distribution data on the wrist. A range of recording capabilities exist including four validated sleep algorithms, periodic leg movement analysis, and a suite of circadian rhythm analyses. Software for device operation and data analysis is available for Windows 2000/XP, and comparable systems. The ActMe Operational Software allows for quick, easy download of actigraph data through Micro Interface/Connector. The actigraph is user exchangeable Lithium battery powered for long use (4,000-hour battery run time) and come with a full one-year warranty. They have a faux watch face as standard. Sleep-wake data for this study were collected at 30-s epochs, yielding up to 22 days of recording time per initialization.

Actigraphy has also been used for unobtrusive and easy long-term investigations of tremor fluctuations and therapeutic response in PD patients (Van Someren et al., 2006). Analysis of frequency and pattern of movement permits detection of basic sleep-wake patterns (Cole, Kripke, Gruen, Mullaney, & Gillin, 1992). Actigraphy was worn on the wrist of the hand that was less affected by tremor in PD group and on the non-dominant hand in the control group for a period of one week (during day and night-time, see Appendix 19).

The following generated variables were included in the analysis:

- time to sleep (time at sleep onset),
- time of final waking (time at sleep offset),
- sleep period (minutes from sleep onset to offset),
- activity mean (amount of movement during the sleep period),
- standard deviation of the activity mean (detecting unusual variability in the movement),
- sleep minutes (total minutes scored as sleep during the sleep period),

- sleep episode (number of blocks of contiguous sleep epochs),
- awakenings after sleep onset (WASO; wake minutes during the sleep period),
- mean wake episode (mean duration in minutes of the wake episodes during the sleep period),
- duration of longest wake episode (in minutes),
- sleep latency (the interval of time between "settling in" to go to sleep and the onset of sleep) and
- sleep efficiency (percent of time in bed spent asleep, calculated by using the following formula: 100*sleep minutes/sleep period).

Sleep Diary

The sleep diary was completed for a subjective assessment of sleep-wake patterns and to aid interpretation of the actigraphy data. Participants (or in 5 cases, where the PD patient had severe micrographia[28], their spouse) recorded their sleep and wake times (including daytime naps), time they went to sleep and time they woke up, bed-time and night-time behaviour, and any other significant events that occurred by night or day (see Appendix 20).

8.2.3 Procedure

PD Group

The study was introduced verbally and information sheets were given out at the monthly meetings in various PD societies throughout the UK between November 2006 and February 2007. Potential participants were encouraged to take part regardless of whether they had sleep problems and VHs or not. Those who decided to take part contacted the researcher either at the end of the meeting or by telephone after deciding to take part. Patients individually agreed on a convenient meeting

[28] Micrographia is abnormally small, cramped handwriting; sometimes one of the early symptoms of PD.

time with the researcher either in their own homes or at the society meeting venue. The first meeting was introductory – the researcher explained the purpose of the study, how to fill in the questionnaires and sleep diary and how the actigraphs worked. Diaries, questionnaires and actigraphs were left with participants. In accordance with the university research ethics, filling in the questionnaire was taken as a written informed consent. The next meeting (at least 5 days later) was for the completed questionnaires and actigraphs to be returned to the researcher and also provided an opportunity for participants to ask further questions about the study. Debriefing took place at the end of the study at the PD society meetings or, if preferred, was sent by post.

Control Group

An age-matched control group was contacted on a snowball principle. Similarly to the PD group, the controls also had two meetings with the researcher; one to explain the purpose of the study and give them the questionnaires, diaries and actigraphs and other to collect these. Again, in accordance with the university research ethics, filling in the questionnaire was taken as a written informed consent. Debriefing was done either in person, by phone or post (depending on their preference).

High and Low-Prone Normal Individuals

Potential participants were 226 students from Oxford Brookes University. After filling in the HQ, 5% of people who scored high (N=12) and 5% of people who scored low (N=13) on HQ (see Section 3.2.1) were invited to participate in the further study between December 2006 and March 2007. At the first meeting they were given the instructions on how to wear the actigraphy and were given the questionnaires and sleep diaries to fill during the one week they were wearing the sleep watch. In accordance with the university research ethics, filling in the questionnaire was taken as a written informed consent. 1 high-prone individual was excluded due to a history of psychiatric disorder, and two individuals from a low-

prone group were wearing the watch inconsistently, which prevented the further analysis. 11 high and 11 low-prone normal individuals finished all stages of the study, and returned the watches, sleep diaries and questionnaires on a second meeting, when they also had a time to ask further questions about the study. All the meetings took place in a University room.

8.2.4 Statistical Analysis

Statistical analysis was performed using SPSS for Windows version 15.0 (SPSS Inc., Chicago, IL). Descriptive statistics and multiple ANOVAs (with Bonferroni correction) were used to describe and compare the profiles of sleep patterns in both PD groups, the controls, and high and low-prone normal individuals. Correlation analysis was used for comparison of the following subjective (as measured by the sleep diaries) and objective (as measured by the actigraphy) sleep variables that could be directly compared: sleep onset, sleep offset, sleep duration and sleep latency.

8.3 Results

8.3.1 Demographics

Using the independent t-tests and ANOVAs, there was no difference between hallucinating and non-hallucinating PD patients on any of the following independent variables: age, gender, daily dopamine dosage, HY disability stage, years since diagnosis, any other concurrent illness, side of body more affected by PD, migraine, or vision problems. The two PD groups only differed in the presence of VHs.

Likewise, using the independent t-tests and ANOVAs, there was no difference between high and low-prone participants in age, gender, vision and hearing problems, dyslexia or handedness.

8.3.2 Sleep Questionnaires

PD Groups and the Control Group

There were large individual differences between hallucinating and non-hallucinating PD patients, and the control group in their sleep habits as measured by the sleep questionnaires (Table 8.2).

Table 8.2. Subjective reports of sleep patterns of both PD groups and the controls: Means, SDs and significance results.

	Hallucinating PD patients	**Non-hallucinating PD patients**	**Control group**	**Notes**
Sleep questionnaires				
- Sleep diary				
Time to sleep	23.02 (1.28)	22.62 (1.07)	21.92 (0.90)	A
Sleep latency (mins)	11.62 (7.06)	14.84 (13.93)	22.50 (13.16)	n.s.
Time of waking	6.53 (1.60)	6.38 (1.47)	6.64 (1.30)	n.s.
Hours/night	5.46 (1.14)	6.05 (1.48)	7.42 (1.43)	A, B
- PSQI				
Factor 1	1.45 (0.69)	1.56 (0.81)	1.00 (0.38)	n.s.
Factor 2	0.75 (0.87)	1.00 (0.97)	1.20 (0.78)	n.s.
Factor 3	1.75 (0.96)	1.31 (1.08)	0.47 (0.64)	A, B
Factor 4	1.17 (1.40)	1.44 (1.21)	0.80 (1.08)	n.s.
Factor 5	1.83 (0.72)	1.63 (0.72)	1.13 (0.35)	A
Factor 6	0.25 (0.87)	0.56 (1.21)	0.27 (0.80)	n.s.
Factor 7	2.58 (0.67)	2.19 (0.83)	1.07 (1.10)	A, B
PSQI	12.92 (6.99)	11.31 (4.50)	5.87 (3.62)	A, B
- ESS				
ESS	14.17 (3.64)	10.13 (4.63)	5.87 (4.76)	A, B
- BSAQ				
Sleep apnoea	4.25 (1.54)	3.38 (1.82)	2.27 (1.53)	A
- Other questions				
Restlessness	1.33 (1.23)	1.31 (1.35)	0.20 (0.78)	A, B
Fidget	1.17 (1.27)	1.81 (1.33)	0.80 (1.01)	n.s.
Nocturnal VHs	1.00 (1.04)	0.50 (0.12)	0.00 (0.00)	B, C
Numbness	1.00 (1.35)	0.88 (1.20)	0.40 (0.81)	n.s.
Cramps	1.42 (1.08)	0.81 (0.99)	0.79 (1.19)	n.s.
Posture	1.33 (1.16)	1.00 (1.32)	0.67 (1.05)	n.s.
Tremor	0.92 (1.38)	1.31 (1.30)	0.00 (0.00)	B
Tiredness	1.33 (1.07)	1.13 (1.26)	0.60 (0.99)	n.s.
Unexpected asleep	2.17 (1.19)	1.06 (1.24)	0.47 (0.99)	A, C

Data are presented as means (±standard deviations). PSQI = Pittsburgh Sleep Quality Index; ESS = Epworth Sleepiness Scale; BSAQ = Berlin Sleep Apnoea Questionnaire;
A = Significant difference ($p < .05$) between hallucinating PD patients and the controls;
B = Significant difference ($p < .05$) between non-hallucinating PD and the control group;
C = Significant difference ($p < .05$) between both PD groups
n.s. = the differences between groups are not significant

Sleep Quality and Sleep Disturbances

There was a general trend that non-hallucinating PD patients reported more sleep disturbances than the controls but less than hallucinating PD patients. Hallucinating PD patients went to bed significantly later than the control group. There was no statistical difference in time of final waking and estimated sleep latency between the three groups. The controls had a longer sleep time per night compared to both PD groups (as measured by the PSQI factor 3 - estimated sleep duration), suggesting more awakenings during the night-time and insomnia related problems in both PD groups. Both PD groups scored high above the clinical cut-off for their global scores on the PSQI. Overall, three factors of PSQI as well as the global PSQI score were significantly higher in PD groups: sleep disturbances were only significant between hallucinating PD patients and the controls; PD groups rated their quality of sleep lower than the controls, they had more often trouble sleeping because of waking up in the middle of the night or early morning, using the bathroom, problems with breathing comfortably, coughing, snoring, feeling too cold/hot, having bad dreams or pain.

Sleep Apnoea

Although no group met the criteria for sleep apnoea, hallucinating PD patients scored significantly higher than the controls on the BSAQ ($p = .007$).

Daytime Sleepiness

Daytime sleep-related problems occurred more often in both PD groups compared to the controls; PD groups reported more problems of daytime functioning (the PSQI factor 7) ($p = .001$) and a higher level of daytime sleepiness measured by the ESS scores ($p = .001$). Hallucinating and non-hallucinating PD patients significantly differed on only two questionnaire items about other sleep-related problems, namely the occurrence of nocturnal VHs and their levels of daytime

sleepiness. The first is not surprising since the groups were divided according to the presence of VHs. The difference in level of daytime sleepiness between both PD groups was assessed both by an item enquiring about unexpectedly falling asleep as well as with the ESS. The difference between the groups was significant on the item, and approached statistical significance on the ESS ($p = 0.065$).

Other Sleep Disturbances Common in PD

Apart from these sleep-related problems, the PD groups also reported the following night-time sleep problems: fidgeting, restlessness of legs and arms or painful posturing of arms or legs causing disruption of sleep, painful muscle cramps, night-time hallucinations, and numbness or tingling of arms or legs. However, the only statistical differences between both PD groups and the controls were for restlessness, night-time VHs and tremor.

High and Low-Prone Normal Individuals

Subjective sleep results of high and low-prone normal individuals, as measured by the sleep questionnaires, are summarized in Table 8.3.

Table 8.3. Subjective reports of sleep patterns of high and low-prone individuals: Means, SDs and t-tests results.

Sleep questionnaires	High-prone normals	Low-prone normals	F	df	p
- *Sleep diary*					
Time to sleep	24.00 (.98)	23.94 (1.72)	-.099	20	.922
Sleep latency (min)	28.86 (30.77)	17.64 12.35)	-1.123	20	.275
Time of waking	8.56 (1.76)	8.24 (1.18)	-.505	20	.619
Hours/night	7.54 (1.27)	7.29 (1.30)	-.472	20	.642
- *PSQI*					
Factor 1	1.09 (.70)	.55 (.52)	-2.070	20	**.050**
Factor 2	1.36 (.92)	1.00(1.00)	-.886	20	.386
Factor 3	.54 (.69)	.64 (.81)	.284	20	.779
Factor 4	.54(1.04)	.45 (.69)	-.243	20	.811
Factor 5	1.45 (.52)	1.00 (.45)	-2.193	20	**.040**
Factor 6	.27 (.65)	.00 (.00)	-1.399	20	.177
Factor 7	1.18 (.75)	.54 (.52)	-2.308	20	**.032**
PSQI	6.09(3.45)	4.18 (2.36)	-1.516	20	.145
- *ESS*					
ESS	6.73 (2.53)	6.00 (3.82)	-.526	20	.605
- *BSAQ*					
Sleep Apnoea	2.55(1.37)	.64 (1.21)	-3.471	20	**.002**

Data are presented as means (±standard deviations). PSQI refers to Pittsburgh Sleep Quality Index; ESS: Epworth Sleepiness Scale; BSAQ: Berlin Sleep Apnoea Questionnaire.

Sleep Quality and Sleep Disturbances

There is a general trend that high-prone group reported more sleep disturbances than the low-prone group. Despite only few components from the questionnaires where the difference between both groups was significant, the high-prone group rated their quality of sleep (the PSQI factor 1) lower than the low-prone group; they more often had trouble sleeping because of waking up in the middle of the night or early morning, using the bathroom, problems with breathing comfortably, coughing, snoring, feeling too cold/hot, having bad dreams or pain (the PSQI factor 5).

Sleep Apnoea

Although no group met the criteria for presence of likely sleep apnoea, the high-prone group scored significantly higher than the low-prone group on the BSAQ ($p = .002$).

Daytime Sleepiness

Daytime sleep-related problems occurred more often in the high-prone group compared to the low-prone group; the high-prone group reported more problems of daytime functioning (the PSQI factor 7) ($p = .032$), but not also a higher level of daytime sleepiness measured by the ESS scores ($p = .605$).

8.3.3 Actigraphy

PD Groups and the Control Group

Actigraphy results for hallucinating and non-hallucinating PD patients, and the age-matched controls are summarized in Table 8.4.

Table 8.4. Sleep patterns of both PD groups and the controls as measured by actigraphy: Means, SDs, and significance results.

	Hallucinating PD patients	**Non-hallucinating PD patients**	**Control group**	**Notes**
Time to sleep	23.60 (3.28)	23.08 (1.39)	21.79 (1.61)	A, B
Time of waking	5.92 (1.84)	6.29 (1.66)	5.43 (1.63)	n.s.
Duration	352.16 (115.50)	395.72 (97.27)	452.46 (59.74)	A
Activity mean	57.31 (21.15)	43.52 (26.68)	18.98 (10.12)	A, B
Activity SD	65.31 (19.50)	60.54 (20.67)	37.46 (12.50)	A, B
Sleep minutes	191.66 (102.09)	284.90 (116.69)	392.56 (48.72)	A, B, C
WASO	152.85 (59.54)	108.94 (46.92)	57.08 (49.54)	A, B, C
Mean WE	12.83 (5.68)	13.60 (20.37)	5.88 (2.85)	n.s.
Long WE	5.84 (2.79)	4.75 (2.15)	3.27 (2.36)	A
Longest WE	49.52 (13.78)	43.42 (31.98)	24.42 (20.15)	A
Sleep efficiency	56.23 (16.21)	71.30 (17.40)	87.65 (9.71)	A, B, C
Sleep latency	51.66 (56.52)	29.26 (34.40)	9.46 (7.85)	A, B
Sleep episode	22.64 (7.29)	18.51 (6.19)	12.02 (5.22)	A, B

WASO = awakenings after sleep onset, WE = wake episode
A = Significant difference ($p < .05$) between hallucinating PD patients and the controls; B = Significant difference ($p < .05$) between PD non-hallucinators and the controls; C = Significant difference ($p < .05$) between both PD groups; n.s. = the differences between groups are not significant.

Differences between both PD groups and the controls were significant for many sleep parameters and similarly to the results from the questionnaires, non-hallucinating PD patients usually reported better sleep patterns than hallucinating PD patients but lower than the controls. Most differences were found between hallucinating PD patients and the controls, and some were found between non-hallucinating PD patients and the controls. Further, only few differences were significant between both PD groups. These findings suggest that PD groups are more similar to each other than to the controls in terms of sleep patterns and that both PD groups have more sleep-related problems than the controls.

Both PD groups differed from the controls on the following sleep parameters: delayed time to sleep, increased activity mean and SD, longer sleep latency and sleep episodes. Hallucinating PD patients also differed from the controls on additional sleep parameters: decreased duration of sleep and increased long and longest wake episode.

All three groups differed significantly between each other in sleep minutes, WASO and sleep efficiency. All three parameters show the same trend: hallucinating PD patients had the least minutes of sleep during the sleep period, followed by non-hallucinating patients and then the controls. The same pattern results were found for sleep efficiency. Hallucinating patients experienced more wake minutes during the sleep period, followed by non-hallucinating patients and finally the controls. This suggests that there are some specific sleep patterns that change with PD and are more pronounced in the hallucinating patients.

Finally, compared to the subjective estimations (see Table 8.2), both PD groups underestimated their sleep latency; and on the other hand, the controls overestimated their latency time.

High and Low-Prone Normal Individuals

Actigraphy results for high and low-prone groups are summarized in Table 8.5. Only four significant differences were noted between the groups, but many of them were close to reaching the statistical significance. The high-prone group had more

sleep related problems as measured with an objective measure of sleep. Most notably the two groups differed on activity mean, sleep minutes, awakenings after sleep onset (WASO) and mean wake episode (Table 8.5).

Table 8.5. Sleep patterns of high and low-prone groups as measured by actigraphy: Means, SDs, and t-tests results.

	High-prone normals	**Low-prone normals**	**t**	**df**	**p**
Time to sleep	23.12 (5.36)	23.06 (6.51)	.024	19	.981
Time of waking	9.21 (1.76)	9.40 (1.74)	-.247	19	.807
Duration	427.38 (90.23)	485.62 (76.21)	-1.603	19	.125
Activity mean	21.90 (8.12)	15.39 (4.17)	2.345	19	.030**
Activity SD	37.89 (9.36)	31.14 (6.96)	1.886	19	.075
Sleep minutes	364.36 (99.48)	445.88 (77.31)	-2.108	19	.049*
WASO	70.21 (43.24)	38.86 (25.08)	2.057	19	.050*
Mean WE	5.90 (2.68)	3.91 (1.58)	2.099	19	.049*
Long WE	4.13 (2.54)	2.31 (1.56)	2.004	19	.060
Longest WE	20.66 (11.09)	12.77 (7.34)	1.940	19	.067
Sleep efficiency	82.59 (12.83)	91.01 (5.37)	-1.996	19	.058
Sleep latency	20.12 (22.81)	10.13 (6.44)	1.395	19	.179
Sleep episode	13.79 (2.73)	11.71 (2.49)	1.823	19	.084

WASO = awakenings after sleep onset, WE = wake episode;
* indicates $p<0.05$ and ** $p<0.01$.

8.3.4 Relation between Subjective and Objective Sleep Measures

Table 8.6. Correlations between subjective and objective sleep measures in PD and student groups.

	PD patients	**Students**
Time to sleep	.357 *	-.474
Time of waking	.677 **	.560 *
Sleep latency	-.011	-.455 *
Sleep duration	.553 **	.551 *

** Pearson r is significant at the 0.01 level (2-tailed).
* Pearson r is significant at the 0.05 level (2-tailed).

The table shows there is a statistically significant agreement between subjective estimations and actigraphy derived measures on several sleep patterns, both in PD groups and in the student groups.

8.4 Discussion

The aim of the study was to examine sleep patterns in hallucinating PD group and in high-prone individuals, which could lead to a better understanding whether the same components present a risk factor for both VHs in PD and hallucination-proneness in the normal population. Hallucinating and non-hallucinating PD patients, as well as the high and low-prone individuals, did not differ in terms of demographic characteristics (see Table 8.1); therefore, all differences in sleep patterns were attributed to the occurrence of VHs in PD group and high hallucination-proneness in the normal group.

8.4.1 Sleep Questionnaires

Both hallucinating and non-hallucinating PD patients showed disrupted sleep patterns compared to the control group on the subjective measures of sleep (see Table 8.2), additionally supported by the significantly lower quality of sleep quality in both PD groups compared to the control group (as indicated by the PSQI factor 1). The first finding from the present study is that disturbed sleep patterns are a hallmark of PD, irrelevant of the occurrence of VHs. This is in accordance with other sleep studies, reporting significantly disrupted sleep in PD patients (Arnulf, 2005; Boeve, Silber, & Ferman, 2004; Chaudhuri, Healy et al., 2006; Dhawan, Healy, Pal, & Chaudhuri, 2006; Partinen, 1997; Thorpy & Adler, 2005).

However, stemming from the continuum hypothesis, the aim of the study was to explore if the same risk factors are identified in both clinical and non-clinical populations. Similarly to the hallucinating PD group, high-prone individuals reported more disrupted night-time sleep patterns, namely more sleep problems (expressed by PSQI factor 5), a higher chance of sleep apnoea symptoms and a lower satisfaction with sleep (see Table 8.3). Additionally, high-prone individuals reported more disturbed daytime sleep patterns, namely "*troubles staying awake while driving, eating meals, or engaging in social activities*" and "*keep up enthusiasm to get things done*" (expressed by the PSQI factor 7).

The results from the subjective sleep measures therefore suggest that similar sleep patterns and sleep problems are related to VHs in PD as well as to hallucination-proneness in the normal population. Although the idea of continuum has been suggested to be replaced by two separate models (see Discussion of Chapter 7), the results from this study are the first to show that very similar sleep patterns might serve as a common risk factor in both VHs in PD and in hallucination proneness in the normal population. A closer look of specific sleep patterns was possible by the use of objective measure of sleep patterns, actigraphy.

8.4.2 Actigraphy

The use of actigraphy in the present study provided a novel account of sleep disturbances in PD, namely fewer sleep minutes, poorer sleep efficiency, more activity during sleep and activity deviation, long wake episodes and awakenings after sleep onset (see Table 8.4). These results suggest that sleep patterns during both night and day in the PD patients are qualitatively and quantitatively different from the sleep patterns in the control group. Additionally, the hallucinating PD patients statistically differed from both the non-hallucinating PD groups and the control group in lower sleep minutes, lower sleep efficiency and more awakenings after sleep onset. Similar results have been proposed by several other authors[29], using the gold standard in sleep research: polysomnography. A high agreement between the first actigraphy study to date and the polysomnographic studies is especially valuable, because it confirms that actigraphy is a valid and reliable measure of sleep patterns in patients with PD.

Few actigraphy and questionnaire sleep measures were significantly more affected in the hallucinating compared to the non-hallucinating PD group, namely sleep minutes and awakenings after sleep onset, sleep efficiency and unexpected sleep attack during daytime. PD patients frequently reported having numerous unwanted awakening periods during the night or in the morning (Grandas & Iranzo,

[29] Comella et al., 1993; Diederich, Vaillant, Mancuso, Lyen, & Tiete, 2005; Manni et al., 2002; Nomura et al., 2003; Onofrj et al., 2002; Pacchetti et al., 2005.

2004; Schapira, 2004). The results from the actigraphy confirm these findings, indicating that the hallucinating PD patients experience more awakenings after sleep onset than the non-hallucinating patients. Consequently, fragmented sleep during night time (expressed by more awakenings, lower sleep minutes and lower sleep efficiency) could explain why the hallucinating PD patients often report a higher level of sleepiness during daytime. This leads to the biggest difference between the three groups, namely the probability of suddenly falling asleep during daytime despite having good night time sleep. According to the results from the present study, the hallucinating PD patients are at a higher risk of daytime somnolence (the ESS was high above the cut-off point, see Table 8.2) and to unexpectedly falling asleep during daytime. These findings are consistent with Arnulf et al. (2000) who noted that VHs coincided with daytime episodes of REM sleep and suggested that VHs in PD might reflect a narcolepsy-like REM sleep disorder. Incidentally, a strong association between narcolepsy and RBD was also reported by Nightingale et al. (2005).

Stemming from the hypothesis that hallucinations occur on a continuum, depending on the risk factors taken into account, the aim of the study was to explore if the same risk factors are identified in both clinical and non-clinical population. Similarly to the hallucinating PD group, the high-prone individuals reported having more sleep related problems and more disrupted sleep patterns than the low-prone individuals (see Table 8.5). Specifically, the high-prone individuals expressed strikingly similar arousal–related problems to the hallucinating PD patients, namely fragmented sleep with decreased sleep minutes, several awakenings and longer wake episodes during night time. The similarities between disrupted day and night-time sleep patterns in the hallucinating PD patients and in the high-prone individuals are the first objectively measured results to date, which provide evidence for the importance of the arousal sleep mechanisms in VHs in PD and in hallucination-proneness in the normal population.

In support of these results, dysfunctional arousal mechanisms have been also proposed in other disorders, such as narcolepsy and narcolepsy with cataplexy, which are often accompanied by vivid VHs (Dauvilliers et al., 2003; Heier et al.,

2007; Ohayon et al., 1996; Overeem, Mignot, van Dijk, & Lammers, 2001; Scammell, 2003). In these disorders, thalamic lesions affect the brain areas that control circadian rhythms (know as ascending reticular activating system). Furthermore, healthy people without psychiatric history frequently report VHs during sleep deprivation (Babkoff et al., 1989; Kollar et al., 1969), before falling asleep (hypnagogic hallucinations) or on awakening (hypnopompic hallucinations) (Ohayon, 2000; Ohayon et al., 1996).

8.4.3 Subjective and Objective Measures of Sleep

PD patients were asked to estimate how long it takes them to fall asleep (in minutes) at night and for each day they were asked to write the time they went to bed and the estimated time they fell asleep. People with PD often report problems on waking, but not problems with sleep initiation (Grandas & Iranzo, 2004; Schapira, 2004). However, the actigraphy data are the first data to date revealing that sleep latency in PD patients is significantly longer than in the control group and that it is significantly underestimated when assessed subjectively (compare Tables 8.2 and 8.4). Although PD patients do not perceive the prolonged sleep latency as troublesome, it may be an important predisposition for the development of VHs in PD. Based on the work of Manford and Andermann (1998), it could be hypothesized that prolonged sleep latency is a prolonged drowsy state when the switching of thalamic relay nuclei into sleeping burst mode takes place. In this state, the transmission of sensory inputs is not completely switched off. Consequently, prolonged sleep latency, as observed in the present study, makes an ideal environment for VHs to occur. Following the work of Garcia-Borreguero et al. (2003), it could also be similarly hypothesized that the prolonged sleep latency extends intrusions of REM sleep into wakefulness, resulting in higher proneness for the development of VHs. In order to examine the link between sleep latency and the occurrence of VHs, further studies need to address this issue with the event related marker on actigraphy to mark the occurrence of VHs. Such studies would provide objective evidence whether a high incidence of VHs (as marked by pressing the

event-related button on the actigraphy) is really related to the prolonged sleep latency.

Manford and Andermann (1998) suggested that suddenly falling asleep during daytime is regulated by the same underlying neurological mechanisms that are also implicated in the occurrence of VHs in any clinical population, but probably different to the mechanisms that control other sleep related problems. The results from both PD groups and the normal group support their idea. Specifically, brainstem areas are affected in PD, resulting in disturbed sleep patterns in both hallucinating and non-hallucinating PD patients; however, thalamic dysfunction is probably more pronounced in hallucinating patients, expressed as arousal disturbances on one hand and as the occurrence of VHs on the other. Similar patterns appear in the normal group, where the arousal disturbances are observed in the high-prone, but not in the low-prone normal individuals. There are therefore two different sources of sleep related disorders in PD; one is related to PD in general (but not VHs), affecting the majority of the sleep patterns, and the other system, which specifically controls for arousal and VHs and is more affected in hallucinating PD patients. A similar pattern is also observed in the high-prone normal individuals who report more arousal-related sleep problems compared to the low-prone individuals. Future neuroimaging studies are warranted to address the extent of thalamic arousal controlling functioning in hallucinating and non-hallucinating PD patients and in high and low-prone normal individuals.

The findings from the present study have also important intervention implications. In the light of what is known about both the pharmacological and behavioural methods to alleviate sleep problems and foster better sleep behaviour (Askenasy, 2003; Boeve et al., 2004; Friedman & Chou, 2004; Gugger & Wagner, 2007; Medcalf, 2005; Rye, 2004), specific sleep hygiene training in this clinical group may help to alleviate some of the sleep problems associated with PD. It is far from confirmed whether sleep related behavioural techniques could help controlling VHs; however, further work is warranted to shed light on the therapeutic sleep techniques in this population.

8.4.4 Future Research Venues

More studies are needed to adequately address the detailed nature of VHs in PD and proneness to VHs in the normal population. Specifically, a carefully designed study with event-related buttons on the sleep watches would be invaluable as the first study to objectively give evidence that VHs are related to the periods of low arousal or transition from wake to sleep mode. A study of this nature would provide further evidence for direct involvement of thalamic dysfunction in the generation of VHs in PD. Further actigraphy studies investigating the role of sleep latency, and neuroimaging studies investigating the role of thalamus are similarly warranted to provide evidence for the involvement of the arousal components in the occurrence of VHs in PD.

The sleep study in the current research raised the additional possibility of an indirect link between dopaminergic treatment and VHs through sleep mechanisms. Somnolence is a recognized adverse effect of dopaminergic agonists. Dopamine agonists have been reported to cause sudden-onset sleep spells in patients with PD (Avorn et al., 2005; Comella, 2002; D. E. Hobson et al., 2002; Homann et al., 2002; Plowman et al., 2005) and Kaynak et al. (2005) demonstrated that daytime sleepiness is not present in untreated PD patients but emerges later during dopaminergic treatment. The strong link between dopaminergic medications and sleepiness suggests that dopaminergic medication has a direct effect on arousal, which consequently creates an ideal environment for the occurrence of VHs. Therefore, PD patients in general are at risk to develop VHs not because of direct, but indirect effect of dopaminergic medication through the mechanisms of arousal. Although this hypothesis is still in its infancy and awaits empirical proof, it is in accordance with the notion that the presence of RBD is significantly related to the development of VHs independently of age, gender or duration of disease but dependent on the amount of dopaminoagonist treatment (Onofrj et al., 2002). If that is indeed the case, PD patients would benefit from good sleep hygiene, paying special attention to properly regulating their sleep habits. Finally, the question of whether an increase of vigilance by pharmacological means, such as modafinil,

could be a strategy to abate VHs in PD remains to be answered (Adler, Caviness, Hentz, Lind, & Tiede, 2003; Diederich et al., 2005; Kulisevsky & Roldan, 2004).

Finally, the main advantage of actigraphy is that it is based on objective measures of sleep, and not subjective estimations. Therefore, the study focused on exploring the sleep patterns as reported by actigraphy and some particular sleep patterns, which could not have been captured by subjective measures alone, arose as important distinctions between hallucinating and non-hallucinating PD patients and between high and low-prone individuals. Therefore, the study did not aim to focus on comparison between actigraphy data and subjective estimations as much as on what do the actigraphy patterns reveal. However, when correlational analysis has been performed, there was a statistically significant agreement between subjective estimations and actigraphy derived measures on several sleep patterns, both in PD groups and in the student groups. However, several authors report about low agreement between subjective reports and objective measures as derived by the actigraphy, and it has been repeatedly demonstrated that subjective reports are limited and biased compared with objective reports (Acebo et al., 2005; Kushida et al., 2001; Sadeh, 1996). Therefore, due to the objective and easy application of the actigraphy, the future of sleep research acknowledges subjective measures as additional or supplementary reports only, and opts for a necessary use of objective sleep measures (Gaina, Sekine, Hamanishi, Chen, & Kagamimori, 2005; van den Berg, Knvistingh, & Tulen, 2008; Werner, Molinari, Guyer, & Jenni, 2008).

8.4.5 Conclusions

Problems with prolonged sleep latency, sleep maintenance during night time and troubles staying awake during daytime (despite having enough hours of night time sleep) all suggest that compared to PD non-hallucinators, hallucinating PD patients have additional sleep dysfunctions related to arousal. These results support the idea there are two different sources of sleep related disorders in PD. The sleep controlling mechanisms are severely affected in PD, but are probably not related to VHs. However, a thalamic arousal controlling system seems to be strongly

implicated in VHs in PD, as expressed by actigraphy and sleep questionnaire measures. Moreover, the current study provides a novel account for the relationship between proneness to VHs and arousal in the normal population. Strikingly similar arousal disturbances occurred in the high-prone individuals and in the hallucinating PD patients, suggesting that it is not sleep related brainstem areas in general, but rather specific thalamic arousal dysfunction that are implicated in both VHs in PD and hallucination-proneness in the normal population. Further actigraphy studies investigating the role of sleep latency, and neuroimaging studies investigating the role of thalamus, are warranted to provide evidence for the involvement of the arousal components in the occurrence of VHs in PD and hallucination-proneness in the normal population.

Chapter 9: Behavioural Cognitive Coping Strategies in Hallucinating PD Patients

9.1 Introduction

PD, as any other long-term illness, has a profound effect on patients and their families, severely affecting their daily life (Lundqvist et al., 1997). As it progresses, the motor signs of PD worsen, medication treatment becomes less effective, dependency increases, and the quality of life of patients and their carers decreases (Secker & Brown, 2005). In addition to the motor complications related to PD, VHs add to the severity of illness, life satisfaction, and shorten life expectancy (Inzelberg et al., 1998). Because of both motor and non-motor disabilities that are related to PD, Frazer (2000) proposed that stress in PD is multidimensional and multifaceted. Moreover, Aarsland et al. (1999) found that psychiatric symptoms often outweigh the physical ones, especially because in the course of PD, VHs are persistent and progressive (Goetz et al., 2001). As suggested in Chapter 2, VHs may intensify anxiety levels, disrupt daily life activities, and diminish self-esteem, therefore gravely affecting both the patient's and the caregiver's quality of life (Diederich et al., 2003).

As outlined in Section 1.6.6, mood modifications, especially depression, have often been linked to the occurrence of VHs in PD. However, the exact nature of the relationship between VHs and mood remains unclear (Fenelon et al., 2000; Holroyd et al., 2001; Inzelberg et al., 1998). The role of depression is likely to be multifaceted and complex and future studies would benefit from exploring the link in a more sophisticated way. One possibility, for example, is to investigate the relationship between depression and specific behaviour strategies that PD patients use in order to manage their hallucinations.

There is controversy concerning what treatment is best to manage VHs in PD (Diederich et al., 2003). To date, the most commonly used means of managing VHs in PD is with antipsychotic medications; pharmacological interventions are the only therapies tested with evidence-based methods. However, little is known about the behavioural management of VHs, which probably stems from a scarce amount of

studies investigating the nature of VHs in PD. As outlined in Chapters 1 and 2, VHs have been under-reported, and the emotional response to hallucinations in PD is different to the emotional response in other disorders. For example, cognitive-behavioural treatment of VHs in other disorders like schizophrenia have been long present and proven efficient (Delespaul et al., 2002). Furthermore, behavioural treatment has been studied extensively in disorders related to stress (i.e., spinal cord injuries, cancer and even students in exam time and the carers of patients with a long-term illness) (Carver et al., 1989; Elfstrom, Ryden, Kreuter, Persson, & Sullivan, 2002; Lundqvist et al., 1997; Moorey, Frampton, & Greer, 2003; Secker & Brown, 2005). Therefore, the role of behavioural coping strategies needs to be addressed in PD patients with VHs.

Lazarus and Launier (1978) defined coping as action-oriented and an intrapersonal skill to manage external and internal demands and the perceived discrepancy between them. The use of appropriate coping strategies has been suggested to be a key factor in determining successful adjustment to severe physical illness/disability (Lazarus & Folkman, 1984). According to Barber and DeRubeis (1989) effective coping strategies do not reduce the generation of negative thoughts, but rather encourage a set of skills that help people deal with their stress and depression when they occur. Taking the studies together, the application of coping strategies promises to be an effective technique for PD patients with VHs.

However, only one study has investigated the prevalence and impact of patient-driven coping strategies to date (Diederich et al., 2003). The authors found that the main types of coping strategies used by PD patients to cope with their VHs are cognitive and interactive techniques. They also noticed that the frequency and emotional response to hallucinations are not related to the type of coping strategies that patients use. However, the authors (ibid) restricted the questions to the three main types (cognitive, interactive and visual) and recognized the need for an open-ended interview which would identify other effective coping strategies in hallucinating PD patients. Furthermore, future studies need to address the relationship between patients' emotional response to hallucinations and how well

they cope with them, and on this basis predict the most and the least efficient coping strategies.

In summary, coping strategies have been effective in dealing with stress in different disorders, but have never been satisfactorily addressed in PD with VHs. The proposed research aims to investigate the most commonly used and effective coping strategies that people with PD use in order to terminate or simply deal with their hallucinations, using a semi-structured questionnaire. Furthermore, the aim of the present study is to investigate if the patients' emotional response to their VHs is dependant on whether or not they are able to terminate them, an issue that was raised in Chapter 2. Apart from asking the patients about the level of stress they feel about their hallucinations, the present study will also use a standardized measure of depression. If the use of specific coping strategies is indeed related to lower depression, then the strategies aiming to effectively deal with VHs in PD might be adopted in the future treatment regimes. Ultimately, such structured interventions could promote healthier lifestyles and a better quality for life of PD patients and their carers.

9.2 Methods

9.2.1 Participants

Hallucinating PD Patients

The 23 hallucinating PD patients from the first study (see Section 2.2.1) were also recruited for the coping strategy study. The demographic data are summarised in Table 9.1.

Table 9.1. Demographic characteristics.

	Hallucinating PD patients	**Non-hallucinating PD patients**	**Control group**
N	23 (16 male)	20 (14 male)	12 (4 male)
Age	68.0 (4.2)	69.8 (6.6)	71.4 (5.0)
Years since diagnosis	14.0 (7.8)	9.2 (7.2)	-
Levodopa, daily dose	498.9(270.6)	502.1 (276.7)	-
HY	2.1 (0.9)	1.7 (0.9)	-

Data (except the number of participants) are presented as means (±standard deviation).

Non-hallucinating PD Patients

20 PD patients, see Table 9.1, from the same PD societies as the hallucinating PD patients were asked to fill in the Beck's Depression Questionnaire (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). All participants had normal hearing and normal or corrected-to-normal vision. The exclusion criterion was a history of psychiatric or neurological disorders.

Control Group

12 age-matched participants (see Table 9.1), who were contacted on a snowball principle, were asked to fill in the Beck Depression Questionnaire (Beck et al., 1961). All participants had normal hearing and normal or corrected-to-normal vision. The exclusion criterion was a history of psychiatric or neurological disorders.

9.2.2 Assessments

Coping Strategies Questionnaire

No questionnaire has satisfactorily addressed the coping strategies in PD with VHs to date; therefore, a new measure was developed for the current study. The Coping

Strategies Questionnaire (CSQ, see Appendix 21) was constructed based on two sources: (a) personal communication with the patients, and (b) the literature review of coping strategies with VHs in PD (Diederich et al., 2003) and on coping with stress in various disorders and illnesses[30]. As discussed in Section 2.1, the nature of VHs is a highly subjective experience (Giorgi, 2006). Hence, understanding the strategies that can be effectively used to manage VHs in PD should arise from the patients themselves, rather than presenting the patients with a fixed set of answers. Therefore, the CSQ combines the findings and knowledge from the previous studies as well as spontaneous reports from the patients themselves.

The CSQ is comprised of 50 questions relating to the various coping strategies. Patients are asked to think about how they coped with their VHs in the past and also indicate how often they used each described method. The answers varied from "Very often", "Often", "Sometimes" and "Not at all". Additionally, patients were asked how often they worried about the images in the last month, ranging from "Most of the time" to "A lot of the time", "Some of the time" and "None of the time". Patients were also asked if they can make the images disappear, and if so, how. Finally, they were encouraged to think of any other useful ways that helped them make the images disappear, especially if they were not stated in the questionnaire, and describe it as much detail as possible.

Beck Depression Questionnaire

The Beck Depression Inventory – BDI (Beck et al., 1961), see Appendix 22, is a 21-question multiple-choice self-report instrument, and one of the most widely used instruments for measuring the severity of depression. BDI is composed of items relating to depression symptoms such as hopelessness and irritability, cognitions such as guilt or feelings of being punished, as well as physical symptoms such as fatigue, weight loss, and lack of interest in sex. Participants respond how they have been feeling in the last week; each question has a set of at least four possible answer

[30] E.g., Carver et al., 1989; Delespaul et al., 2002; Elfstrom et al., 2002; Lundqvist et al., 1997; Moorey et al., 2003; Perron & Munson, 2006; Secker & Brown, 2005.

choices, ranging in intensity. For example: (0) "I do not feel sad", (1) "I feel sad", (2) "I am sad all the time and I can't snap out of it", (3) "I am so sad or unhappy that I can't stand it".

When the test is scored, a value of 0 to 3 is assigned for each answer and then the total score is compared to a key to determine the severity of depression. The standard cut-offs are as follows:

- 5–9 is considered normal,
- 10–18 indicates mild-moderate depression,
- 19–29 indicates moderate-severe depression and
- 30–63 indicates severe depression.

Higher total scores indicate more severe depressive symptoms. Total score below 4 points indicates a possible denial of depression, faking good, and is below the usual score for the general population.

9.2.3 Procedure

The study was introduced verbally and information sheets were given out at the monthly meetings in different PD societies throughout the UK between October 2006 and September 2007. Potential participants with VHs were encouraged to take part. Those who decided to participate contacted the researcher at the end of the meeting. Patients individually agreed on a convenient meeting time with the researcher either in their own homes or at the society meetings venue. All participants were then given the VHs questionnaire and were asked to fill it in before the scheduled meeting. In accordance with the university research ethics, completing the questionnaire was taken as a written informed consent. Questionnaires were returned at the next meeting and further questions were asked if the patients' responses were ambiguous. A debriefing document was sent by post to the patients at the end of the study.

9.2.4 Statistical Analysis

The aim of the study was to provide detailed descriptions of the strategies that PD patients use to cope with their VHs. Therefore, the participants' answers were taken as qualitative descriptions of the phenomena. In order to identify the predominant strategy, descriptive statistics were used to describe the profile of hallucinating PD patients and their coping strategies. ANOVAs were used to compare depression level between PD hallucinating, non-hallucinating and the control group. Correlation analysis was used to explore the link between stress, control over VHs and subjective disturbing nature of VHs.

All quantitative analyses were performed using SPSS for Windows version 15.0 (SPSS Inc, Chicago, Ill., USA).

9.3 Results

9.3.1 Coping Strategies

From the results of the coping strategies questionnaire, the following eight coping strategies were classified (Table 9.2):

Table 9.2. Coping strategies by classification.

Coping strategy	Example	Frequency
1. Acceptance	I learnt to live with the images. I accept the images and that the situation cannot be changed I get used to the idea that the images come and go. I admit to myself I cannot deal with the images and quit trying. I reduce the amount of effort I am putting into making the images disappear. I try to make the best of life despite the images. Seeing the images does not prevent me from enjoying the things I used to enjoy.	10
2. Cognitive approach	Ask people with similar experience. Get advice from someone who knows about hallucinations. I try to find out more about the nature of the images. I say to myself: These images are not real.	8
3. Emotional coping	I discuss the fears related to the images with someone. I talk to someone how I feel about the hallucinations. I get sympathy and understanding from someone. I get upset by the images and let my emotions out.	8
4. Action oriented	I take a positive action to solve hallucinations. I concentrate my efforts on doing something about it. I try to come up with a strategy. I see someone who could do something about the images. I would be willing to take medications to cease the images.	7
5. Humour	I make jokes about the images with my family and friends. I can laugh and see the funny side of images.	7
6. Stepping out of situation	I stand back to get the images into proportion. I try to see if the images are pessimistic.	3
7. Religious help	I seek God's help. I put my trust in God.	2
8. Relaxation	I try breathing slowly and deeply. I practice relaxation.	2

"Frequency" refers to the number of patients that reported using specific types of coping.

Most patients used more than one coping strategy when dealing with their VHs. The majority of patients have accepted that their hallucinations come and go. Other frequent coping strategies can be classified as cognitive approach and emotional coping (used in at least 35% of patients), and action-oriented and humour coping strategy (used in at least 30% of patients). Other strategies were not commonly reported.

All patients were asked to describe the coping strategy they found most useful, and the following answers were given (see Table 9.3):

Table 9.3. Descriptions of the most useful coping strategies.

Coping Strategy	Examples
1. Action-oriented Approach	I look directly at the image. I concentrate on them. I look away from the image and when I look back, the hallucination is gone. I blink and they go away or change. I blink my eyes very quickly. I close my eyes and when I look back, the image is gone. I rub my eyes. I turn on the lights. They appear in the dark when the lights are off, so I turn the light on. I turn off the lights. There is usually bright white background when looking intensely, so I turn the lights off. It seems to be when I am really tired and cannot concentrate on reading my book, so I stop reading and turn off the lights. When I am not stressed but slightly fatigued, I turn off the lights and go to sleep. I watch TV.
2. Cognitive Approach	I persuade myself that the images are just my imagination and not really there. I am aware that they are not really there. I just understand that the images are not real. I know my brain just misinterprets what my eyes see. When I tell my husband about what I am seeing his response is to tell me, 'don't be stupid there is nothing or nobody there', and the images disappear. If I want to make the images disappear, I close my eyes for few seconds and tell myself they have gone.
3. Emotional Coping	I talk to someone.
4. Acceptance	The images appear when I wake up during the night. As I am asleep, I cannot create a strategy to make them go away, so I just wait for the images to disappear.
5. No strategy	I don't do anything. [2 reports]

The results indicate that the majority of patients described a simple action oriented coping strategy (56% of all patients) or cognitive approach (26%) to best deal with their images. One patient used emotional coping and one used acceptance. Two patients did not try to make them disappear (one of whom enjoyed having the company of his hallucinations).

9.3.2 Emotional Response to VHs

Means and standard deviation of PD hallucinating, non-hallucinating and age-matched control group on the BDI are displayed in Table 9.4. The non-hallucinating PD group and the control group just made the criteria for a mild depression (5-9 points are considered normal), and hallucinating PD patients fell in the mild-moderate depression range (10-18 points). However, the multiple ANOVA showed no significant difference between the three groups ($F=2.052$, $df=2,37$, $p = 0.143$).

Table 9.4. BDI: Means and SDs.

	M	**SD**
PD hallucinators	15.45	5.46
PD non-hallucinators	9.94	9.06
Control group	10.45	5.94

Apart from the coping strategies they use, patients were also asked if they felt stressed about their VHs ("*Stress*"), if they have control over them (i.e., can at least occasionally make them disappear) ("*Control*") and if they found the images disturbing ("*Disturb-subjectively*"). The images reported by patients were also classified as (non-)disturbing ("*Disturb-objectively*") by the researched based on the patients' reports of the images (e.g., spider and rodents were classified as disturbing and ordinary people and unspecific images and ordinary people were classified as non-disturbing). The data is displayed in table 9.5.

Table 9.5. Emotional responses of PD patients to their VHs.

Patient	Gender	Age	Stress	Control	Disturb - subjectively	Disturb- objectively	Brief description of VHs (for full description, see Table 2.2)
1	M	80	-	Yes	Yes	No	People, animals.
2	M	79	No	Yes	No	No	Ordinary people.
3	M	71	No	No	No	No	Wife.
4	M	80	No	No	No	Yes	Animals, children, insects.
5	M	68	No	No	No	Yes	Spiders, people.
6	M	54	No	Yes	No	Yes	A spider with its legs kicking.
7	M	67	No	Yes	No	No	Shadows of people around cars, animals, children.
8	F	65	No	Yes	No	No	People, a dog.
9	M	59	No	No	No	No	People.
10	M	59	No	No	No	No	Hallucinations are blurred.
11	M	74	No	No	No	Yes	Shadowy animals, usually small rodents (mice) and spiders.
12	M	62	No	Yes	No	No	Mainly human faces or animal shapes.
13	M	72	No	Yes	No	No	Fine pattern of fine lines on bright white background, moving back and forward. People.
14	F	72	No	Yes	No	No	People. Shapes – usually bright light or fireworks.
15	F	62	Yes	Yes	Yes	No	People.
16	F	63	Yes	Yes	Yes	Yes	People trying to harm me. People (family) being buried. Images are often coming towards me and trying to "get" me
17	M	65	Yes	Yes	No	No	Hallucinations are blurred.
18	M	78	No	No	No	No	A girl sitting in a settee. A dog. People walking up and down the street.
19	M	67	No	Yes	No	Yes	Mainly people and insects.
20	M	66	No	Yes	No	No	Hallucinations are blurred.
21	F		No	No	No	Yes	People standing. People coming down from ceiling, when they hit the floor, they disappear.
22	F	61	No	Yes	No	No	People's faces. Trees. Buildings.
23	F	61	Yes	No	Yes	No	Hallucinations are blurred.

- indicates missing data

Control over VHs was not related to the perceived stress ("*Stress*), to the subjective disturbing nature of VHs ("*Disturb-subjectively*") or to the objective disturbing nature of VHs ("*Disturb-objectively*", see Table 9.6). Furthermore, there was no correlation between subjective and objective rating of the disturbing nature of the VHs. However, the perceived stress was strongly correlated with the subjective disturbing nature of VHs.

Table 9.6. Spearman Rho correlations between stress, control, and subjective and objective disturbance.

	Stress	**Control**	**Disturb-subjectively**
Control	.175		
Disturb-subjectively	.842**	.133	
Disturb-objectively	-.038	-.132	-.011

** Correlation is significant at the 0.01 level (2-tailed).

9.4 Discussion

23 PD patients with VHs and relatively early motor stages of PD participated in the study. With the exception of 2 patients, each patient used more than one constructive coping strategy. Simple behavioural strategies (either action oriented or cognitive approaches), mainly based on the visual modifications (e.g., rubbing their eyes, looking away, concentrating on the images, etc.) were reported as the most efficient strategies. Very differently, Diederich et al. (2003) reported that the interactive techniques, where the patients verify the non reality of the hallucinations, were the most common strategy in their study; however, no patients reported touching the images as an efficient mean of coping with VHs in the present study.

Dopaminergic over-stimulation of the retinal neurons have been related to partial sensory deprivation (Diederich et al., 1998), which is a long-appreciated risk factor for hallucinations in other clinical contexts (e.g., in Charles Bonnet syndrome, see Rosenbaum et al., 1987; Teunisse et al., 1996), as it permits the

(re)emergence or release of previously recorded percepts (Diederich et al., 2005). PD patients from the present study frequently reported lightening the environment (e.g., turning the lights on) as a beneficial means of ceasing the hallucinations. Similar to the results from the study on the nature of VHs (see Chapter 2) this coping strategy further illuminates the importance of a dimly lit environment as an important predisposition for the occurrence of VHs. Likewise, closing the eyes (or just blinking) and focusing on the images were described as a frequent coping strategy. It is possible that through these strategies PD patients could improve their visual acuity, a factor proposed to be critical in the generation of VHs (Buttner et al., 1996; Diederich et al., 1998; Matsui, Udaka et al., 2006; Menon, 2005, see also Chapter 4). In support of this hypothesis, some patients reported their VHs are peripheral and they disappear when they concentrate on them, i.e., bring hallucinations to their central vision (Barnes & David, 2001; Diederich et al., 2003). Similarly, Holroyd et el. (1992) report that sensory stimulation eliminates VHs in Charles-Bonnet Syndrome.

The majority of the coping strategies that were used by the hallucinating PD patients in the present study combined practical action-oriented behavioural and cognitive components that enhanced patients' understanding of their hallucinations. The same combination is a basis for cognitive behavioural therapies, which aim to develop both cognitive and behavioural skills to cope with stressors, and are beneficial for the patients with long-term illnesses and their carers (Starker & Jolin, 1982). The use of these active coping strategies is also in line with Frazier's (2000) notion that problem-focused active coping may be best for behavioural change, and emotional regulation may be best for psychological reactions to illness. Further, emotional coping may be more efficient when dealing with the ambiguity and unpredictability of illness (Maes, Leventhal, & de Ridder, 1996), which is especially true for patients with PD.

Apart from the coping strategies, the aim of the study was also to explore a link between specific coping strategies and the level of depression. Although there was a trend that VHs might add up to depression in PD, the difference on the BDI between PD hallucinating, non-hallucinating and the control group was not

significant. A mild-moderate depression in PD patients with VHs is therefore probably due to the disease itself, rather than being related to VHs specifically. This is in accordance with the reports from only 4 patients who were stressed over their VHs in the past month (see Table 9.5). Morrison et al. (2000) suggesting that hallucinations become distressing only when appraised as uncontrollable and dangerous. However, this was not the case in the present study, where the control over the images was not related to how stressed patients felt about their VHs (see Table 9.6). Moreover, the stress about VH was not related to the objective disturbance of images (e.g., spiders tend to have a more emotional reaction than unspecific images); the level of stress about VHs was solely related to how disturbing the images were for the patients themselves (even when the images were unthreatening or even unspecific and blurred). Therefore, the level of stress in hallucinating PD patients from the present study was rare, as most patients more or less efficiently managed their VHs. A broad range of coping strategies that PD patients use to cope with their VHs is probably related to low-level stress over hallucinations; therefore, the present study gives an insight into a beneficial role of the cognitive-behavioural approach when dealing with VHs and strongly encourages application of a set of cognitive-behavioural skills.

9.4.1 Limitations

Apart from Diederich et al. (2005) the present study is the first study addressing the behavioural coping strategies in hallucinating PD patients. As a pioneer study it retrospectively needs to address several issues which were not anticipated before the beginning of the study.

First, the questionnaire (see Appendix 21) states that "People have many ways of coping with the images they see and stress that they put them under". During the testing it became clear that the majority of hallucinating PD patients are in fact not worried about the images themselves; if anything, they worry about how others will perceive them because they have hallucinations. Furthermore, the introductory sentence implies that PD patients with VHs should have a coping strategy; however,

during the testing it became clear that although the majority of patients use (often more than one) coping strategies, there were in fact two people who did not use any coping strategies. Therefore, the introductory sentence needs to be rephrased in the future studies.

Finally, no attempts were made to provide information about the reliability and validity of the questionnaire. As discussed in Chapter 2, this poses some serious limitations to the study. However, apart from the aforementioned difficulties that come with the assessment of reliability and validity in this particular patient group (see Chapter 2), another important issue should be raised about the reliability and validity of qualitative data, such as the data gathered in the present study.

When working in subjective aspects of social sciences, and particularly in a study undertaken with a small, select group of people, it is not humanly possible for a study to be replicated (Lipscombe, 1999). This view is supported by Dey (1993, p.221) who states 'qualitative studies aim to be sensitive to factors embedded in a specific time and place, replication is therefore difficult'. It is widely acknowledged in qualitative work (Flick, 2009) that no qualitative study can be replicated in the way quantitative studies can because human behaviour is never static. The important feature, therefore, is not replication of the study 'but the possible replication of ideas and constructs which have developed during the study' (LeCompte & Goetz, 1982, p.34).

Furthermore, Lipscombe (1999) suggests that validity, reliability and objectivity are contrasted with 'credibility, transferability, dependability and confirmability' (p.272) in qualitative research. Therefore, several strategies have been adopted in order to ensure trustworthiness and methodological rigour, such as devoting enough time to build rapport; spending extended periods of time in PD societies to get more knowledgeable about PD in general (and not only about VHs in specific); systematically gathering and recording the data (writing notes when patients describe their coping strategies keeping a note of their own words); acquiring feedback from PD patients by repeating what they wrote in the questionnaire to PD patients for verification of accuracy; etc.

9.4.2 Conclusions

PD patients with VHs from the present study most commonly used a combination of behavioural and cognitive coping strategies (including emotional coping and acceptance). Specific behavioural strategies reflect the nature of VHs, emphasizing the role of peripheral vision in the occurrence of VHs and calling for further investigation of its role in the occurrence of VHs. The hallucinating and non-hallucinating PD patients and the control group had a comparable BDI score, reflecting that depression in PD is probably related to the disease itself and not to the presence of VHs. Further, only 4 out of 23 patients found their VHs disturbing, probably indicating that PD patients use active behavioural management in order to cope with their VHs. Stress over VHs was related to patients' subjective perception of the images, rather than to the disturbing nature of the images or the types of coping strategies. The present study gave evidence that the use of cognitive-behavioural techniques is encouraged in dealing with VHs in PD.

Summary of Part II

The results from Part I suggest that common cognitive, rather than demographic, variables are implicated in both VHs in PD and in hallucination-proneness in the normal population. Part II examined the role of the following risk factors: visual memory and visual imagery (Chapter 4), early visual processing components (Chapter 5), executive functions (Chapter 6), meta-cognitive processes (Chapter 7) and sleep patterns (Chapter 8). The final empirical study (Chapter 9) addressed behavioural cognitive strategies that PD patients themselves develop to cope with their VHs. Putting the results together and comparing the risk factors in both groups has led to a proposal of a new model for VHs, which will be discussed in Chapter 10.

Part III

Chapter 10: Conclusions and Recommendations

Chapter 10: Conclusions and Recommendations

10.1 Summary of the Thesis

VHs occur in a range of clinical disorders and in the normal population; different aetiologies can therefore manifest strikingly similar symptoms. Despite various origins, similar risk factors have been implicated in playing a role in the occurrence of VHs in both PD and the normal population (see Section 1.6), suggesting that a unitary model could be applied for both phenomena. However, to date no studies have systematically explored the role of different risk factors from a continuum hypothesis perspective, stating that VHs are expressed in varying degrees across the clinical and non-clinical population. The aim of the present thesis was therefore to explore whether the same risk factors are involved both in hallucinating PD patients as well as in high-prone individuals from the normal population. Consequently, the main contribution of the present work is in its investigations as to whether a unitary model can be proposed for the occurrence of recurrent complex VHs in PD and for high hallucination-proneness in the normal population. If the same set of suggested risk factors plays a role in the occurrence of VHs in PD and in hallucination-prone normal individuals, it could be hypothesised that VHs throughout different clinical and non-clinical population could arise from the same deficits. This view, for example, has been supported by Collerton et al. (2005) who suggested that one model could be applied to all disorders where VHs arise. On the other hand, if VHs in PD and hallucination-proneness in the normal population do not overlap, the continuum hypothesis needs to be rejected, at least in the light of continuum between these two specific clinical and non-clinical populations.

To this end, a range of reliable and valid neuropsychological and cognitive tasks, questionnaires, and (in the normal population) ERPs were employed. Five empirical studies were conducted on the basis of the risk factors that were suggested by several authors (see Section 1.6), namely visual memory and visual imagery study (Chapter 4), study on early visual processing components (Chapter 5), study on executive functioning (Chapter 6), personality study (Chapter 7) and study on

sleep patterns (Chapter 8). In addition, Chapter 9 addressed the role of coping strategies in PD patients with VHs and emotional responses that are related to the experiences of VHs.

All studies were carried out on carefully selected groups of participants. The selection of inclusion and exclusion criteria was set for both PD patients and the normal group before the studies commenced. In the latter group, all participants were healthy participants with normal vision and hearing, and with no history of any neurological or psychiatric disorders. The criterion for categorisation into a high or low-prone group was the score on the HQ (see Section 3.2.1).

Strict criteria were used in the studies with PD participants. Due to confusion in the literature about the possible effects of dementia on the generation of VHs (see Section 1.6.3), no PD participants were recruited that had obvious signs of dementia or were unable to take care of themselves independently. Similarly, due to the Mayeux et al.'s (1985) claim of a strong association between the occurrence of extrapyramidal signs and psychotic symptoms, special attention was given to the presence and absence of extrapyramidal signs (rigidity, bradykinesia, gait and resting tremor), as assessed by the HY disability scale (Hoehn & Yahr, 1967). All patients were monitored in respect to their age, years since diagnosis, the dosage of dopaminergic and other medication, ocular disorders, side more affected by tremor and the presence/absence of migraine.

The hallucinating and non-hallucinating PD patients that participated in the studies did not differ in any of the independent variables. Likewise, PD patients with and without ocular pathologies performed equally well on all CANTAB tests of visual memory and executive functions (see Table 2.4), ruling out the possible additional effect of ocular pathology on performance. Furthermore, there was no interaction between the presence of VHs and ocular pathology on any of the visual memory CANTAB tasks (see Table 4.4), suggesting that the significantly worse performance of hallucinating PD patients is more likely to be due to visual memory, rather than perceptual, deficits. The only difference between both groups was the presence or absence of VHs. Similarly, high and low-prone individuals only differed in the amount of bizarre visual experiences they reported. Thus, it was

postulated that cognitive, rather than demographic variables, play a role in the generation of VHs and hallucination-proneness. The equality of the hallucinating and non-hallucinating PD groups and high and low-prone normal groups made further comparisons on various tests (Chapters 4 – 8) clearer, because the differences between the two groups could not be attributed to the independent variables.

As far as the nature of hallucinations was concerned (see Chapter 2), age-related ocular problems were a frequent complication factor in the hallucinating PD patients, probably affecting the already compromised dopaminergic-based visual processing. The impoverished data from the early stages of visual processing onwards may give rise to aberrant subsequent visual processing, as well as to altered top-down processing. Well-formed and moving images suggested suboptimal functional specialization of the visual association cortex in the hallucinating PD patients. It was suggested that the nature of the images moulds the emotional responses and behavioural coping strategies for PD patients with VHs.

The occurrence of hallucination-proneness was investigated in the normal population as measured by the HQ in Chapter 3. Although it was expected that the majority of people would report having no hallucinatory-like experiences (and therefore a positively skewed distribution), a substantial number of participants from the normal population reported having hallucinatory experiences on a frequent basis. This lends weight to the argument that hallucinations exist on a continuum with normal mental events, as suggested by several authors (Crow, 1998; Lopez-Rodrigo et al., 1997; Slade & Bentall, 1988). It has been suggested that hallucinatory predisposition is a one-dimensional construct where high predisposition of hallucinatory experiences in the visual modality was significantly related to the hallucinatory experiences in all other modalities. It could be argued that the hypothesis is inconsistent with the results reported in Chapter 2, as VHs in PD occur exclusively in the visual modality. Moreover, the presence of any other hallucinations in PD has been suggested to reflect the presence of additional pathology, independent of PD (Bodis-Wollner, 1996). The different phenomenological manifestation of both phenomena could therefore cast a doubt on

the existence of a continuum between hallucination-proneness in the normal population and VHs in PD.

However, both Chapters 2 and 3 (Part I) suggested that demographic variables are not implicated in the occurrence of VHs in PD nor in hallucination-proneness in the normal population. Instead, a set of risk factors were proposed which formed a basis for the subsequent studies in Part II.

The suggested activation of the association visual cortex during the experience of VHs in PD led to the visual memory study (Chapter 4). Hallucinating PD patients did not differ from their non-hallucinating counterparts with the exception of one task in the visual memory battery. The findings pointed to the simultaneous aberrant functioning of both the visual and frontal areas in the hallucinating PD patients which was supported by an earlier fMRI study (Stebbins et al., 2004) where a pattern of relatively increased cortical activation in the frontal cortex, in conjunction with a relatively decreased cortical activation in the posterior areas, were proposed to play a role in the pathophysiology of VHs. The study was the first to reveal the dysfunctions of the visual memory in the hallucinating PD patients. However, there was no difference in performance of high and low-prone individuals on any of the tasks of visual memory. Similarly to the aforementioned differences in the phenomenological manifestation of VHs in PD and hallucination-proneness in the normal population, these results could argue against the continuum hypothesis, as visual memory failure was shown to play a role in VHs in PD, but not in hallucination-proneness in the normal population. However, although no difference on visual memory was found between the high and low-prone individuals, the results may reflect intact behavioural, but not necessarily intact neural, functioning. It is possible that both hallucinating PD patients and high-prone normal individuals share the same underlying deficits, but the pathology of PD might make the deficits more pronounced and easier to observe with the neuropsychological testing in the PD group, but not in the high-prone normal participants. Therefore, the electrophysiological study in the current research to investigate the role of the visual system was conducted with the high and low-prone normal group using the ERPs (see Chapter 5).

In the study investigating early visual processing components, significantly lower P1 and P2 amplitudes were found in the high-prone individuals compared to the low-prone individuals. It was suggested that the aberrations of the early visual processing components which seemed independent of the face recognition processes would affect the visual processing of high-prone individuals. The effect would not be extensive enough to manifest in VHs but enough to cause frequent occurrences of hallucinatory-like experiences in the normal population. The results from the visual memory study gave evidence that hallucinating PD patients show deficits of visual memory, pointing to the suboptimal functioning of the tempo-frontal brain activity. It was suggested that the high-prone individuals have not shown the same deficits due to the less extensive pathology compared to patients suffering from PD, but that the same underlying mechanisms could be observed using a neurophysiological methodology. Using the EEG, high-prone individuals displayed significantly lowered ERP responses than the low-prone individuals in the temporo-frontal areas for early and late visual processing components. The results from the visual memory and the EEG study could therefore hypothetically suggest that both hallucination-proneness in the normal population and VHs in PD are related to the similar deficits in the visual processing pathways. However, a special caution needs to be taken into account, as the results have not been obtained in the same way. In order to confirm whether or not the same deficits occur in high-prone normal individuals and in hallucinating PD patients, an EEG study needs to be carried out on PD patients during a face-perception task. Such study would not only ascertain whether or not the continuum hypothesis is plausible for hallucination-proneness in the normal population and VHs in PD, but could also give an insight whether or not there is a possible threshold, which defines the likelihood for an individual to experience VHs.

Further, the EEG results also suggest that (early and late) ERP modulations are especially associated with frontal activity during processing of complex Mooney faces (see Figure 5.2, D). Similarly, the results from the visual perception study (Chapter 4) suggest that frontal lobe functioning might be impaired in VHs in PD, as hallucinating PD patients performed significantly worse on the temporo-

frontal DMS task. These results present new evidence for the possible role of frontal dysfunction in high-prone normal individuals and in hallucinating PD patients, either through executive functions (Chapter 6) or personality factors (Chapter 7).

Contrary to what was expected, performance on executive functioning in the hallucinating PD patients was comparable to the non-hallucinating PD patients and to the age-matched control group (Chapter 6). Similarly, no differences were found between high and low-prone individuals from the normal population on any measures of executive functioning or the source memory task. The results suggested that if VHs and executive dysfunctions are linked by the same underlying neural mechanism, VHs are the first to be expressed and therefore precede the development of executive dysfunctions. In the light of the continuum hypothesis, the results could point to the possibility that executive functions do not serve as a risk factor for the occurrence of VHs in PD and hallucination-proneness in the normal population. More likely, it was suggested that intact executive functions might serve as a protecting mechanism for intact insight, rather than for facilitating the generation of VHs, as both hallucinating and non-hallucinating PD patients had a clear insight into the hallucinatory nature of the images they perceived.

As expected from the perception study, high-prone individuals were characterised by some specific personality traits, namely vivid fantasy proneness, emphasised meta-cognitive beliefs, and sociable, enthusiastic and venturesome personality characteristics (Chapter 7). The results from the study suggest that specific personality traits reflect a general response bias to endorse bizarre items, resulting in higher hallucination-proneness in the high-prone normal individuals. An alternative explanation, however, is that modifications of the early and late visual processing components consequently lead high-prone normal individuals to accept bizarre stimuli more willingly, as seen by higher scores on fantasy proneness and metacognitive beliefs. On the other hand, the hallucinating and non-hallucinating PD patients did not differ on any personality measures, possibly reflecting the nature of VHs in PD, which is independent of the top-down processes. On the basis of these results, it was suggested that personality traits are implicated

in proneness to VHs in the normal population, but not in full-blown VHs in PD. The results have important implications as they suggest that despite some similarities, the visual systems in hallucinating PD patients and high-prone individuals function differently. Therefore, these results argue against the continuum hypothesis and suggest that instead of one unitary model of VHs, two different models should be proposed: one for VHs in PD and the other for hallucination-proneness in the normal population.

The final experimental study (Chapter 8) provides a novel account of the relationship between VHs and specific sleep disturbances that PD patients face during the course of their illness. The findings support previous studies reporting that PD patients with or without VHs have more sleep problems than the control group. This was measured by subjective and objective measures of daytime and night time activity. It has been suggested that the sleep-controlling brain areas are severely affected in PD, but are probably not related to VHs. However, the arousal controlling system (probably reflecting the thalamic dysfunction) is, on the basis of the current results, strongly implicated in hallucinating PD patients. Moreover, strikingly similar arousal disturbances also occurred in the high-prone individuals. The findings from the study suggest that it is not sleep related brainstem areas in general, but rather specific arousal dysfunction that predisposes both PD patients and normal individuals to VHs and hallucination-proneness, respectively. The evidence from the previous studies have not offered a strong case for a continuum hypothesis, and suggested that two, rather than one, model should be applied for hallucination-proneness in the normal population and VHs in PD. However, the results from the sleep study suggest that the two models might share some very specific arousal-related risk factors. Therefore, the results from the sleep study are the first to argue there might be an overlap in the pathology of the arousal related sleep problems, associated with hallucination-proneness in the normal population and VHs in PD.

Finally, Chapter 9 examined the cognitive-behavioural strategies that hallucinating PD patients use in order to cope with their VHs. The data revealed that PD patients with VHs most commonly use a combination of behavioural and

cognitive coping strategies. Specific behavioural strategies reflect the nature of VHs (e.g., modifying the lights of the environment and changing the focus of visual attention). Anxiety over VHs was extremely rare in the hallucinating PD patients; therefore, depression in PD may be related to the disease itself and not specifically to the existence of VHs. The study offered a detailed list of coping techniques which need to be implemented in the future development of the cognitive-behavioural approach to a treatment of VHs in PD.

In summary, a line of evidence suggests that although there are similar risk factors which are implicated in both hallucination-proneness in the normal population and VHs in PD, the two phenomena also have specific and unique non-shared risk factors. The main contribution of the thesis has been to suggest that on the basis of the current studies, the continuum hypothesis probably does not hold true, at least not in the case of VHs in a clinical population of PD patients and in hallucination-proneness in the non-clinical normal population. Instead of the continuum hypothesis, two separate models have been proposed, where some risk factors may overlap to a certain degree: one for VHs in PD and the other for hallucination proneness in the normal population.

10.2 A Proposed Model for VHs in PD

Different aetiologies sometimes generate surprisingly similar phenomenologies and recurrent complex VHs are often manifested in very different disorders. Therefore, it is important to understand a full delineation of a specific phenomenon in different disorders and to explore whether a set of the same risk factors predisposes individuals to a higher occurrence of VHs in different disorders. The aim of this thesis was to determine whether the same set of risk factors are implicated in the occurrence of VHs in PD and in the high hallucination-prone normal population. Based on the data from this thesis, a new conceptual framework will be proposed to explain VHs in PD and hallucination-proneness in the normal population.

Several models have been proposed for the occurrence of VHs across different disorders (Section 1.6). For example, Cogan (1973) suggested that VHs are release

phenomena, caused by disruption of the normal flow of visual impulses, with subsequent release of endogenous cerebral activity from the visual system. This idea was later developed by Manford and Andermann (1998) who recognized the importance of midbrain (especially thalamic) involvement in the generation of VHs. The main contribution of their model is its acknowledgement that VHs are attributed to abnormalities of the ascending cholinergic and serotonergic brainstem and thalamic pathways involved in the control of sleep-waking state, and/or to the defective visual processing accompanied by abnormal cortical release phenomenon. The model of Manford and Andermann (1998) was further developed by Barnes et al. (2003) who provided neuropsychological evidence for a multi-factorial model for the occurrence of VHs in PD. The model included the combination of degraded visual information about the environment, impaired source monitoring, together with failing memory and an over-reliance on previously stored schemata, which on occasion "fill in" for missing detail and provide the basis for visual hallucinations. Diederich and colleagues (2005) also suggested that VHs should be considered as a dysregulation of the gating and filtering of external perception and internal image production. Additional contributing elements and anatomical links for their model include poor primary vision, reduced activation of primary visual cortex, aberrant activation of associative visual and frontal cortex, lack of suppression or spontaneous emergence of internally generated imagery through the ponto-geniculo-occipital system, intrusion of rapid eye movement dreaming imagery into wakefulness, errative changes of the brainstem filtering capacities through fluctuating vigilance, and medication-related overactivation of mesolimbic systems. Compared to the models of Manford and Andermann (1998) and Barnes et al. (2003), Diederich et al. (2005) focused on visual impairment, probably reflecting dopaminergic dysfunction from the level of retinal functioning onwards.

The data from the present research support the multifactorial nature of the risk factors that are involved in the generation of VHs in PD. The proposed model suggests that visual acuity, primary and associative visual system and the arousal system all play an important role in the occurrence of VHs in PD (see Figure 10.1).

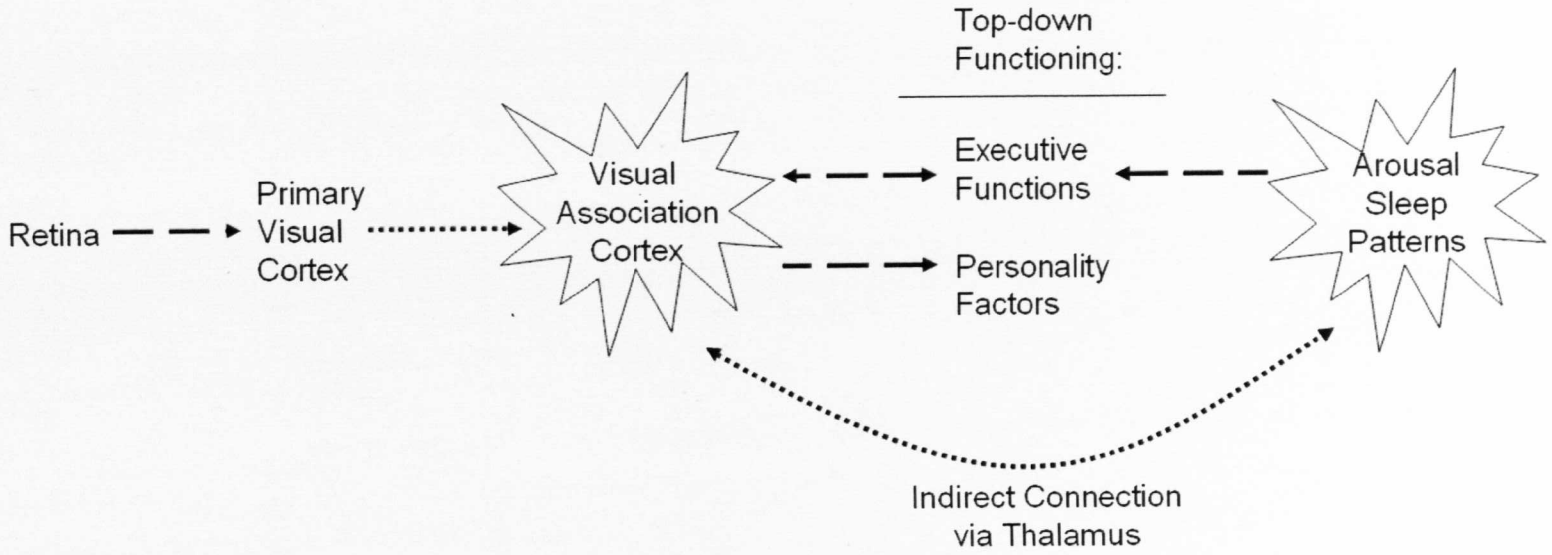


Figure 10.1. A hypothetical model of VHs in PD.

The flowchart presented in Figure 10.1 indicates the major areas of compromised functioning. The dotted arrows indicate compromised connections and the finer dotted arrows denote even more impoverished connections. The orientation of the arrows indicates the most likely flow of information between different regions of interest.

Age-related vision problems, not sufficient on their own to cause VHs, add to dopamine deficiency in the retina, causing reduced signals to the primary visual cortex. Suboptimal input may therefore be a necessary, but not sufficient, risk factor for the generation of VHs. Carefully designed ophthalmologic studies are the future area of research in hallucinations in PD, addressing the role of specific ocular pathologies in relation to VHs, which will lead to innovative and holistic approach to the treatment options and preventive management for VHs in PD. Moreover, future studies need to examine how, if at all, the extent of ocular pathology affects the nature of VHs and its effect on the retina and functioning of the primary visual cortex.

Reduced activation of the primary visual cortex, while not extensive enough to give rise to simple hallucinations (as often happens in severe ocular pathologies, e.g. Charles Bonnet Syndrome, blindness, etc.) may consequently result in higher activation in the visual association cortex (Holroyd & Wooten, 2006). However, to date, a scarce amount of neuropsychological studies have addressed the role of functioning of the association visual cortex in hallucinating PD patients. The data from the visual memory study (see Chapter 4) were the first to give evidence that compared to non-hallucinating PD patients, hallucinators display deficits in visual memory. The study showed a link between the specific visual memory task (Delayed Matching to Sample) and the presence of VHs; however, the link between higher visual processing system and the occurrence of VHs in PD needs to be addressed in further detail. An obstacle in achieving this goal is a lack of reliable, valid and standardized tasks of higher visual processing that are appropriate for the population with substantial motor disabilities.

The arousal dysfunction in the hallucinating PD patients diverts the current attention from dopaminergic to serotonergic and cholinergic systems, and probably reflects a complex neuropharmacological imbalance in the occurrence of VHs in PD (see Section 1.3). Dopaminergic agonists are not likely to cause VHs when used for other illnesses or even when induced in healthy volunteers (Turner et al., 1984). This may be, in part, because PD patients tend to be older and neurodegeneration is more widely spread, but also because the pattern of pathophysiology in PD

predisposes the individual to the hallucinatory effects of these drugs (Manford & Andermann, 1998). In addition, administration of levodopa in PD corrects visual abnormalities (Bodis-Wollner, 1990) and a direct toxic effect of levodopa on vision seems an unlikely cause for the generation of hallucinations (Manford & Andermann, 1998). Therefore, while the role of dopaminergic systems is well recognized in predisposing PD patients to VHs, hallucinations are not a simple dopaminergic result, but an interactive connection of various processes. Some of these processes are based on, and facilitated by, dopaminergic medications whereas the others, like arousal sleep patterns, are not. Research about the precise link between VHs, the "on-off" dopaminergic states, and the medication fluctuations is also warranted to shed a light on the possible facilitating medication effects upon VHs.

These findings are in accordance with the qualitative descriptions of VHs (see Chapter 2), where PD patients often report that hallucinations are especially frequent in the evenings when the environment is dim or when patients feel relaxed and drowsy. Conversely, the reports decline during the times of high activation or during sleep. The pathways between the retina and the visual association cortex on the model (see Figure 10.1) are therefore modified depending on the patients' arousal states as well as on the environment's lighting.

In addition to the arousal dysfunction, hallucinating PD patients significantly overestimated their sleep latency times (see Chapter 8), which has been suggested to reflect dysfunctions in the basal ganglia (Harrington, Haaland, & Hermanowicz, 1998; J. G. Smith, Harper, Gittings, & Abernethy, 2007). Similarly, Naish (2003) has suggested that there are parallels between hypnotically induced hallucinations and those of conditions such as schizophrenia, highlighting that the distortion of time-estimation is a particular parallel that accompanies all hallucination-provoking conditions. Whereas previous studies have shown a striking similarity between PD and hypnosis, the present research offers the first evidence that the link is especially pronounced in PD patients with hallucinations. Further neuroimaging studies on time distortion in hallucinating and non-hallucinating PD patients are needed to ascertain the definite underlying mechanisms.

Poor performance of hallucinating PD patients on the DMS task suggests that the compromised functioning of the visual association cortex may be linked to frontal functioning. Similar suggestions were proposed by Barnes et al. (2003), who noted that hallucinating PD patients subscribe a meaning to an unknown object much earlier than their non-hallucinating counterparts (although not always correctly), indicating a role of specific, possibly frontal, top-down processing. Contrary to what was expected (see Section 1.6.3), little evidence was found that frontal lobe functioning is a risk factor for the generation of VHs in PD. Except for the aforementioned visual memory task, no other measures of either executive functioning or personality factors suggested a role of the frontal lobe functioning in the occurrence of VHs. The current results suggest that the executive functions measured have a protective function in hallucinating PD patients, most likely in preserving the insight into hallucinatory nature of the images that patients perceive. Once the neurodegeneration affects these functions (for example, in patients with dementia), the insight diminishes. However, other as yet unknown inhibitory executive functions may suppress the spontaneous firing from the visual association cortex, hence preventing the generation of VHs. It remains to be seen in future studies whether different kinds of executive functions act as protective agents in non-hallucinating PD patients, inhibiting the spontaneous firing of information, and not being able to suppress it in patients with hallucinations. One possible route of investigation is via extrastriatal functions, similar to the ones observed by "go/no-go" tasks (Barnes & Boubert, 2008).

The results of the current research suggest strong posterior, bottom-up processing of information in VHs in PD. The hypothesis is in line with the unimodal experience of VHs, which are typically perceived in the visual modality. A more evident role of the frontal lobe involvement would conversely suggest a multimodal experience of hallucinations, which is in line with the results from the high-prone normal individuals (see Chapter 7 and Section 10.3) as well as from the literature about patients with epilepsy, Alzheimer's Disease, and schizophrenia who typically experience multimodal hallucinations and present frontal lobe dysfunctions (Bassiony & Lyketsos, 2003; Cummings, 1992; La Vega-Talbot, Duchowny, & Jayakar, 2006; Moberg et al., 1999).

In summary, the results from the studies of the present thesis support the multifactorial nature of the risk factors that are implicated in the generation of VHs in PD, namely the visual system from retina onwards and the arousal system, but not the executive functioning. These results go against some integrative models (Barnes et al., 2003; Diederich et al., 2005), which emphasise a strong reliance on the executive functioning in the process of generation of VHs. The results, however, support the model of Manford and Andermann (Manford & Andermann, 1998), and offer neuropsychological evidence for their neurological-neuropharmacological model. The main research avenue in the future will be to provide more empirical evidence for the proposed model and to broaden the current understanding of the interaction of different functions in the occurrence of VHs in PD (see Section 10.4).

10.3 A Proposed Model for Hallucination-Proneness in the Normal Population

VHs are not necessarily symptomatic of pathology: the study on hallucination-proneness in the normal population (see Chapter 2) has established the occurrence of hallucinatory experiences in a substantial number of individuals from the normal population. Following the continuum hypothesis (Peters, Joseph, & Garety, 1999) which holds that psychosis-like experiences are distributed, to varying extents, throughout the general population and that full-blown psychosis represents the most extreme end of the population continuum, it was proposed that VHs in PD and proneness to VHs in the normal population might share similar predispositions, expressed in a lesser degree in the normal population.

However, on the basis of the results from these studies it was suggested that two separate models could explain hallucination-proneness in the normal population and VHs in PD better than one unitary model, even though some risk factors might be shared by the underlying mechanism of both phenomena. For example, the results from the studies revealed that surprisingly similar disturbances of the arousal system are implicated in both hallucinating PD patients as well as in high-prone individuals from the normal population. Further, suboptimal functioning of the visual system has been implicated to play a role in hallucination-proneness in the normal population as

well as in VHs in PD; however, a certain degree of caution needs to be taken into account, as the results were gathered with different methodologies: dysfunction of the visual memory in the hallucinating PD patients was tested by the neuropsychological battery and the modifications of early and late ERP responses has been observed using EEG.

Apart from the risk factors that were shared by both hallucinating PD patients and high-prone normal individuals, a number of personality-related risk factors were suggested to have an impact in the development of hallucination-proneness in the normal population, but not in the group of hallucinating PD patients. Unlike in the hallucinating PD group, high-prone normal individuals expressed a range of specific personality traits (see Chapter 7), which were suggested to make them more susceptible for rich visual perception and higher vulnerability to hallucinatory experiences. Alternatively, specific modifications of early visual processing components may modify their personality traits. Furthermore, the phenomenological nature of both phenomena in PD and in the normal population was expressed in different ways. A crucial difference between the two phenomena, for example, is that PD patients reported on hallucinations that were almost exclusively related to visual modality, whereas high-prone individuals from the normal population had hallucinatory-like experiences in several different modalities (the implications of this will be discussed later in this subsection). VHs in PD are therefore not likely to be a continuation of hallucination-proneness in the normal population, as some risk factors are implicated in proneness to VHs in the normal population, but are not a risk factor in full-blown VHs in PD (see Figure 10.2).

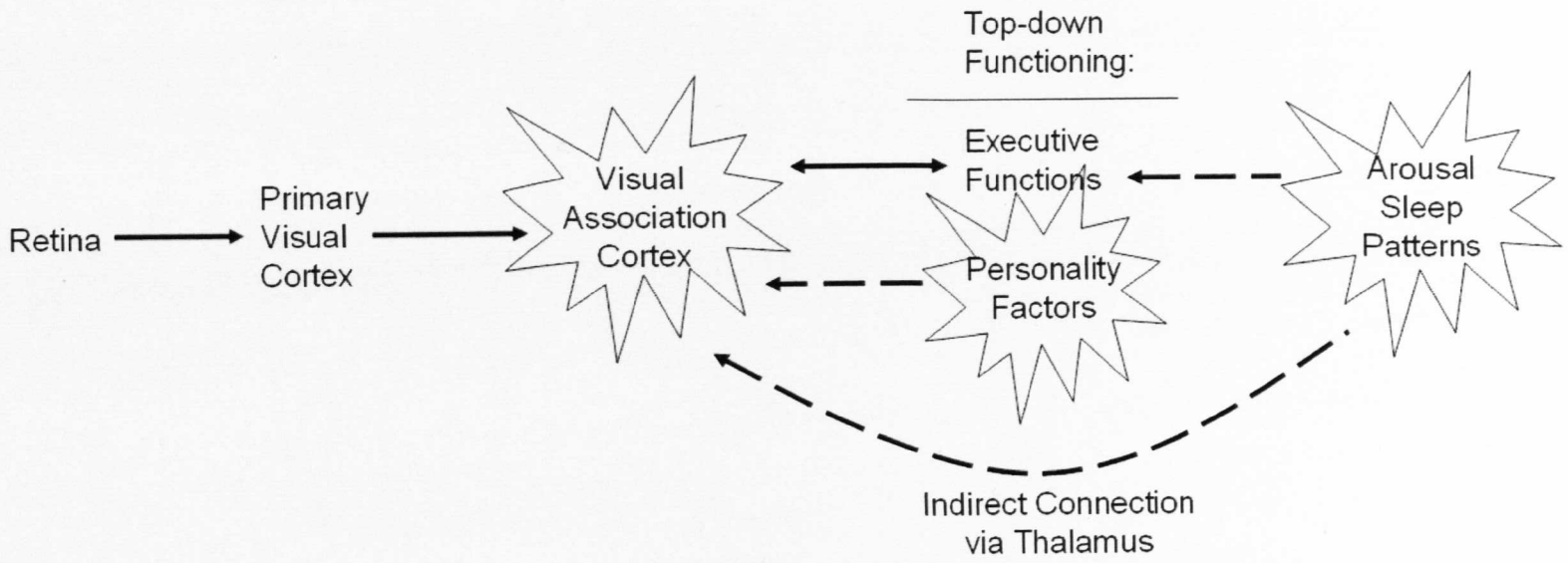


Figure 10.2. A hypothetical model of hallucination-proneness in the normal population.

The flowchart presented in Figure 10.2 indicates the major areas of compromised functioning. The dotted arrows indicate weakened connections. The orientation of the arrows indicates the most likely flow of information between different regions of interest.

Van de Ven and Merckelbach (2003) speculated whether the fact that participants with hallucinatory reports score higher on fantasy proneness than those without such reports reflects a general response bias to endorse bizarre items or a subtle reality-testing deficit. The EEG study from the present thesis (see Chapter 5) was the first study to date to give evidence that high-prone individuals show aberrant modifications of the early visual processing components in the face paradigm, and therefore supports a hypothesis that high-prone individuals without clear hallucinations or a history of psychiatric disorder actually have bizarre experiences and process information differently. Altered modifications of the early visual processing components were suggested to give rise to additional facilitating factors, namely the top-down processing. However, it remains to be seen in future studies to what extent bottom-up processes modify top-down processing and vice versa. Hughlings Jackson has argued that hallucinations and illusions are caused by a loss of higher centre control on lower centres resulting in lower centre over-activity and increased sensitivity to peripheral input: "Evolutionary accent is a passage from centres easily transmitting accustomed stimuli and resisting novel stimuli, up to centres which have to be forced into activity" (p.33, Jackson, 1887). A similar idea that visual perception depends on feedback connections from higher to lower visual areas has been suggested by the re-entrant processing theory (Di Lollo, Enns, & Rensink, 2000; Fahrenfort, Scholte, & Lamme, 2007). Some authors (Schneider, Crosby, Bagchi, & Calhoun, 1961; Vignal, Chauvel, & Halgren, 2000) have suggested that activity related to hallucinations can be propagated from one brain region to another, namely from the frontal lobe along white matter pathways to face specialised cortex in the ventral occipitotemporal lobe.

It has been suggested that the generation of VHs in PD rely strongly on the dysfunction of the posterior areas, as opposed to hallucination-proneness in the normal populations which seems to be much more dependent on the functions of the frontal lobe areas. This hypothesis would also explain why high-prone normal individuals, prone to have hallucinatory-like experience in the visual modality, also express a higher tendency of hallucinatory-like experiences in the other modalities (see Chapter 3). Hallucinating PD patients, on the other hand, exhibit little evidence

for a frontal lobe dysfunction and characteristically present their hallucinations in the visual modality.

The arousal dysfunctions in the high-prone, but not in the low-prone, normal individuals were strikingly similar to the ones observed in the hallucinating PD patients. These dysfunctions point to an important role of the arousal system in predisposing healthy young individuals to a higher incidence of hallucinatory-like experiences which is probably due to deficient gating of sensory inputs. Implications for future research concerning disrupted arousal system on VHs will be discussed in Section 10.4.

In summary, a predisposition to VHs in the normal population is probably alleviated by a set of risk factors, namely the aberrant modifications of the early visual processing components, deficient arousal functioning and a specific personality profile, but not on the failing executive functions (including source memory, see Chapter 6). Although in its infancy, this model is the first to date to suggest the multifactorial nature of hallucination-proneness in the normal population. Further empirical evidence is needed to confirm the model and its implications for other disorders accompanied by recurrent complex VHs (see Section 10.4).

10.4 Methodological Limitations and Implications for the Future Studies

New avenues for research and several limitations have arisen during the stages of data acquisition, analysis and interpretation. The present work is composed of several experimental chapters, each designed to examine one risk factor at a time, and the models for VHs in PD and hallucination-proneness in the normal population have put these risk factors together. However, both models raise the issue of how different risk factors that were implicated to play a role in the generation of VHs and high hallucination-proneness, relate to each other. In other words, one of the main perspectives of the future research in the area of VHs should be to determine

how specific brain functions, reflecting the activity of specific brain areas, relate to each other.

In a recent paper, Ffytche (2008) has proposed dual perspectives of hallucinations: topological (topos = place) which emphasise dysfunction localised to specific brain regions and hodological (hodos = path) which emphasise dysfunction related to connections between brain regions. Stemming from the two perspectives, the topological approach would suggest the hypo-function in the primary visual cortex and hyper-function of associate visual centres in the hallucination-prone brain, while the hodological approach would suggest a weakened connection between the two. In addition, hallucinating PD patients and high-prone normal individuals express specific arousal-related sleep patterns; however, their hodological relation to the aforementioned systems remains unclear, but probably through the loss of ascending brainstem inputs to the visual system (Ffytche, 2005b, 2007). A supporting argument for hodological dysfunction has been proposed in schizophrenia and hypnotised participants who hallucinate under hypnosis, where a reduction of effective connection has been observed between frontal and posterior temporal regions (Lawrie et al., 2002; Spiegel, 2003).

Ffytche (2008) argues that hodological and topological perspectives interact in a multifaceted and dynamic way, and that it is imperative for future studies to offer a better understanding of "how different connectivity measures relate to one another and the conditions under which such relationships break down" (p.1080). A clear advantage of the combined hodotopic perspective is that it highlights areas that remain poorly understood. Therefore, future studies should use measures that can examine hodotopic differences in the brain of hallucinating PD patients and high-prone normal individuals. However, although several approaches have been suggested, e.g. tractography, fMRI and EEG connectivity measures (ibid), the hodotopic perspective in its existing form is too simple to appropriately address all the aspects of hallucinations or hallucination-proneness.

Furthermore, in order to fully validate the suggested models for VHs in PD and hallucination-proneness in the normal population, three approaches should be considered, namely multifactor, longitudinal and multidisciplinary approach. Future

studies would benefit from taking all risk factors into consideration in one comprehensive project. Such a project would have an immediate effect on the length of the project and on ethical considerations (especially in PD group). However, it would provide a valid and reliable approach in delineating the risk factors and, ultimately, models for the occurrence of VHs in PD and for hallucination-proneness in the normal population. Furthermore, in order to provide evidence for multiply determined nature of VHs in PD and hallucination-proneness in the normal population, all the possible risk factors need to be taken into account. The present studies, however, usually took only one risk factor at a time into account. This poses another limitation, namely, that a one-factor-at-a-time approach offers correlational evidence, but precludes assessment of causality. Therefore, a major limitation of the present work is that it takes one at a time, rather than a number of possible risk factors into account. Such an approach is needed in the future when exploring a concept which is highly likely to be multiply determined. On the basis of such approach it would be possible to get evidence of which factors have the strongest predictive value.

However, the main obstacle in carrying out research in a fragile population such as PD must be exposed here. Although it has been acknowledged that VHs in PD are most likely to be multiply determined, one must not forget that due to several considerations it would be very difficult (if not impossible) to carry out such a big study. Because of its length, a project would have to be carried out in smaller units over a period of several meetings. Because of the diminishing effectiveness of parkinsonian medications over a period of time which cause severe tremor or dyskinesia, each meeting would need to be scheduled to last no more than one hour. Several meetings would therefore need to be carried out, which can pose ethical problems for the use of participants in lengthy studies. As discussed before, the progression of PD varies greatly among patients, so some patients who experience an abrupt progression of symptoms might well show a very different clinical picture from their first testing and change radically until the end of testing. Often, PD patients have some additional, usually age-related, disorders apart from PD, which could delay testing or some would opt out. Furthermore, the dosages are frequently

changed (usually to increased dosages of dopaminergic agonists), which not only poses higher risks for developing hallucinations (so non-hallucinating patients could become hallucinating before the end of testing), but is often related to other (usually motor-related) disorders, which would make testing prolonged until the patients get used to the medications (or change them again, which is also common). Therefore, although the correlational approach may not be ideal and as many factors as possible should be taken into account, this is not really possible in practice.

The present studies have taken only the most recognized risk factors into account; but there are many other risk factors proposed in other disorders related to VHs, such as the Perception and Attention Deficit model in dementia with Lewy-bodies (Collerton et al., 2005, see Section 1.7.4). Longitudinal studies are highly warranted in the research of progressive illness, aiming to understand the pathological development of PD as well as to verify the proposed models for the occurrence of VHs in PD and for hallucination-proneness in the normal population. Such studies would not only reveal how risk factors develop over time, but also elucidate the potential protecting mechanisms (e.g., through the development of non-hallucinating PD patients or through patients who start hallucinating later in the course of their illness). Finally, a multidisciplinary approach is necessary to fully comprehend the neurological, pharmacological, ophthalmologic, psychological, and statistic implications of VHs in PD.

The majority of studies investigating the differences between hallucinating and non-hallucinating PD patients have been conducted on a limited amount of participants, and the studies from the present thesis faced the same difficulty. However, one must recognise not only the rarity of condition, but also specific subgroups (i.e., the presence/absence of VHs, relatively mild motor signs of PD, preserved cognitive abilities, no history of psychiatric disorder, etc.). Therefore, although the small number of participants represents a higher risk for statistical errors in the data analysis, the subgroups have been carefully selected and represent the "pure" examples of idiopathic PD in mild-moderate stages of PD. Similarly, although small groups of high and low-prone individuals participated in the present

studies, all participants were carefully chosen and represented the low and the high end of the proneness continuum.

Another specific problem related to the low number of PD participants is an unclear risk effect of years since diagnosis. PD is a neurodegenerative disorder; it is therefore expected that the dopaminergic doses will increase and the neurodegeneration will get widely spread over time. Therefore, some aspects of PD are concurrent with, rather than dependant on, the progress of the illness. For example, the dopaminergic dosages are increased with progressive neurodegeneration, and there is a higher risk of developing psychiatric signs, such as VHs, dementia or depression; however, these signs might not be dependant on the dopaminergic medication itself but to the general neurodegeneration processes. It is possible to take the years of diagnosis into consideration and divide patients according to their years of diagnosis (Graham et al., 1997); however, such an analysis was not possible in the present work due to a limited amount of patients in the hallucinating PD group.

Several treatment related issues have occurred during the personality (Chapter 7), sleep patterns (Study 8) and coping strategies (Chapter 9) studies. It is imperative that future work expands beyond neuropharmacological treatment to the area of cognitive-behavioural therapy, not only for VHs but for other non-motor signs of PD as well. Longitudinal studies are necessary to reveal the efficacy of behavioural coping strategies PD patients use in order to cope with their VHs. Further, if sleep treatment is efficient in treatment of sleep related problems (using simple sleep hygiene techniques), then such treatment could have a beneficial effect, reducing or stopping VHs due to the suggested link between sleep problems and VHs. A strict relationship between RBD and VHs has yet to be demonstrated, which would have immediate effect on the treatment of VHs.

10.5 Concluding Remarks

VHs in PD are associated with a higher risk for nursing home placement, higher mortality rate and a financial burden upon society (Pappert et al., 1999). Early recognition of non-motor symptoms is crucial not only for the quality of life of patients with PD, but also for the holistic approach, including support for carers (Chaudhuri, Healy et al., 2006). A multidisciplinary and comprehensive understanding of the non-motor signs of PD, one of them being VHs, provides better cognitive-behavioural support and in turn improves the quality of life of patients and their carers. As life expectancy increases, more people are diagnosed with PD. In order to efficiently cope with the stress, symptoms of PD and financial outcomes, future studies are crucial to explore long-negligent, complex and dynamic non-motor signs of PD, and how they relate to each other and to the possible risk factors.

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Appendices

1. Visual Hallucinations Questionnaire for PD patients
2. Participant Information Sheet for PD Patients
3. University Research Ethics Committee Approval (UREC)
4. Hallucination-Proneness Questionnaire for the Normal Population
5. Participant Information Sheet for Students
6. Factor Matrix of the PCA
7. The Neuropsychology of Visual Hallucinations in Parkinson's Disease and the Continuum Hypothesis (Maravic, in press).
8. Invitation for High and Low-Prone Normal Individuals
9. Vividness of Visual Imagery Questionnaire (Marks, 1973)
10. Consent Form
11. Altered Early Visual Processing Components in Hallucination Prone Individuals (Schwartzman et al., 2008)
12. Instructions for 16PF Questionnaire (R. B. Cattell, 1956)
13. Meta-cognitive Beliefs Questionnaire (Cartwright-Hatton & Wells, 1997)
14. Creative Experiences Questionnaire (Van de Ven & Merckelbach, 2003)
15. Sleep Disturbances and Visual Hallucinations in Parkinson's Disease (Maravic et al., 2007)
16. Epworth Sleepiness Scale (M. W. Johns, 1991)
17. Berlin Sleep Apnea Questionnaire (Netzer et al., 1999)
18. Pittsburgh Sleep Quality Index (Buysse et al., 1989)
19. Instructions for the Sleep Watch Monitors (a version for PD patients and a version for the control group and the normal participants)
20. Sleep Diary
21. Coping Strategies Questionnaire for Hallucinating PD Patients
22. Beck Depression Inventory (BDI) (Beck et al., 1961)

Appendix 1. Visual Hallucinations Questionnaire for PD patients.

Visual changes in Parkinson's Disease Questionnaire

Name: _____

Age: _____

Gender: Female Male

1. Are you taking any medication at present? Yes No

☐ ☐

If yes, please state the drug(s) and the dose you take each day

Drug	Dose

2. How long have you been diagnosed with Parkinson's Disease?

_____

3. Do you suffer from any other long term illness? Yes No

☐ ☐

If yes, please state which one and approximately when it was diagnosed.

_____

_____

4. Which side are your symptoms of Parkinson's Disease more pronounced?

Left	Right	Both
☐	☐	☐

5. Do you suffer from migraine? Yes ☐ No ☐

6. Can you still get around the house unassisted (without help from another or a wheelchair)? Yes ☐ No ☐

7. Have you ever consulted a doctor about an eye problem?

Yes	No
☐	☐

If yes, please give details

_____

_____

_____

8. Do familiar things around you ever appear to change their appearance unnaturally in some way? Yes ☐ No ☐

If yes, how often does this happen

More than 5 times a week	1-5 times a week	Less than once a week
☐	☐	☐

9. Do you see things that are not really there? Yes ☐ No ☐

If yes, how often does this happen

More than 5 times a week	1-5 times a week	Less than once a week
☐	☐	☐

If you answered "Yes" to question 8 or 9 (or both), please answer the following questions.

10. Do these things you see have a particular form? (eg. people, objects, animals, shapes etc.) Yes No

☐ ☐

If "Yes", please give details on the most common images that you see:

_____

_____

_____

_____

_____

11. Do these visual images come suddenly? Yes No

☐ ☐

12. How long do the images appear for? Hours Mins Seconds

☐ ☐ ☐

13. Do these images move? Yes No

☐ ☐

14. Do these images appear:

- **when you wake up** ☐
- **when you go to sleep** ☐
- **morning** ☐
- **afternoon** ☐
- **evening** ☐

15. How many images appear? One 2-5 More than 5

☐ ☐ ☐

16. Do these images talk to:

You ☐

To each other ☐

They don't talk ☐

17. What is the clarity of these images?

- **Sharp** ☐
- **Blurry** ☐
- **Transparent** ☐
- **Variable** ☐

18. What is the colour of these images?

- **Black and white** ☐
- **Single colour** ☐
- **Multiple colour** ☐

19. When these images appear are your eyes open or closed?

- **Open** ☐
- **Close** ☐
- **Both** ☐

20. How do these images appear to you? **Real** **Unreal** **Not sure**

☐ ☐ ☐

21. What is the ambient light when you see these images appear? (For example, do you often see the images more in a darkened room or a bright day lit room etc.)

- **Bright** ☐
- **Dim** ☐
- **Dark** ☐
- **Variable** ☐

22. Do these images start with or derive from the real perception? (eg. when you are looking at an object or person) **Yes** **No**

☐ ☐

23. What is the content of the images (e.g. are the images always the same or do they change in their activities)?

- **Stereotyped** ☐
- **Different** ☐

24. Do these images occupy your field of vision?

- **Completely** ☐
- **Partially** ☐

25. Are the images distorted in some way? **Yes** **No**

☐ ☐

If "Yes", please give detail

26. Do you think that it is your medication which causes the images? **Yes** **No**

☐ ☐

Please give your explanation:

27. Is there anything else that you would like to tell about the images and was not stated in the questions?

- THANK YOU VERY MUCH FOR YOUR HELP! -

Appendix 2. Participant Information Sheet for PD Patients.

Participant Information Sheet

VISUAL DISTURBANCES IN PARKINSON'S DISEASE

Visual disturbances in Parkinson's disease can be extremely distressing; there is frequency under-reported and sometimes inadequately treated. We are studying the neurological and psychological processes underlying visual disturbances in normal aging and in patients with Parkinson's disease. This will be achieved by carrying out detailed neuropsychological tests and questionnaire based research.

We would like you to help us in taking part in this study, but before you decide to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully.

What is the purpose of the study?
The aim of this study is to determine cognitive factors that underlie the emergence of visual disturbances in Parkinson's disease as well as in a normal population. Aside from the basic scientific interest, the issue of visual disturbances has important implications for the treatment, and remediation of these symptoms in Parkinson's disease and other neurological disorders.

Do I have to take part?
Taking part in the research is entirely voluntary. You are under no obligation to do so, but your help would be much appreciated. If you do decide to take part you will be given this information sheet to keep as a reference sheet and at some time in the future you will be asked to sign a consent form. All the information will be treated in strictest confidence and you can withdraw from the study at any time without giving your reasons for doing so.

What will happen to me if I take part?
The study will involve filling in questionnaires designed to test your visual perception and the nature of your visual disturbances. Before taking part in any of the tests used, you will be given a brief description and rationale for using it, as well as instructions for each part. Again, there are no right or wrong answers in any of the tests used. It is important you understand that taking a part in this study is entirely voluntary and that you will be free to withdraw from the study at any time without giving your reasons for doing so. You are also free to ask any questions before, during or after taking part in a study.

What are the possible benefits of taking part?
You will be given the opportunity to make a contribution to our scientific understanding of visual disturbances in Parkinson's disease, which will be important for future treatment options and patient care.

Will what I say in this study be kept confidential?
All information collected will be kept strictly confidential and used for the purposes of this study only. All of the data will be coded with the subject number in a way that will not allow you to be identified individually. This anonymisation will occur at the point of the data collection. Only the named researcher will have the access to data, stored in a computer file available by password only. Data generated by the study will be retained in accordance with the University's policy on Academic Integrity.

What will happen to the results of the research study?
The data collected will be used for the purposes of this study only. If you wish to withdraw from the study at any stage, we will also withdraw every unprocessed data.
Further, if you express an interest you will be informed of the results of the study and will be given a copy of the article or conference abstract. This information will be given to you using a mean that you prefer (a personal meeting, by phone or by post). For any other queries about the results of the study, you can contact either the primary researcher or their supervisors on the address or a phone stated below.

Who has reviewed the study?
The research has been approved by the University Research Ethics Committee, Oxford Brookes University.

Contact for further information
This is a project by a research student Ksenija Maravic from Oxford Brookes University, supervised by Dr Vince Connelly and Dr Jim Barnes. If you have any questions regarding this study or about any issues raised in this information please feel free to contact one of us in the Psychology Department at Oxford Brookes University, Tel: 01865 483771 or at our email address below.

Ksenija Maravic	Dr Vince Connelly	Dr Jim Barnes
kmaravic@brookes.ac.uk	vconnelly@brookes.ac.uk	jim.barnes@brookes.ac.uk

If you should have any other questions about the way in which the study has been conducted, you should contact the Chair of the University research Ethics Committee on ethics@brookes.ac.uk.

THANK YOU VERY MUCH FOR YOUR HELP!

Appendix 3. University Research Ethics Committee Approval (UREC).

University Research Ethics Committee

Wheatley Campus, Wheatley Oxford OX33 1HX UK
t. +44 (0)1865 485741
ethics@brookes.ac.uk
www.brookes.ac.uk/research/ethics/ethicshome.html

Dr Jim Barnes
School of Social Sciences and Law
Oxford Brookes University
Gipsy Lane
Headington

18 May 2006

Dear Dr Barnes

UREC 060193 Title: Visual Hallucinations in Parkinson's Disease

Thank you for your recent letter outlining your response to the points raised in my previous letters for the above study and attaching the revised documents. I am pleased to inform you that, on this basis, I have given Chair's Approval for the study to begin.

The UREC approval period for this study is six months after the completion date of the data collection component, so until 30 March 2009. If you need the approval to be extended please do contact me nearer the time of expiry.

In order to monitor studies approved by the University Research Ethics Committee, we will ask you to provide a (very brief) report on the conduct and conclusions of the study in a year's time. If the study is completed in less than a year, could you please contact me and I will send you the appropriate guidelines for the report.

Yours sincerely

Teresa Smallbone
Chair
University Research Ethics Committee

Cc Ksenija Maravic
Vince Connelly
Morag Maclean

Appendix 4. Hallucination-Proneness Questionnaire for the Normal Population.

Introduction

This questionnaire asks questions about sensations and perceptions you may have experienced. Some of the experiences are unusual, some of them are more everyday.

We realise ticking answers may not always represent your experience as accurately as you might like. However, we would ask you to tick the answers that most closely match your experience and avoid missing any questions out.

There are no right or wrong answers, and we would appreciate it if you could be as honest as possible when giving your answers. The data will be used for research purposes only. It takes 5-10 minutes to fill out the questionnaire.

If you have any queries about the study, please contact us on kmaravic@brookes.ac.uk (Ksenija Maravic) or jim.barnes@brookes.ac.uk (Jim Barnes).

Age: ____
Gender: F M
Vision problems (including contact lenses, glasses, etc): YES NO
Comment: _____
Hearing problems: YES NO
Comment: _____
Any known neurological or psychiatric disorder: YES NO
Comment: _____
Dyslexia: YES NO
Handedness: RIGHT-HANDED LEFT-HANDED

Student email account:

_____

Important!:
If you decide to take part in a second stage of the study, we will ask you to provide us with your student account email address, via which we can contact you. Information about your email account will be kept confidential. Further, all of the data from the second stage will be coded with the subject number in a way that will not allow you to be identified individually. Only the named researcher will have the access to data, stored in a computer file available by password only. Data generated by the study will be retained in accordance with the University's policy on Academic Integrity.

Section 1

Instructions

Please read the statements about **auditory** sensations, and tick either
0 – Certainly does not apply to me
1 – Possibly does not apply to me
2 – Unsure
3 – Possibly applies to me
4 – Certainly applies to me

1) The sounds I hear in my daydreams seem so true that sometimes I think they are real

0	1	2	3	4
☐	☐	☐	☐	☐

Comments: _____

_____

2) Sometimes I hear a voice speaking my thoughts aloud (not talking to yourself)

0	1	2	3	4
☐	☐	☐	☐	☐

Comments: _____

_____

3) In the past I have had the experience of hearing a person's voice and then found that no one was there

0	1	2	3	4
☐	☐	☐	☐	☐

Comments: _____

_____

4) I have been troubled by hearing voices in my head

0	1	2	3	4
☐	☐	☐	☐	☐

Comments: _____

_____

5) Sometimes I notice that sounds are much louder than they normally would be

0	1	2	3	4
☐	☐	☐	☐	☐

Comments: _____

_____

6) I can hear my own thoughts repeated or echoed

0	1	2	3	4
☐	☐	☐	☐	☐

Comments: _____

_____

7) Sometimes I have heard voices commenting on what I was thinking or doing

0	1	2	3	4
☐	☐	☐	☐	☐

Comments: _____

_____

8) In the past I have had the experience of hearing two or more unexplained voices talking with each other

0 1 2 3 4

☐ ☐ ☐ ☐ ☐

Comments: _____

_____

9) I can hear sounds or music that people near me don't hear

0 1 2 3 4

☐ ☐ ☐ ☐ ☐

Comments: _____

_____

10) Some days I find that sounds are distorted in strange or unusual ways

0 1 2 3 4

☐ ☐ ☐ ☐ ☐

Comments: _____

_____

Section 2

Instructions

Please read the statements about **visual** sensations, and tick either
0 – Certainly does not apply to me
1 – Possibly does not apply to me
2 – Unsure
3 – Possibly applies to me
4 – Certainly applies to me

1) People in my daydreams seem so true to life that sometimes I think they are real

0 1 2 3 4

☐ ☐ ☐ ☐ ☐

Comments: _____

_____

2) On occasions I have seen a person's face in front of me when no one was in fact there

0 1 2 3 4

☐ ☐ ☐ ☐ ☐

Comments: _____

_____

3) Sometimes I can sense the presence of animal or person, despite being unable to see any evidence

0 1 2 3 4

☐ ☐ ☐ ☐ ☐

Comments: _____

_____

4) Occasionally I see shapes, lights or colours even though there is nothing really there

0 1 2 3 4

☐ ☐ ☐ ☐ ☐

Comments: _____

5) Sometimes I find the appearance of things or people seems to change in a puzzling way, e.g. distorted shapes or sizes or colour

0 1 2 3 4

☐ ☐ ☐ ☐ ☐

Comments: _____

6) *From time to time my face seems different from usual*

0 1 2 3 4

☐ ☐ ☐ ☐ ☐

Comments: _____

7) Some days lights or colours seem brighter or more intense than usual

0 1 2 3 4

☐ ☐ ☐ ☐ ☐

Comments: _____

8) Sometimes everyday things look abnormal to me

0 1 2 3 4

☐ ☐ ☐ ☐ ☐

Comments: _____

9) It has happened that I have seen things, people or animals that other people cannot

0 1 2 3 4

☐ ☐ ☐ ☐ ☐

Comments: _____

Section 3

Instructions

Please read the statements about **other types** of sensations, and tick either
0 – Certainly does not apply to me
1 – Possibly does not apply to me
2 – Unsure
3 – Possibly applies to me
4 – Certainly applies to me

1) No matter how hard I try to concentrate, unrelated thoughts always creep into my mind

0 1 2 3 4

☐ ☐ ☐ ☐ ☐

Comments: _____

2) Sometimes a passing thought will seem so real that it frightens me

0 1 2 3 4

☐ ☐ ☐ ☐ ☐

Comments: _____

_____

3) From time to time I experience unusual burning sensations or other strange feelings in or on my body

0	1	2	3	4
☐	☐	☐	☐	☐

Comments: _____

_____

4) Sometimes I have the sensation that my body, or a part of it, is changing or has changed shape

0	1	2	3	4
☐	☐	☐	☐	☐

Comments: _____

_____

5) Often I can detect smells which don't seem to come from my surroundings

0	1	2	3	4
☐	☐	☐	☐	☐

Comments: _____

_____

6) Everyday odours sometimes smell unusually different

0	1	2	3	4
☐	☐	☐	☐	☐

Comments: _____

_____

7) Sometimes I notice smells or odours that people next to me seem unaware of

0	1	2	3	4
☐	☐	☐	☐	☐

Comments: _____

_____

8) Occasionally my skin is more sensitive to touch, heat or cold than usual

0	1	2	3	4
☐	☐	☐	☐	☐

Comments: _____

_____

9) Sometimes food or drink seems to have an unusual taste

0	1	2	3	4
☐	☐	☐	☐	☐

Comments: _____

_____

10) From time to time I find that my experience of time changes dramatically

0	1	2	3	4
☐	☐	☐	☐	☐

Comments: _____

_____

- Thank you! -

Appendix 5. Participant Information Sheet for Students.

Participant Information Sheet

STUDY ON VISUAL EXPERIENCES AMONG STUDENT POPULATION

The present study is designed to gather data related to the continuum hypothesis of hallucinations. According to this hypothesis, hallucinations can be considered to be one end of a continuum of normal conscious experience that includes vivid imagery, daydreams and thoughts. Previous research has suggested that the mechanisms responsible for the occurrence of hallucinations have a common origin in normal people and clinical patients that are age independent (Slade and Bentall, 1988). The purpose and procedure of the present study is to test whether hallucinatory experiences respond to the continuum hypothesis and whether they occur in all age groups in the normal population.

We would like you to help us in taking part in this study, but before you decide to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully.

What is the purpose of the study?
The aim of this study is to test whether hallucinatory experiences respond to the continuum hypothesis and whether they occur in all age groups in the normal population.

Why have I been chosen?
In order to achieve the aim, we are trying to take a look at some cognitive factors in a large group of normal student population. We will take a look at these factors in students who are highly-, medium- or low-prone to have hallucinatory like experiences. However, this is not a clinical study, so falling in any of these categories has no clinical implications whatsoever; we are simply interested in your point of view.

Do I have to take part?
Taking part in the research is entirely voluntary. You are under no obligation to do so, but your help would be much appreciated. If you do decide to take part you will be given this information sheet to keep as a reference sheet and at some time in the future you will be asked to sign a consent form. All the information will be treated in strictest confidence and you can withdraw from the study at any time without giving your reasons for doing so.

What will happen to me if I take part?
The study will involve filling in questionnaires designed to test your visual perception, visual imagery and some personality traits questionnaires. Before taking part in any of the tests used, you will be given a brief description and rationale for using it, as well as instructions for each part. Again, there are no

right or wrong answers. It is important you understand that taking a part in this study is entirely voluntary and that you will be free to withdraw from the study at any time without giving your reasons for doing so. You are also free to ask any questions before, during or after taking part in a study. Further, you will be reimbursed for your time (maximum 2 hours) and any out of pocket expenses that you may have incurred (£10).

What are the possible benefits of taking part?
You will be given the opportunity to make a contribution to our scientific understanding of different visual experiences in normal population, which might have important future implications for understanding and treatment options in patient population.

Will what I say in this study be kept confidential?
All information collected will be kept strictly confidential and used for the purposes of this study only. All of the data will be coded with the subject number in a way that will not allow you to be identified individually. This anonymisation will occur at the point of the data collection. Only the named researcher will have the access to data, stored in a computer file available by password only. Data generated by the study will be retained in accordance with the University's policy on Academic Integrity.

What will happen to the results of the research study?
The data collected will be used for the purposes of this study only. If you wish to withdraw from the study at any stage, we will also withdraw every unprocessed data. Further, if you express an interest you will be informed of the results of the study and will be given a copy of the article or conference abstract.

Who has reviewed the study?
The research has been approved by the University Research Ethics Committee, Oxford Brookes University.

Contact for further information
This is a project by a research student Ksenija Maravic from Oxford Brookes University, supervised by Dr Vince Connelly and Dr Jim Barnes. If you have any questions regarding this study or about any issues raised in this information please feel free to contact one of us in the Psychology Department at Oxford Brookes University, Tel: 01865 483771 or at our email address below.

Ksenija Maravic	Dr Vince Connelly	Dr Jim Barnes
kmaravic@brookes.ac.uk	vconnelly@brookes.ac.uk	jim.barnes@brookes.ac.uk

If you should have any other questions about the way in which the study has been conducted, you should contact the Chair of the University research Ethics Committee on ethics@brookes.ac.uk.

- THANK YOU VERY MUCH FOR YOUR HELP! -

Appendix 6. Factor Matrix of the PCA.

Table 3.5. Factor matrix of the PCA.

	Factor					
	1	**2**	**3**	**4**	**5**	**6**
Visual						
Item 1	.508				.527	
Item 2	.465					
Item 3	.512		.404			
Item 4	.594					
Item 5	.613			-.430		
Item 6	.649					
Item 7	.656					
Item 8	.617					
Item 9	.473					.409
Auditory						
Item 1	.525					
Item 2	.479	.432				
Item 3	.465					
Item 4	.442	.487				
Item 5	.599					
Item 6	.524					
Item 7	.549	.440				
Item 8	.462	.463				
Item 9	.535					
Item 10	.607					
Other						
Item 1	.496					
Item 2	.642					
Item 3	.611					
Item 4	.552					
Item 5	.626					
Item 6	.642					
Item 7	.620					
Item 8	.571					
Item 9	.634	-.427				
Item 10	.615					

All 29 items of the HQ loaded on the first factor, even with the .40 suppression value (Stevens, 1992). The factor analysis supports the one-dimensional solution of the hallucination-proneness in the normal population.

Appendix 19. Instructions for the Sleep Watch Monitors (a version for PD patients – left and a version for the control group and the normal participants - right).

INSTRUCTIONS FOR THE SLEEP-WATCH MONITOR
(to be worn for 5 nights)

1. The strap should be tight enough to stop the monitor wobbling but not so tight that it causes discomfort.

2. If you have a more pronounced tremor on the RIGHT, it should be worn on the LEFT wrist. If you have a stronger tremor on the LEFT, it should be worn on the RIGHT wrist.

3. This monitor is to worn 24 hours a day.

4. It may be worn during shower and all normal activities.

5. If you prefer to remove the monitor during showering or contact sports, please accurately record any and all instances that the activity monitor was removed and reason for removal.

6. Each day that the monitor is worn, you should record the bed time (when you got into bed) and when you fall asleep as well as wake and rise time (when you actually got up and started daily activities). These times should be recorded as close to the minute as possible.

BE SURE TO RETURN ALL PAGES TO INVESTIGATOR!

IF YOU HAVE ANY QUERIES, PLEASE DO CONTACT ME:
kmaravic@brookes.ac.uk
01865 483 776

INSTRUCTIONS FOR THE SLEEP-WATCH MONITOR
(to be worn for 5 nights)

1. The strap should be tight enough to stop the monitor wobbling but not so tight that it causes discomfort.

2. If you are RIGHT handed it should be worn on the LEFT wrist. If you are LEFT handed it should be worn on the RIGHT wrist (scoring algorithm).

3. This monitor is to worn 24 hours a day.

4. It may be worn during shower and all normal activities.

5. If you prefer to remove the monitor during showering or contact sports, please accurately record any and all instances that the activity monitor was removed and reason for removal.

6. Each day that the monitor is worn, you should record the bed time (when you got into bed) and when you fall asleep as well as wake and rise time (when you actually got up and started daily activities). These times should be recorded as close to the minute as possible.

BE SURE TO RETURN ALL PAGES TO INVESTIGATOR!

IF YOU HAVE ANY QUERIES, PLEASE DO CONTACT ME:
kmaravic@brookes.ac.uk
01865 483 776

Appendix 20. Sleep Diary.

Date	
Time woke/woken?	
Time got up?	
Did you feel tired at any time today? When and for how long?	
Time of breakfast (B), lunch (L) and dinner (T)	B: L: D:
What did you do in the hour before bed?	
Time to bed?	
Time to sleep?	
What happened in between going to bed and falling asleep? Please describe what you did once in bed. If you had difficulty falling asleep please say why (if known) and what strategies you used (if any) to try and fall asleep.	
Time and length of any wakes during the night? Please describe why you woke (if known) and what you did to try and get back to sleep again.	
Anything else of importance? Hallucinations – what time?	

Appendix 21. Coping Strategies Questionnaire for Hallucinating PD Patients.

COPING STRATEGIES

People have many ways of coping with the images they see and stress that they put them under. We would like to find out more about your response to the images and how you perceive them. First are some general questions you might like to consider:

How stressful has the last month been for you?

Very stressful	Moderately stressful	Slightly stressful	Not at all stressful
☐	☐	☐	☐

Did you worry about the images in the last month?

Most of the time	A lot of the time	Some of the time	None of the time
☐	☐	☐	☐

And now on the following pages is a list of different methods for coping. Think about how you have coped with the images you see in the past and circle how often you have used each method described. No one uses all the ways of coping described, but most people use some of them.

	Very often	Often	Some-times	Not at all
I try breathing slowly and deeply to cope with anxiety because of the images.	4	3	2	1
I stand back to get the seriousness of images into proportion.	4	3	2	1
I practice relaxation.	4	3	2	1
I try to see if my thoughts about the images were unduly pessimistic.	4	3	2	1
I discuss my fears about the images with someone close to you.	4	3	2	1
I take positive action to solve a problem related to the images.	4	3	2	1
I cope with the images by talking myself through it.	4	3	2	1
I concentrate my efforts on doing something about it.	4	3	2	1
I try to come up with a strategy about what to do with the images.	4	3	2	1
I make a plan of action about the images.	4	3	2	1
I think hard about what steps to take.	4	3	2	1
I think about how I might best handle the images.	4	3	2	1

I put aside other activities in order to concentrate on the images.	4	3	2	1
I focus on dealing with my images, and if necessary let other things slide a little.	4	3	2	1
I ask people who have had similar experiences what they do.	4	3	2	1
I try to get advice from someone about what to do.	4	3	2	1
I talk to someone to find out more about the nature of the images.	4	3	2	1
I talk to someone who could do something concrete about the images I see.	4	3	2	1
I talk to someone about how I feel.	4	3	2	1
I get sympathy and understanding from someone.	4	3	2	1
I look for something good in what is happening.	4	3	2	1
I have learnt to live with it.	4	3	2	1
I accept that this has happened and that it can't be changed.	4	3	2	1
I get used to the idea that the images come and go.	4	3	2	1
I seek God's help.	4	3	2	1
I put my trust in God.	4	3	2	1
I get upset by the images and let my emotions out.	4	3	2	1
I feel a lot of emotional distress because of the images I see.	4	3	2	1
I get upset because of the images I see, and am really aware of it.	4	3	2	1
I say to myself: "These images are not real"	4	3	2	1
Sometimes I sit back and enjoy the images in front of me	4	3	2	1
I admit to myself that I can't deal with the images, and quit trying.	4	3	2	1
I would be willing to take medications that would make the images disappear.	4	3	2	1
I reduce the amount of effort I'm putting into making the images go away.	4	3	2	1
I look forward to seeing the images.	4	3	2	1
I feel like I have no control over the images.	4	3	2	1
I feel like the others do not understand how it is to see the images.	4	3	2	1
The images seem like an undeserved punishment.	4	3	2	1

The images have somehow made me more humble.	4	3	2	1
I try to make the best of life despite the images.	4	3	2	1
I make jokes about the images I see with my friends/family.	4	3	2	1
I am doing fewer social activities because of my images.	4	3	2	1
I can laugh and see the funny side of things.	4	3	2	1
I restrain myself from doing anything about the images too quickly.	4	3	2	1
I gain comfort from seeing the images.	4	3	2	1
Seeing the images does not prevent me from enjoying the things I used to enjoy	4	3	2	1

Can you make the images appear? Yes ☐ No ☐

If "Yes", please describe how:

In order for the images to go away, have you ever tried:

	Yes	No	Tried, but were not useful
- to look directly at the image	☐	☐	☐
- to look away from the image	☐	☐	☐
- to turn on the lights	☐	☐	☐
- to turn the lights off	☐	☐	☐
- to try to touch the images	☐	☐	☐
- to persuade yourself the images are not really there	☐	☐	☐
- just waiting for the images to disappear	☐	☐	☐

Could you think of any other useful ways that you could make the images go away (please describe as detailed as possible):

***** Thank you for answering the questionnaire *****