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COGNITIVE DEFICITS AND STRUCTURAL BRAIN CHANGES ASSOCIATED WITH DEMENTIA AND VISUAL HALLUCINATIONS IN PARKINSON'S DISEASE

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Cualesquiera que hayan sido nuestros logros,
alguien nos ayudó siempre a alcanzarlos.

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Foreword

This dissertation, presented to obtain the degree of Doctor by the University of Barcelona, is the result of five studies carried out during a 4-year period at the Psychiatric and Clinical Psychobiology Department, Faculty of Medicine, University of Barcelona. The following articles have been published in international journals, as a result of the work performed, with a global impact factor (IF) of 9.32 (Isiknowledge, JRC 2004):

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Glossary of Abbreviations

PD	*Parkinson's disease*
PDD	*Parkinson's disease with dementia*
NDPD	*Non-demented Parkinson's disease*
NCs	*Normal controls*
LB	*Lewy bodies*
AD	*Alzheimer's disease*
DLB	*Dementia with Lewy bodies*
UPDRS	*Unified Parkinson's disease Rating Scale*
H&Y	*Hoehn and Yahr Rating scale*
MMSE	*Mini-Mental State Examination*
MRI	*Magnetic Resonance Imaging*
ROI	*Region of Interest*
VBM	*Voxel-based morphometry*
SPECT	*Single-photon Emission Computed Tomography*
rCBF	*Regional cerebral blood flow*
PET	*Positron Emission Tomography*
fMRI	*Functional Magnetic Resonance Imaging*
BA	*Brodmann area*
VH	*Visual hallucinations*
APOE4	*Apolipoprotein E4*
DA	*Dopamine*
RAVLT	*Rey's auditory verbal learning Test*
VOSP	*Visual object space perception*
VFDT	*Visual Form Discrimination Test*
BFRT	*Benton Facial RecognitionTest*
ANOVA	*Analysis of variance*
ANCOVA	*Analysis of covariance*
DSM IV-TR	*Diagnostic and Statistical Manual of Mental Disorders, Revised Fourth Edition*

I. INTRODUCTION

I. INTRODUCTION

1.1. DEMENTIA ASSOCIATED WITH PARKINSON'S DISEASE

Parkinson's disease is among the most frequent chronic neurodegenerative diseases in the elderly. Clinical definitions of Idiopathic Parkinson's disease (IPD) describe a disorder of unknown aetiology, characterized by bradykinesia, resting tremor, cogwheel rigidity, and postural reflex impairment. Neuropathologically, IPD is defined as the selective degeneration of pigmented, dopaminergic neurons of the substantia nigra pars compacta (SNc) and other brain-stem nuclei with the presence of alpha-synuclein positive staining inclusions (known as Lewy bodies and Lewy neurites) in the surviving neurons. The underlying pathological process progresses slowly yet relentlessly, affecting the human central, peripheral, and enteric nervous systems (Braak and Braak, 2000) and as result PD patients also experience nonmotor symptoms that can greatly contribute to the suffering of the patients. These nonmotor symptoms include dysautonomia, depression, pain and other sensory symptoms, hyposmia, sleep alterations and behavioral and neuropsychological disturbances (Ford, 1998; Hawkes, 2003; Thanvi et al., 2003).

The presence of cognitive decline in Parkinson's disease (PD) has always been controversial. The first clinical description of Parkinson's disease began with the monograph entitled 'An Essay on the Shaking Palsy' by James Parkinson in 1817. In this paper many of the motor symptoms were mentioned, such as resting tremor, rigidity and postural reflex embarrassment. However, regarding the mental functions, James Parkinson said that 'the senses and intellect are uninjured' (Bak and Lennox, 2006). Over fifty years later, Charcot was even more adept in distinguishing bradykinesia as a cardinal feature of the illness and separating it from rigidity. Charcot and his students described the clinical spectrum of this disease, noting two prototypes, tremorous and rigid/akinetic form. Charcot was also the first to suggest the term "Parkinson's disease", rejecting the earlier designation of "paralysis agitans" (Goetz et al., 2001a). Conversely, Charcot and Vulpian were convinced of the existence of deficits in mental state and Charcot stated that 'in general, psychic faculties are definitely impaired' (Bak and Lennox, 2006).

The positions taken by Parkinson and Charcot respectively had a lasting influence on the predominant views in their countries: while French authors regularly reported dementia, depression, hallucinations and bradyphrenia in their parkinsonian patients, Anglo-Saxon authors usually stressed normal behavior and cognition (Bak and Lennox, 2006). For a long time, cognitive functioning in PD was neglected and the disease was conceptualized as a motor system disorder. However since the early 1970s, it has been increasingly recognized that an array of cognitive impairment and neuropsychiatric symtoms occur in patients with

PD. In this chapter, the epidemiology, clinical profile of mental dysfunction, neuroimaging findings and clinicopathological correlations are reviewed.

1.1.1. Epidemiology

Incidence

Incidence studies may give a more accurate estimate of risk of dementia in PD because of their prospective nature and their relative freedom from survival bias (Emre, 2003). Risk for patients becoming demented compared with healthy controls was found ranged from 1.7 times over 2 years (Marder et al., 1995) to 6 times over 5 years of follow-up (Aarsland et al., 2001a). In a prospective study of 249 PD patients, Mayeux et al., 1990 found that by 85 years of age, over 65% of the surviving PD subjects of the cohort were demented. The cumulative incidence in two longitudinal studies investigating the risk of dementia in PD compared to healthy controls was found to be 38% and 53% after 10 and 14 years of follow-up respectively (Hughes et al., 2000; Read et al., 2001). Finally, in a recent study using a combination of information given by subjects and informants, review of medical records, the CAMCOG Test scores and the application of DSM-IV criteria Hobson et al. (2004) found an estimated risk of developing dementia in PD approximately five times greater compared with the control cohort.

Prevalence

Both the prevalence and the incidence of dementia in PD have been reported to be very variable. The estimates vary according to the nature of the population studied, diagnostic accuracy of PD, criteria used to diagnose dementia, tools for determining the cognitive function and method of sample collection. Cross-sectional studies examining the occurrence of dementia in patients with PD have found rates ranging from 2% (Hietanen & Teravainen 1988) to 81% (Martín et al., 1973). In an earlier review of 27 studies representing 4336 PD patients, Cummings (1988) found that the lowest prevalence of dementia was 30%. These results are based on studies critically considered but the majority of patients studied were referred to university neurology clinics and may not be representative of unselected PD populations. In addition, at that time studies did not include the identification of dementia with Lewy bodies (DLB). For this reason Aarsland et al., 2005 conducted a systematic review of the prevalence of dementia in PD employing strict methodological inclusion and exclusion criteria. Based on studies carried out mostly in European and North American populations, the authors found that, 24 to 31% of PD patients have dementia, and that 3 to 4% of the dementia in the population would be due to PD.

Few longitudinal studies of dementia have been conducted in PD and they have usually reported incidence of new cases (Marder et al., 1995; Hughes et al., 2000; Aarsland et al.,

2001a). In an early follow-up study Portin and Rinne (1987) examined 52 PD patients for 8-10 years and found that about one-third eventually manifested moderate to severe mental impairment. Recently, in a prospective longitudinal study in a well-defined diagnostic criteria PD sample, the cumulative prevalence of dementia was reported to be as high as 78% over 8 years follow-up, meaning that three quarters of this representative PD cohort developed dementia during the period of study (Aarsland et al., 2003).

Risk factors

Prevalence studies

Frequently, several features are reported to be associated with prevalence of dementia. These risk factors include age at onset (Hietanen and Teravainen, 1988; Mayeux et al., 1992; Aarsland et al., 1996), age at the time of study (Mayeux et al., 1988; Aarsland et al., 1996;), disease duration (Aarsland et al., 1996), tremor at disease onset (Vingerhoets et al., 2003), depression (Aarsland et al., 1996) and atypical neurologic features such as early occurrence of autonomic failure, symmetrical disease presentation, and only moderate response to dopaminergic treatment (Aarsland et al., 1996). The ApoE 4 allele, which has been consistently shown to be associated with a higher risk of Alzheimer's disease (AD), does not constitute a risk factor for dementia in patients with PD (Inzelberg et al., 1998a; Camicioli et al., 2005), although other authors found that the presence of ApoE 4 allele raises the likelihood of dementia (Pankratz et al., 2006). Finally, some authors suggest a possible familial aggregation of AD and PD with dementia given the increased risk of AD found in siblings of demented PD patients compared with siblings of normal subjects (Marder et al., 1999).

Incidence studies

Prospective studies have also reported a range of factors associated with the risk of dementia. These include age at onset of PD (Giladi et al., 2000; Read et al., 2001; Hobson et al., 2004), older age (Hughes et al., 2000; Aarsland et al., 2001a; Read et al., 2001; Levy et al., 2002b) and severe parkinsonism (Giladi et al., 2000; Hughes et al., 2000; Aarsland et al., 2001a; Hobson et al., 2004). Levy et al. (2002b) suggested that, the increased risk of incident dementia in PD associated with age and severity of extrapyramidal signs may be related primarily to their combined effect rather than separate effects. The mixed tremor/akinetic form of PD (Aarsland et al., 2003) and symptoms indicative of predominantly non-dopaminergic deficiency such as speech and axial impairment (Levy et al., 2000), presence of depression (Starkstein et al., 1992; Stern et al., 1993a; Marder et al., 1995; Giladi et al., 2000) have also been associated with a higher risk of developing dementia. As regards educational attainment, the results are contradictory: while some studies found that lack of education may increase the risk of cognitive decline in PD (Glatt et al., 1996; Levy et al., 2000) others authors found no such association (Hobson et al., 2004). Finally, other characteristics related

to incidence of dementia in PD are confusion or psychosis caused by levodopa (Stern et al., 1993a, Giladi et al., 2000) and hallucinations (Aarsland et al., 2003; Hobson et al., 2004).

Dementia in PD not only constitutes an important factor for caregiver distress and nursing home placement (Aarsland et al., 1999a; Hobson et al., 2004), but is also a predictor of mortality (Hughes et al., 2004). As these symptoms are potentially treatable (Emre, 2004 for a review), their identification is of major clinical importance, both for the patients and for their caregivers.

1.1.2 Cognitive dysfunction in PD

The possibility that cognitive alterations in Parkinson's disease arise principally from disruption of the dopaminergic system has been postulated on the grounds that dopaminergic neuronal loss represents one of the main hallmarks of the illness. However, earlier studies supported the hypothesis that many of the cognitive deficits are largely independent of frontostriatal dopamine deficit (Pillon et al., 1989; Richards et al., 1993a). The deficits in serotonergic, noradrenergic, and cholinergic systems might provide a rationale for the neuropsychological impairment seen in PD patients (Zgaljardic et al., 2004 for a review). Moreover, in addition to the subcortical Lewy bodies (LB) known as part of the parkinsonian nosology, cortical LB and Alzheimer type changes may also contribute to cognitive dysfunction (Burn, 2004). The neuropsychological abnormalities in PD vary from an almost normal profile to severe dementia, but it has not yet been established beyond doubt whether cognitive deficits found in non-demented PD patients are harbingers of dementia, or whether dementia represents a separate entity at the end of a continuous spectrum of cognitive impairment sharing the same pathology. In this section we will review the main neuropsychological deficits in PD with and without dementia.

Memory deficits

Memory dysfunction is probably one of the most relevant cognitive disturbances in PD. However, not all the memory components are affected: PD patients show impairment in working memory, episodic memory and procedural learning (Dujardin and Laurent, 2003 for a review). The findings in verbal declarative memory will be discussed here.

Declarative memory encompasses the acquisition, retention, and retrieval of knowledge that can be consciously and intentionally recollected. Generally, the abilities of non-demented PD (NDPD) patients to encode, store and consolidate new information are preserved, but they have difficulties in retrieving this information. Classically, it has been assumed that NDPD patients showed impairment on free recall, but normal results on recognition measures and normal long-term memory compared to normal controls (NCs) (Pahwa et al., 1998 for a review). The deficits are observed particularly when patients have to self-initiate strategies

(Buytenhuijs et al., 1994). Morever, unlike NCs subjects, who tend to organize recall in a semantic, i.e. internally generated, manner, NDPD patients prefer a serial, i.e externally guided, strategy (Buytenhuijs et al., 1994). The fact that defective explicit memory can largely be remedied by semantic cueing or probing (Pillon et al., 1993; Van Spaendock et al., 1996) has been interpreted as an impairment in the generation of spontaneous efficient encoding and retrieval strategies (Dubois and Pillon 1997; Ivory et al., 1999) or in a more general way as a deficit in problem solving (Van Spaendock et al., 1996). These disturbances have been considered reflect of executive dysfunction, and to be related to the disruption of the nigro-striato-thalamo-cortical circuit interconnecting the associative striatum to the prefrontal dorsolateral cortex (Higginson et al., 2003).

The disexecutive syndrome hypothesis as an exclusive responsible of memory deficits in PD patients is not supported by other studies. Faglioni et al., 1997 found that NDPD patients show selective impairment of the more automatized memory function, with the preservation of the effortful ones. Portin et al. (2000) reported that mildly impaired patients with PD (mean MMSE = 25.0) showed deficits on semantic memory tasks that were not alleviated by cueing. Beatty et al. (2003) in a sample of NDPD patients found non-significant benefits in acquiring stories relative to lists and non-significant differences between recognizing relative to recalling lists. Finally, in a recent study a test of verbal memory (the California Verbal Learning Test) was administered to PD patients and their performance was compared to a well-matched normative sample. NDPD exhibited deficits on measures of cued recall and delayed recognition that were similar in magnitude to that of free recall. The poor recognition was due to an elevated number of false positive errors (Higginson et al., 2005). This memory impairment could be related to dysfunctions of medial temporal regions. Neuropathological studies indicate that the entorhinal region and hippocampal formation are significantly damaged in PD (Braak & Braak, 2000), and that lesions in the anteromedial temporal mesocortex occur relatively early on the illness evolution (Braak et al., 2003).

The presence of verbal memory impairments has been indicated as an early sign associated with a later development of dementia in PD (Levy et al., 2002a; Woods and Troster, 2003). Whether the dementia is present, PD patients showed significant deficits relative to NCs and NDPD patients on both free recall and recognition measures (Beatty et al., 1989; Richards et al., 1993a; Higginson et al., 2005). The cross-sectional studies comparing PDD patients and Alzheimer's disease (AD) patients found that the former had comparable recall deficits but better results in recognition memory (Stern et al., 1993b) and a slower rate of forgetting from immediate to delayed recall (Stern et al., 1993b). However, in a longitudinal study demented PD patients showed a faster decline on delayed recall measures (Stern et al., 1998). Finally, studies comparing different types of dementia [PDD, AD and Dementia with Lewy Bodies (DLB)], showed that PDD and DLB patients showed a similar memory impairment and better

results in all cognitive memory measures when compared with AD subjects (Noe et al., 2004). These results are in agreement with structural MRI investigations which found a relative preservation of temporal lobe medial structures in PDD and DLB patients compared with AD subjects (Burton et al., 2004).

In conclusion, distinct memory patterns have been reported in PD patients and the memory impairment in PD depends greatly on the presence or absence of dementia. Although some studies have suggested that involvement of frontal lobe function accounts for memory impairment in PD patients the presence of varying degrees of impairment in subcortical, frontal, limbic and also temporal cortex structures may lead to heterogeneity in memory performance in PD.

Visual memory deficits

There is some evidence that visual recognition memory is preserved in PD patients. Flowers et al. (1984) found normal performance in recognition memory for objects, histograms and abstracts designs in PD patients compared to NCs. Regarding recognition memory for faces, whereas some authors found no impairment relative to healthy controls (Lees and Smith, 1983; Sprengelmeyer et al., 2003) other studies reported a selective impairment of this neuropsychological function. Specifically, Levin et al., 1989 reported deficits on the short form of Benton's Facial Recognition Test in a sample of 'early' PD patients (duration of illness less than 3 years). Another study using an experimental task of face processing found that 'late-onset' PD patients (> 55 years at onset) performed similarly to controls on recognition test of words, phrases and numbers, but they were impaired on a recognition memory test for unfamiliar faces (Dewick et al., 1991). A similar pattern of performance was seen in 'early-onset' PD patients (< 55 years at onset) (Haeske-Dewick et al., 1996). The deficits found in face recognition in PD patients have been related to an impairment in configural processing ability, specifically with deficits on visual closure (Cousins et al., 2000).

The pathological bases of face perception and memory dysfunctions in Parkinson's disease remain unclear, although both peripheral and central nervous affectations have been suggested to be involved in the impairments observed. Primary visual deficits such as defects in color and contrast discrimination (associated with dopamine loss in the visual system) and lower visual acuity have been pointed as basic visual sensory functions which could interfere with the initial processing of visual stimuli (Diederich et al., 2005 for a review; Uc et al., 2005). With regard to brain cortical structures, face perception and memory for faces are mediated by a distributed neural system. The core of the human neural system for face perception consists of three bilateral regions in the occipitotemporal visual extrastriate cortex. These regions are in the inferior occipital gyri, the lateral fusiform gyrus, and the superior temporal sulcus

(Haxby et al., 2000 for a review). The major functional components of the memory's faces network included fusiform face area, medial temporal lobe (hippocampus and related structures) and prefrontal cortex (Rapsack, 2003 for a review). Face encoding activates primarily the ventral system including bilateral temporal and fusiform regions and left prefrontal cortices whereas face recognition activates a primarily dorsal set of regions including right prefrontal and parietal areas (Bernstein et al., 2002). Some authors support the involvement of the striatum in face recognition deficits, given the afferences from the striatum with temporal and parietal associative visual areas (Haeske-Dewick, 1996; Cousins et al., 2000). However, given that PD patients suffer from extensive extranigral pathology (Braak et al., 2003), primary lesions in visual associative areas by themselves may also contribute to the deficits observed in face perception and recognition memory.

Language

Patients with PD have exhibited selective impairments in linguistic abilities. Confrontation naming performance was reported to be reduced in NDPD patients in comparison with NCs (Goldman et al., 1998, Green et al., 2002). Word list generation, using semantic and/or phonemic cueing, has also been found to be impaired in NDPD patients (Henry and Crawford, 2004 for a review). Although verbal fluency impairment has usually been attributed to a frontal/executive deficit, the possible contribution of semantic memory deficit to this cognitive impairment is unclear.

NDPD patients have also demonstrated impairments on tasks assessing complex comprehension and grammar relative to NCs (Grossman, 1999 for a review). Several explanations have attempted to identify the causes of the patient's deficits. Some investigators have attributed the impairment to a grammatical processing deficit (Ullman et al., 1997). Others have argued that a limitation in cognitive resources such as working memory and information processing speed could contribute to sentence comprehension difficulty (Grossman et al., 2000; Lee et al., 2003). Whereas some authors found a relationship between comprehension impairment in PD and dopaminergic medication (McNamara et al., 1996), other studies did not find that deficits in sentence processing in PD were related to alterations in dopamine levels (Skeel et al., 2001). Regarding brain areas involved in these comprehension deficits, the latest studies suggest that basal ganglia dysfunction does not solely account for sentence comprehension (Skeel et al., 2001) and support a critical role of neocortical regions in language functions (Longworth et al., 2005). Findings using functional magnetic resonance imaging are in agreement with this hypothesis. Grossman et al., 2003 found differences in the activation of the brain network involved in linguistic aspects of sentence pre-processing in PD compared with healthy controls. The authors reported that in comparison with healthy controls, PD patients showed a lesser recruitment of striatal, anteromedial prefrontal (BA32/10) and posterolateral temporal cortical regions (BA

21/22/39). However, further studies are needed to investigate whether language deficits in PD reflect true language impairment or are secondary to attentional, memory and executive dysfunctions.

Similarly to memory impairment, naming deficits have been identified as a predictive factor of PDD. Studies of naming deficits in demented PD patients showed that although PDD patients had naming difficulty, subjects with AD produced significantly more types of aphasic language disturbances (Huber et al., 1989a). However, demented PD patients showed a rapid rate of decline on naming compared to AD subjects (Stern et al., 1998). These naming deficits have been related to a deterioration of access to semantic field rather than deficits in visuoperceptive functions (Frank et al., 1996).

Visuospatial and visuoperceptive and deficits

The visual system is organized in two pathways: the ventral occipito-temporal pathway, which is required for object and form recognition, and the dorsal occipito-parietal pathway, required for computing the location of objects in spaces and visuospatial analysis (Ruiz-Sanchez de Leon and Fernandez-Guinea, 2005 for review). There is considerable evidence of visuospatial dysfunction in PD. Several studies reported impairment in unifactorial measures of visual–spatial ability (e.g., Judgment of Line Orientation) (Alegret et al., 2001; Green et al., 2002; Uc et al., 2005) although other authors failed to find a different visuospatial performance in PD groups compared to healthy controls (Levin et al., 1991; Richards et al., 1993b). The deficits are seen especially on multifactorial tasks (e.g., mental object rotation) (Lee et al., 1998; Crucian et al., 2003) suggesting that visual–spatial deficits in PD are not universal, and are related to deficits in other cognitive domains such as working memory or attention (Kemps et al., 2005). However other authors reported evidence for a visual–spatial deficit in PD that is independent of executive skills pointing to a specific visuo-spatial deficit (Cronin-Golomb and Braun, 1997; Janvin et al., 2003).

Demented PD patients are impaired relative to controls and nondemented PD subjects on motor free visual-spatial task (Huber et al., 1989a; Levin et al., 1991; Mosimann et al., 2004). Also, as in PD subject without dementia, the impairment in visuospatial functions is especially evident in more complex task requiring planning and sequencing of responses or self generation strategies (Levin et al., 1991; Mosimann et al., 2004). Not only dementia but also disease duration contributes to the decline of visuospatial abilities. Demented PD patients with medium duration of the illness (approx 7 years) exhibited deficits in assembling puzzles, formulating angular judgments and identifying embedded objects and geometric figures. At advanced stage PDD patients (approx. 16 years) showed pervasive impairments in all areas of visuospatial functioning (Levin et al., 1991).

Several neuroimaging studies have found parietal and parieto-occipital hypoperfusion in PD and PDD (Antonini et al., 2001; Firbank et al., 2003). Furthermore, other studies have shown deficits in parieto-occipital regions in PD subjects, which correlated with visuospatial performance (Abe et al., 2003; Mentis et al., 2002). However, it remains unclear if the cortical hypoperfusion in the visual cortex may be explained by primary pathological findings in the cortices such as neuronal loss, presence of Lewy bodies or AD changes (Armstrong et al., 2005) or as a result of damage to subcortical structures. Animal literature demonstrates that there are projections from basal ganglia to parieto-occipital visual associative areas. Studies in macaques showed that lesions in the caudate head and dorsal portions of the striatum caused visuospatial deficits. Conversely, lesions in caudate tail and ventral portions of striatum yielded visual discrimination impairment. (Ruiz-Sanchez de Leon and Fernandez-Guinea, 2005 for a review). These results indicate a link between subcortical structures and cortical areas involved in the processing of higher-order visual stimuli.

The visuoperceptive disabilities observed in patients with PD were found to be relatively independent of mental deterioration (Villardita et al., 1982) although this is not corroborated by other studies which found greater impairments in face and object recognition, form and space perception in cognitively deteriorated and demented PD patients compared to NDPD and NCs (Levin et al., 1991; Laatu et al., 2004; Mosimann et al., 2004). The pattern of visuoperceptive impairment found in PDD is similar to that found in dementia with Lewy bodies but it is different from Alzheimer's disease (Mosimann et al., 2004). This is consistent with previous neuroimaging studies reporting hypoactivity in cortical areas involved in visual processing in PDD and DLB (Donnemiller et al., 1997; Firbank et al., 2003).Various mechanisms have been proposed to explain these perceptual impairments in PD from cortical Lewy body pathology and cortical cholinergic deficits affecting areas involved in visual perception (Harding et al., 2002a, Bohnen et al., 2003) to primary visual factors such as retinal abnormalities by disruption of dopaminergic processes in the retina (Diederich et al., 2005).

Attention

Attentional control is believed to rely on a distributed fronto-parietal network (Posner and Petersen, 1990; Posner, 1994; Reza-Naghavi and Nyberg, 2005 for reviews). Performance on digit repetition tasks representative of vigilance or sustained attention was found intact by earlier studies in NDPD (Huber et al., 1986; Dalrymple-Alford et al., 1994). However, a recent study found that prefrontal cortical atrophy is related to a prolonged reaction time in tests measuring vigilance in non-medicated and non-demented patients at the early stage of PD (Bruck et al., 2004).

On more complex attentional tasks, PD subjects tend to perform adequately when external cues are provided, but poorly when the task requires self-directed allocation of attentional resources (Brown and Marsden, 1988; Wright et al., 1990) or when the task demands speed cognitive processing (Berry et al., 1999). NDPD were also showed more prone to interference in presence of distractor items than NCs (Filoteo et al., 1999; Vingerhoets et al., 2003). Impairments of both choice reaction time and cognitive reaction time have also been described in PD patients compared to elderly controls (Ballard et al., 2002).

Attentional impairment has also been identified in patients with PDD, as demonstrated by measures such as cognitive reaction time and vigilance (Litvan et al., 1991, Ballard et al., 2002). Furthermore, evidence of comparable attentional deficits has been found in patients with PDD and DLB. Ballard et al., 2002, using measures of simple reaction time, choice reaction time and cognitive reaction time, found that demented PD patients showed a profile of impairment similar to that seen in DLB. They also found similar attention fluctuations in both demented groups. However, there was no evidence of significantly greater fluctuations of choice reaction time in non-demented PD patients than in elderly controls (Ballard et al., 2002).

Frontal/Executive functions

Frontal cortical regions play a critical role in high level cognitive functioning. Although no consensus has been reached regarding the fractionation of functions within the frontal cortex, previous studies support associations between three frontal cortical regions and cognitive and behavioral functions: (1) the anterior cingulate cortex (ACC) is believed to be involved in response initiation, intention, inhibition, and conflict monitoring; (2) the dorsolateral prefrontal cortex (DLPFC) mediates executive cognitive functions, such as set shifting, complex problem solving, activation of remote memories, organizational strategies, and working memory; and (3) the orbitofrontal cortex (OFC) has been associated with functions requiring frontal monitoring of the limbic system such as inhibition, making decisions based upon a reinforcement/reward schedule required to maintain a behavioral set, impulse control, perseveration, mood, and personality. PD patients with or without dementia have shown impairments in working memory, trial-and-error learning, planning, response monitoring and set shifting (Zgaljardic et al., 2003; Owen, 2004 for a reviews).

Word list generation, using semantic and/or phonemic cueing has also been used to evaluate the frontal/executive functioning. During phonemic tasks neural activity has been reported in several prefrontal areas including anterior cingulate (BA 24 and 32), inferior frontal gyrus (BA 44/6; BA 45) and superior frontal sulcus (BA 8) (Paulesu et al., 1997; Phelps et al., 1997;). In semantic verbal fluency the dorsolateral prefrontal cortex is involved but activations are also seen in temporal regions (Vitali et al., 2005).

Verbal fluency performance has been extensively studied in PD patients although the literature reports contradictory results. Some studies have found significant deficits on measures of phonemic fluency in non-demented PD while others have failed to do so. Preserved semantic fluency has also been reported but the most consistent finding is impaired performance (Henry and Crawford, 2004 for a review). These authors applied meta-analytic techniques to compare performance on tests of phonemic and semantic fluency in PD, and concluded that the deficit for semantic fluency is significantly larger than the deficit for phonemic fluency. The most accepted interpretation for the greater impairment seen in semantic fluency task is the presence of a retrieval deficit more than a degradation of semantic store in PD, given the possibility that recovery of semantic items may depend on additional retrieval mechanisms that are different from those required in phonemic retrieval. However, other authors suggested that fluency impairment in PD is associated with deficits in semantic memory.

Impaired phonemic and semantic fluency have been identified as neuropsychological characteristics predictive of later dementia in PD (Jacobs et al., 1995a; Mayeux et al., 1998) and deficits in both semantic and phonemic fluency are large in magnitude in demented PD patients compared to PD patients without dementia (Henry and Crawford, 2004). A common assertion is that whilst cortical dementias (AD as prototype) are typified by a pattern of worse semantic relative to phonemic fluency performance, subcortical dementias (Huntington disease as prototype) are typified by the opposite deficit profile (Rosser and Hodges, 1994). However, this was not the case in a recent meta-analysis study which reported that, like patients with Alzheimer's disease, demented PD patients are more impaired on semantic fluency than fluency based on orthographic criteria (Henry and Crawford, 2004).

Frontal/Executive impairments in PD have been attributed to a deficit using internal control of action (Fimm et al., 1994; Taylor et al., 1986), impairment of self-generation of problem solving strategies (Van Spaendonck et al., 1995), deficit in set-shifting processing (Brown and Marsden et al., 1991, Richards et al., 1993c) and depletion of attentional resources (Brown and Marsden, 1988; Woodward et al., 2002). A recent fMRI study (Monchi et al., 2004) suggests that both nigrostriatal dopamine depletion and intracortical dopamine deficiency may play a role in these cognitive deficits.

The cognitive heterogeneity in Parkinson's disease

In early years, the cognitive performance in PD was defined by the presence of absence of clinical dementia. Later, specific neuropsychological deficits were identified (Emre, 2004 for a review) and recent studies report discrete patterns of cognitive deficits in PD suggesting the existence of neuropsychological heterogeneity and distinct cognitive profiles. Foltynie et al. (2004) studied a population-representative cohort of newly diagnosed Parkinson's disease.

The authors characterized different patterns of cognitive deficits using the MMSE, a test sensitive to impairment of temporal lobe function (Pattern recognition memory Test) and a test measuring frontal functions (Tower of London task). They found that 65% of the patients were cognitively intact, 12% showed a specific frontostriatal type deficit, 8% had specific temporal lobe type deficit and 15% of patients showed deficits in both domains. The authors suggested that the existence of sub-groups based on cognitive ability might be identifiable even in the early stages of the disease, which may reflect regional differences in the underlying neuropathological process. Janvin et al. (2003) investigated the cognitive profile of a study-population sample of patients with PD. Using a wide neuropsychological battery they found that 55% of PD patients showed mild cognitive impairment (that is, scores on at least one neuropsychological test 2 SD below the mean values for the control group). Within the cognitive impaired group, the authors found different types of cognitive profile. Twenty-six per cent showed only executive dysfunction, 16.6% had impaired visual memory and/or visuospatial abilities without executive dysfunction, and 45.2% showed a more widespread cognitive impairment affecting visual memory, executive and visuospatial skills.

The pattern of cognitive profile within a community-based sample of patients with PD without and with dementia (PDD), DLB and AD subjects has also been investigated. Using cluster analyses based on the Dementia Rating Scale subtest, the authors identified two subgroups with a subcortical cognitive profile (one with mild and one with moderate dementia), one subgroup with global impairment and severe dementia, and one subgroup with a cortical cognitive profile and moderate dementia. Of the PDD patients and subjects with DLB, 56% and 55%, respectively, had a subcortical cognitive profile, compared with only 33% of the AD patients. Conversely, 30% of the PDD patients and 26% of those with DLB had a cortical cognitive profile, compared with 67% of the patients with AD. The authors proposed that in some PDD patients, frontosubcortical changes are the main contributing factor to dementia whereas in other patients, cortical and hippocampal changes are more important (Janvin et al., 2006, in press).

1.1.3. Neuroimaging findings

Cognitive deficits that occur even early in the course of disease have received increasing attention in current imaging research. In the following overview we will (1) summarize studies using structural brain imaging techniques; and (2) review functional imaging studies that use single photon emission computerised tomography (SPECT) and positron emission tomography (PET) and have been related cognitive deficits with resting state metabolism and activation paradigms in PD and PDD.

Structural imaging techniques

The relationship between structural degeneration and cognitive impairment in PD was initially studied by computed tomography (CT) (Becker et al., 1979; Steiner et al., 1985). Starkstein and Leiguarda (1993) found that the enlargement of the frontal hors of lateral ventricles did significantly correlate with frontal impairment and the enlargement of the body of lateral ventricles was related to verbal memory deficits. Likewise, the third ventricle enlargement reflected memory impairment (Elwan et al., 1996)

The development of magnetic resonance imaging (MRI) allowed more accurate identification of global and regional atrophy. Early MRI studies found no evidence of generalized atrophy and ventricular enlargement in NDPD compared with NCs (Huber et al., 1989b). In contrast, diffuse cerebral atrophy was found in non-demented PD patients with longer disease duration (Alegret et al., 2001). Later studies have used volumetric techniques which are based on either visual inspection or a definition of region-of-interest (ROI) analysis. Analysis using this MRI method showed that NDPD patients showed reductions in striatum, thalamus, substantia innominata, hippocampus and medial temporal lobe (Lisanby et al., 1993; Laakso et al., 1996; Camicioli et al., 2003; Oikawa et al., 2004; Tam et al., 2005). In addition, some volumetric studies have linked the brain volume reductions with cognitive measures. Specifically, relationships have been found between hippocampal volume reduction and memory impairment and between prefrontal cortex atrophy and prolonged reaction time in NDPD (Riekkinen et al., 1998; Bruck et al., 2004). Given the high risk of dementia in people with PD, some authors suggest that the hippocampal atrophy could provide a presymptomatic marker for dementia (Camicioli et al., 2003) in conjunction with changes indicatives of frontostriatal dysfunction (Tam et al., 2005).

The presence of cognitive impairment in PD is accompanied by more severe brain atrophy. Volumetric studies comparing PDD patients with healthy controls found that PDD patients with dementia showed reductions involving subcortical and cortical structures, specifically substantia innominata, hippocampus and medial temporal lobe (Laakso et al., 1996; Camicioli et al., 2003; Oikawa et al., 2004; Tam et al., 2005). These studies failed to find differences in hippocampus and medial temporal lobe atrophy between demented and non-demented PD patients which would indicate that PD subjects have progressive medial temporal lobe atrophy before the onset of dementia (Tam et al., 2005)

Recently, the use of voxel-based morphometry (VBM) methods has allowed the study of density and/or volume changes in the whole brain without a priori region of interest selection. Studies using this technique have shown that PD patients without cognitive impairment compared to healthy controls showed gray matter and volume reductions involving the frontal lobe (anterior cingulate gyrus; inferior, middle, medial and superior frontal gyrus) and

temporal lobe (hippocampus; superior temporal and parahippocampal gyrus) (Burton et al., 2004; Nagano-Saito et al., 2005; Summerfield et al., 2005). Nagano-Saito et al. (2005) also found a positive correlation between the Raven Colored Progressive Matrices (RCPM) score (a test which measure visuospatial functions) and gray matter density in the dorsolateral prefrontal cortex and fusiform and parahippocampal gyri. The authors related the atrophy of the parahippocampal gyrus with an impairment of the visuospatial component of RCPM and suggested that intrinsic frontal lobe degeneration may play a role for executive dysfunction in PD.

Voxel-Based-Morphometry studies revealed that in comparison to healthy controls demented PD patients showed a widespread pattern of brain atrophy in cortical and subcortical structures. The gray matter volume loss affects especially temporal, occipital and frontal areas and to a lesser degree the parietal lobe. The atrophic temporal areas include superior, inferior as middle temporal lobes, insula, parahippocampal gyrus, hippocampus and amygdala. In the occipital lobe Brodmann areas 18 and 19 are particularly involved. The most affected areas in the frontal lobe are middle and inferior frontal gyrus and anterior cingulated gyrus. Finally, the patients also showed a reduction in subcortical structures such as thalamus, putamen and caudate. The reductions showed by demented patients when compared with Parkinson's patients without cognitive impairment are basically located in the temporal lobe (hippocampus and superior temporal gyrus) and the occipital lobe (fusiform and lingual gyrus) (Burton et al., 2004; Summerfield et al., 2005).

There are two recent studies which compare the pattern of brain atrophy between different dementia groups including Parkinson's disease dementia, Dementia with Lewy bodies (DLB) and Alzheimer's disease (AD). The study performed using VBM technique found that AD relative to PDD patients showed significant atrophy in the temporal structures including hippocampus, parahippocampal gyrus and inferior temporal gyrus. There was no difference in gray matter atrophy between PDD and DLB groups (Burton et al., 2004). Similar results were found using a volumetric MRI approach, which showed that the AD group had more medial temporal lobe atrophy than PDD and DLB groups but the degree of atrophy was similar between demented PD patients and subjects with DLB (Tam et al., 2005). These results would support the finding of greater memory impairment in AD compared to patients with PDD and DLB (Noe et al., 2004; Tam et al., 2005).

The studies of the progressive brain atrophy over time between demented and non-demented patients show contradictory results. Using the technique of coregistration of serial MRI scans Hu et al., 2001 found that non-demented PD patients had significant reductions in both percentage and absolute annual brain volume loss when compared to age-matched controls. In contrast, Burton et al., 2005 found that compared to NCs, only demented PD patients showed

a significantly increased rate of brain atrophy. These discrepancies could be explained partially by the different characteristics of the sample (cognitive status and duration of the illness) and follow-up time study. The technique of coregistration of serial MRI scans has been demonstrated to be a sensitive method for measuring global atrophy and for monitoring disease progression in several neurodegenerative diseases (O'Brien et al., 2001; Scahill et al., 2003). However, in contrast to the voxel-based morphometry technique, the subvoxel coregistration did not allow the specific quantification of volume loss in specific brain areas.

Functional imaging techniques

Positron emission tomography (PET) using the tracer 6-[18F] fluoro-l-dopa (Fdopa), has been used to demonstrate the gradual loss of nigrostriatal dopaminergic neurons and the functional impairment in the dopaminergic system in PD (Colloby et al., 2005 for a review). Several imaging studies have indicated an association between the dopaminergic hypofunction in the basal ganglia and the executive functions in different stages of PD given the close interrelationship through anatomofunctional circuits between basal ganglia and prefrontal cortex (Owen et al., 1998; Bruck et al., 2001; Bruck et al., 2005). These authors suggest that frontal-like cognitive deficits in patients in the early stages of PD are not the result of dysfunctions in the prefrontal cortex per se, but are related to impaired dopaminergic function in basal ganglia. Conversely, other functional imaging studies reported frontal hypometabolism in PD patients compared with healthy controls with metabolic preservation in basal ganglia (Antonini et al., 2001; Kikuchi et al., 2001; Kasama et al., 2005). A relationship between frontal abnormalities and executive functions has been reported by some authors (Nagano-Saito et al., 2004a) but not by others (Antonini et al., 2001; Dujardin et al., 2004).

Apart from brain abnormalities affecting frontal lobes and basal ganglia in NDPD, positron emission tomography (PET) and single photon emission computerized tomography (SPECT) studies have reported metabolic changes affecting other cerebral structures. Blood flow reduction has been found in the temporal (Hu et al., 2000) insular (Kikuchi et al., 2001), parietal (Hu et al., 2000; Firbank et al., 2003; Bruck et al., 2005; Kasama et al., 2005) and occipital (Bohnen et al., 1999; Hu et al., 2000; Mito et al., 2005) cortices. The reductions in regional cerebral blood flow (rCBF) in parietal and occipital areas have been shown to be accompanied by deficits in choline acetyltransferase activity (Kuhl et al., 1996). Some studies have been able to establish a relationship between cerebral hypoperfusion and cognitive deficits. For example Mentis et al., 2002 studied 15 moderately advanced NDPD, using [18F] fluorodeoxyglucose positron emission tomography. They found that PD patients showed an abnormal metabolic pattern at rest in regions subserving memory (medial temporal) and visuospatial functioning (parieto-occipital) and suggest that cognitive dysfunction may be caused by a pathophysiology process that affects the cortex globally rather than

frontosubcortical regions locally. Using single photon emission computed tomography, Abe et al. (2003) found significant reductions in rCBF in the bilateral occipital and posterior parietal cortices in NDPD patients compared to a healthy control group. The authors also found a strong positive correlation between the score on Raven's colored progressive matrices and the regional cerebral flood in the right visual association area in the PD patients, showing a relationship between occipital hypoperfusion and impairment of visual cognition according to the RCPM Test. Visual functions, specifically visuospatial functions, have also been related to the cortical cholinergic deficits observed in PD patients (Bohnen et al., 2006).

PET studies using [^{18}F] fluorodeoxiglucose in PDD patients supported a contribution of the basal ganglia in the cognitive deficits of PD. A PET study assessing dopaminergic function in patients with PD dementia showed reduced 18F-dopa uptake bilaterally in the striatum, midbrain and anterior cingulate area compared with normal controls. A relative difference in 18F-dopa uptake between PD and PD dementia patients was a bilateral decline in the anterior cingulate area and ventral striatum and in the right caudate nucleus in the PD dementia group. The authors concluded that dementia in PD is associated with impaired mesolimbic and caudate dopaminergic function (Ito et al., 2002). Other brain areas have also been identified and reductions of glucose metabolism involving lateral parietal, lateral temporal and lateral frontal association cortices and posterior cingulated cortex have been described in PDD in comparison to normal controls (Vander Borght et al., 1997). Compared to NDPD patients, PDD had greater reductions in parietal cortex (Piert et al., 1996). The pattern of metabolic abnormalities has been found to be different between PDD and AD; although PDD showed metabolism abnormalities in the posterior cortex, demented PD patients displayed a relatively metabolism preservation in the medial temporal cortex with a greater reduction in the visual cortex. The loss of cholinergic neurons has also been described in patients with PD dementia; in-vivo imaging of cortical cholinergic function using positron emission tomography revealed that compared with controls mean cortical acetylcholinesterase activity was lowest in patients with PD dementia (20%), followed by patients with PD without dementia (13%) and AD (9%). Reduced cortical acetylcholinesterase activity thus seemed to be more characteristic of patients with PD dementia than of patients with mild AD (Bohnen et al., 2003).

SPECT imaging techniques showed differences in cerebral blood flow in demented PD patients compared to non-demented PD patients and healthy controls in a variety of brain regions. Compared to healthy controls, PDD patients have demonstrated hypoperfusion affecting parietal (Antonini et al., 2001; Firbank et al., 2003; Osaki et al., 2005; Mito et al., 2005), temporal (Antonini et al., 2001; Osaki et al., 2005; Mito et al., 2005), occipital (Kasama et al., 2005; Mito et al., 2005) and frontal (anterior and posterior cingulate) areas (Kasama et al., 2005; Mito et al., 2005). The differences observed between PD patients with and without dementia are also not consistent and decreased rCBF have been reported in

posterior cingulated gyrus (Kasama et al., 2005; Osaki et al., 2005) temporal (Spampinato et al., 1992; Osaki et al., 2005), parietal (Spampinato et al., 1992; Kasama et al., 2005; Osaki et al., 2005) and occipital cortices (Spampinato et al., 1992; Kasama et al., 2005). The reductions involving medial parietal lobes, parietal association areas and dorsal occipital lobes have been related to fluctuating cognition, one of the most common neuropsychological deficits affecting DLB and PDD (Osaki et al., 2005). Some authors found similarities between the regional patterns of blood flow reduction in demented PDD patients and those observed in AD patients (Spampinato et al., 1992; Kuhl et al., 1996). Nevertheless, other studies found different regional brain perfusion between AD and PDD but similarities between demented PD and DLB patients, with similar rCBF reductions affecting particularly parietal and occipital areas (Firbank et al., 2003; Kasama et al., 2005; Mito et al., 2005).

Longitudinal studies of cerebral perfusion in non-demented PD patients found reductions in parietal (Tachibana et al., 1993) and temporo-insular and temporo-parieto-occipital areas which were associated with cognitive decline in executive functions and verbal memory (Dujardin et al., 2004). Firbank et al. (2005) reported a rCBF loss in frontal regions with a trends to reduced perfusion in the parieto-occipital regions in non-demented PD patients. However, these reductions were not associated with a significant cognitive decline measure by the Cambridge Cognitive Examination (CAMCOG). Finally, Colloby et al. (2005) reported progressive dopaminergic loss in striatum in PD patients with and without dementia compared with NCs. In demented PD patients, lower scores in MMSE at baseline corresponded to a higher rate of decline in striatal (putamen) binding.

1.1.4. Clinicopathological associations

The pathology underlying dementia in PD is still controversial, both in terms of site and type of pathology (Apaydin et al., 2002, for review). Three types of pathology have been associated with the presence of dementia in PD: subcortical pathology, limbic or cortical Lewy-body-type degeneration, and those suggesting coincident AD-type pathology.

Subcortical pathology

Rinne et al. (1989) found a negative correlation between the neuronal count in the SN and the severity of dementia in PD patients and suggested that the degeneration of nigral projections may constitute a subcortical component contributing to cognitive impairment. Involvement of other subcortical structures such as basal ganglia, amygdala and thalamus (de la Monte et al., 1989), locus coeruleus and tegmental ventral area (Zweigh et al., 1993) and nucleus basalis of Meynert (Perry et al., 1985), might also underlie dementia. Components of the thalamus assigned to the limbic loop were recently identified as targets for LB pathology, and it was suggested that damage to the thalamic components of the limbic loop contribute to cognitive, emotional, and autonomic symptoms in patients with PD (Rüb et al., 2002)

AD-type pathology

Coincident AD-type pathology might cause dementia in PD. Boller et al. (1980) found AD-type pathology in the cerebral cortices of all severely demented patients (9/9), but in only a proportion of non-demented patients with PD (3/7). In a study of 100 patients with histologically confirmed PD, 30% of the patients with well-documented dementia showed changes of AD (Hughes et al., 1993). De Vos et al., (1995) found that patients with PD and dementia had a higher degree of cortical Alzheimer-type changes (especially in the entorhinal region). Similarly, Braak et al. (1996) concluded that fully developed PD with concurring incipient AD is likely to be the cause of impaired cognition, and stage III or higher AD pathology is the most common cause of intellectual decline in PD. Mattila et al. (1999) investigated the severity of neuritic change in CA2-3 sector of the hippocampus and in the periamygdaloid cortex. The authors found that neuritic changes in CA2-3 sector of the hippocampus were related to LBs whereas neurites in periamygdaloid cortices were related to co-existing AD pathology. Finally, in two hundred consecutive autopsy examinations of patients with PD it was observed that ninety-four percent of those patients classified as having PD with dementia showed cortical neuropathologic changes of AD, whereas 6% did not (Jellinger et al., 2002). In a later study, Jellinger (2003) again found a significant additional neuritic Alzheimer pathology in demented PD vs non-demented patients. Other authors (Mastaglia et al., 2003) did not support this association and suggested that AD-type pathology could contribute to dementia and cognitive decline when combined with other neuropathological changes such as alpha-synuclein deposition and/or cortical LB in the cerebral cortex.

Lewy-body-type pathology

Several studies supported the view that dementia in PD correlates with Lewy pathology. Mattila et al. (1998) found that Lewy-body densities in the cortex (especially in temporal neocortex) correlated significantly with cognitive impairment in patients with PD, independent of or in addition to AD-type pathology. In three studies in which synuclein antibodies _a more sensitive marker of Lewy bodies_ were used, a similar conclusion was reached: synuclein positive cortical Lewy bodies (especially frontal), were associated with cognitive impairment independent of AD-type pathology (Mattila et al., 2000). In another study, cortical Lewy bodies were found to be a more sensitive and specific correlate of dementia than AD-type pathology in 22 demented patients as compared with 20 non-demented patients with PD; AD-type pathology was found in only a few patients (Hurtig et al., 2000). Diffuse or transitional Lewy-body disease was found to be the primary pathological substrate in 12 of 13 patients with PD who later developed dementia. The occurrence of AD-type pathology was modest, but correlated highly to Lewy body pathology, suggesting common origins or one triggering the other (Apaydin et al., 2002).

Contrarily, other authors suggested that the presence of limbic or cortical Lewy bodies may not always be associated with dementia in PD. In a clinico-pathological study, the brains of 17 patients with PD pathology and no history of cognitive impairment were examined. Nine of these patients showed a neuropathological picture consistent with limbic (or transitional) category of DLB, and eight with neocortical DLB. The authors suggested that important factors other than the absolute number of Lewy bodies in the neocortex and limbic system may influence the development of cognitive impairment in PD (Colosimo et al., 2003). Parkkinen et al. (2005) studied 904 cases from autopsy material regardless of clinical phenotype which had alpha-synuclein pathology in the dorsal motor nucleus of vagus, substantia nigra, and/or basal forebrain nuclei. Retrospective clinical assessment showed that only 32 (30%) of 106 alpha-synuclein-positive cases were diagnosed with a neurodegenerative disorder. The distribution or load of alpha-synuclein pathology did not permit a dependable postmortem diagnosis of extrapyramidal symptoms or cognitive impairment. Some neurologically unimpaired cases had a reasonable burden of alpha-synuclein pathology in both brainstem and cortical areas. The authors suggest that alpha-synuclein-positive structures are not definite markers of neuronal dysfunction.

Possibly, not only the total number of LB but also their topography may be a crucial factor for the development of dementia. Churchyard et al. (1997) correlated Mini-Mental State Examination scores and DSM-III dementia ratings with the density of Lewy bodies, Lewy neurites, neurofibrillary tangles, neuritic plaques, gliosis, and neurons in the hippocampus and amygdala of 27 PD patients without Alzheimer's disease changes. The degree of cognitive impairment was correlated with the density of Lewy neurites in the CA2 hippocampal field. The authors hypothesized that disruption of the connection between the dentate gyrus, entorhinal cortex, septal nuclei, and hypothalamus and the CA1 field contributes to dementia in PD. Kovari et al. (2003) performed a clinico-pathological study in 22 elderly PD patients in whom Parkinsonism preceded cognitive decline by at least 3 years. The authors found a highly significant correlation between clinical dementia rating scores and regional LB scores in the entorhinal cortex and Brodmann area 24. In a multivariate analysis only LB densities in the entorhinal cortex and anterior cingulate cortex were significantly associated with CDR scores.

A recent study suggested an ascending order of LB pathology in PD in six neuropathological stages. The selective vulnerability of nerve cells induces a distinctive distribution pattern of lesions which remains remarkably consistent across cases. The lesions initially occur in the dorsal motor nucleus of the glossopharyngeal and vagal nerves and anterior olfactory nucleus. Thereafter, less vulnerable subcortical and cortical areas gradually become affected. The disease process in the brain stem pursues an ascending course with little interindividual variation. The pathology in the anterior olfactory nucleus makes fewer incursions into related

areas than that developing in the brain stem. Cortical involvement ensues, beginning with the anteromedial temporal mesocortex. From there, the neocortex succumbs, commencing with high order sensory association and prefrontal areas reaching finally, first order sensory association/premotor areas and primary sensory/motor fields (Braak et al., 2003). Moreover, a significant correlation was described between stage of the PD pathology and cognitive status (measured by MMSE), in addition to correlations between cognitive status and Hoehn and Yahr stages, as well as between PD neuropathological stages and Hoehn and Yahr stages. However, it was also reported that in some individuals cognitive decline can develop in the presence of mild Parkinson disease-related cortical pathology and, conversely, widespread cortical lesions do not necessarily lead to cognitive decline (Braak et al., 2005). Conversely, Jellinger (2006) did not find differences between Lewy body stages between demented and non-demented PD patients. The authors also reported that the severity of neuronal loss in substantia nigra was insignificantly greater in PDD cases than in NDPD.

Although the physiological function of alpha-synuclein remains to be definitely established, it seems that this protein controls cell death. From the contradictory and divergent interpretations about the putative functions of alpha-synuclein in cell death, the first unifying conclusion is that PD related mutations all lead to an exacerbated proapoptotic response or, alternatively, increase the cell responsiveness to toxic insults (Kim et al., 2004 for a review). However, other authors found that LB formation does not significantly correlate with neuronal loss (Gomez-Isla et al., 1999, Terry et al., 2000) or apoptosis (Broe et al., 2001).

Overlap between neurodegenerative disorders

Overlap has been reported between PDD, DLB and AD. Recent studies showed that the pathological substrate of PDD is comparable to the neocortical type or the transitional type of DLB suggesting that the two clinicopathological syndromes may be attributable to the same biological abnormality (Colosimo et al., 2003; Mori, 2005 for a review). Distribution and density of LB did not distinguish dementia with Lewy-bodies from dementia in PD cases, although semi quantitative thresholds in the parahippocampus could separate demented from non-demented cases with high sensitivity and specificity (Harding et al., 2001). Jellinger (2006) again observed that there were few neuropathological differences between PDD and DLB cases. The most significant differences between the groups were a more severe substantia nigra neuronal loss in PDD cases and a more frequent involvement of the hipocampal C2/3 area, amygdala and neocortex by Lewy bodies in DLB patients.

Though of PD and AD are generally considered to be separate and distinct diseases, they share common clinical and neuropathological features and overlap extensively. Pathological changes in the substantia nigra, including the formation of LB, are not uncommon in AD, and neither is the formation of senile plaques and neurofibrillar tangles in demented PD cases

(Armstrong et al., 2005 for a review). Alpha-synuclein has been implicated in the pathogenesis of AD, and studies using alpha-synuclein/beta-amyloid double transgenic mice suggested that beta-amyloid peptides may contribute to the development of Lewy-body diseases by promoting the aggregation of alpha-synuclein and exacerbating alpha-synuclein-dependent neuronal pathologies (Masliash et al., 2001). A synergistic effect between Lewy bodies and AD pathology has been suggested, given that patients with the Lewy body variant of AD, in which the neuropathology also warrants the diagnosis of AD, are much more severely demented than DLB patients with the same cortical LB count. Dementia is also more severe and Lewy bodies are more frequent when AD and Lewy body pathology coexist (Duda, 2004 for review).

1.2. HALLUCINATIONS IN PARKINSON'S DISEASE

1.2.1. Epidemiological and phenomenological studies

Although it remains difficult to estimate the prevalence of hallucinations in the natural course of PD before the introduction of levodopa therapy, there are historical documents suggesting that hallucinations may be part of PD itself especially in the context of late dementia, depression and confusional state (Fenelon et al., 2006). Nowadays, it remains difficult to draw precise conclusions about the prevalence of hallucinations due to a lack of a uniform definition and classification of the symptom, the lack of a PD-specific scale for psychotic symptoms and differences in patient populations and methodologies used. Bearing in mind these limitations a recent review of published work (Papapetropoulos and Mash, 2005) concluded that hallucinations are the most common psychotic symptom and that psychotic phenomena occur in 20-40% of medication-treated PD. Hallucinations have a persistent and progressive nature (Goetz et al., 2001b) and their prevalence increases over time (Goetz et al., 2005).

Formed visual hallucinations (VH) are documented by cross-sectional studies in about 25% of patients with PD (Sanchez-Ramos et al, 1996; Fenelon et al., 2000) although a recent retrospective autopsy study reported that VH occurred in 50% of patients with PD (Williams and Lees, 2005). VH could be associated with other types of hallucinations, mainly minor or auditory. When verbal hallucinations are present, they are always neutral and clearly different from the pejorative and threatening auditory hallucinations characteristic of schizophrenia. Minor hallucinations include "presence "and "passage" hallucinations. "Presence" hallucinations consist in a vivid sensation of the presence of somebody either somewhere in the room or, les often, behind the patients. In "passage" hallucinations patients experience a brief vision of a person or an animal passing sideways (Fenelon et al., 2000). Other types of hallucination, such as tactile and olfactory, are less prevalent (Fenelon et al., 2000; Holroyd et al., 2001; Fenelon et al., 2002; Chou et al., 2005; Grossi et al., 2005). However, a recent longitudinal study found that the type of hallucination seems to depend on patient age. The authors documented that nonvisual hallucinations were most frequently observed as the first form of hallucinations in older patients (Goetz et al., 2005).

Formed visual hallucinations consisted in persons, animals and less often objects which are frequently mobile, appearing for short periods, generally lasting for a few seconds (Barnes et al., 2001; Holroyd et al., 2001). The figures are involved in appropriate activities and do not usually disturb the patient. Due to their repetitive and stereotyped character, the figures become familiar to the patient, who usually observes them with bemused interest and indifference. Although usually favored by dim light or reduced vigilance, VH can appear suddenly, without any known trigger or voluntary effort (Fenelon et al., 2000; Barnes et al.,

2001; Holroyd et al., 2001). They often have blurred borders, but there is neither color predominance nor localization to a specific field of vision (Barnes et al., 2001) Affectively, patients usually express little concern about the VH; however, as reality testing and insight further decreases, the content of hallucinations may change to frightening images (insects, rats) inducing anxiety and panic attacks (Melamed et al, 1999; Wolters, 1999). Insight into the hallucinatory nature of the phenomenon is normally maintained in all the patients without dementia, and more than half of those with dementia (Fenelon et al., 2000). Hallucinations may become predominant, malignant, disabling, and intermingled with paranoid pattern, including suspiciousness, negativism and sexual accusations (Melamed et al., 1999). Psychosis can be a disabling complication and its association with death, nursing home placement and development and progression of dementia has been reported (Factor et al., 2003).

1.2.2. Risk factors for the development of VH

Several studies have examined the clinical associations that distinguish PD patients with and without psychotic manifestations. Results have been remarkably consistent and have identified cognitive impairment, dementia, depression, age and duration of the illness, disease severity, and sleep disorder as independent risk factors for visual hallucinations. In addition, some studies have also highlighted the contribution of visual sensory dysfunction to visual hallucinations.

Cognitive impairment and dementia

Although some studies excluded patients with significant dementia (Chou et al., 2005) cognitive disorders have been identified as an independent predictive factor for visual hallucinations (Fenelon et al., 2000). In prospective studies, cognitive impairment was significantly more frequent in Parkinson's disease patients with VH, whether cognition was studied using the Folstein Mini-Mental State Examination (Sanchez-Ramos et al., 1996; Aarsland et al., 1999b; Paleacu et al., 2005; Papapetropoulos et al., 2005), the Blessed dementia scale (Graham et al., 1997) the 'short mental test' (Inzelberg et al., 1998b) or the telephone interview for cognitive status (Holroyd et al., 2001). Similarly, most studies have found greater prevalence of VH in demented versus non-demented patients with PD (Papapetropoulos et al., 2004). In the study by Fenelon et al. (2000), visual hallucinations were recorded in 70% of the patients with dementia versus 10% of non-demented patients.

Spontaneous VH are among the cardinal features of dementia with Lewy bodies (DLB) (Mckeith et al., 2005) where up to 60% of patients have prominent degrees of psychosis, specifically visual hallucinations and delusions (Ballard et al., 1999). In a prospective population study, neuropsychiatric symptoms were compared between non-demented PD (PDND), PDD and DLB patients. Delusions and hallucinations occurred with increasing

frequency in PDND (7% and 14%), PDD (29% and 54%), and DLB (57% and 76%), suggesting the importance of dementia as a risk factor for VH (Aarsland et al., 2001b).

Depression

Although some studies did not identify depression as a predictive or associated factor for developing VH (Graham et al., 1997; Fenelon et al., 2000) several studies found a close relationship between hallucinations and depression. Hallucinating PD patients were found to have a history of depression more frequently (Sanchez-Ramos et al., 1996) or to have a higher score than non-hallucinating patients on the Montgomery and Asberg Depression Rating Scale (Aarsland et al., 1999b) and on the Geriatric Depression Scale (GDS) (Holroyd et al., 2001). Inzelberg et al. (1998b) reported depression requiring treatment in half of their patients with auditory hallucinations. Finally, the presence of major depression according to DSM-IV criteria correlated with higher UPDRS 'thought disorder' score (an item of the UPDRS which include hallucinations) in the community-based study by Aarsland et al. (1999b).

Age, Disease duration and Severity

Several studies detected associations between increased age and the presence of hallucinations (Aarsland et al., 1999b; Fenelon et al., 2000; Goetz et al., 2005). However, when analyzing the influence of age and duration of PD Fenelon et al. (2000) found that duration of disease but not current age or age at onset was an independent predictor of VH. Positive association between the occurrence of hallucinations and disease duration were also observed in other studies (Sanchez-Ramos et al., 1996; Grossi et al., 2005; Papapetropoulos et al., 2005).

Regarding the severity of the illness, Aarsland et al. (1999b) found a relationship between higher UPDRS thought disorder scores and impairment on the UPDRS activities of daily living subscale. Positive associations between the presence of hallucinations and disease severity as measured by UPDRS and Hoehn and Yahr scales have also been reported (Holroyd et al., 2001; Papapetropoulos et al., 2005). Concerning motor status, several studies reported a greater motor impairment in PD patients with hallucinations (Graham et al., 1997; Fenelon et al., 2000; de Maindreville et al., 2005), but there are contrasting results about predictive nature of this factor for the presence of VH (Fenelon et al., 2000; Doe de Maindreville et al., 2005). Finally, a retrospective autopsy study found that in patients with DLB and PD, VH were associated with falls, postural instability, speech disturbance, dysphagia and autonomic dysfunction (Williams and Lees, 2005).

Sleep disorders

The association between hallucinations and sleep-wake disturbances in PD was first stressed by Moskovitz et al. 1978. They suggested that the symptoms begin with sleep disruption, continues with altered dream phenomena, and ends with hallucinations. Pappert et al. (1999)

tested this controversial hypothesis and found that 82% of PD patients with hallucinations showed some form of sleep disorder. The authors observed an interaction between sleep fragmentation, altered dream phenomena and between altered dream phenomena and hallucinations/illusions. However, there was no interaction between sleep fragmentation and hallucinations/illusions. Therefore, the conclusion was that sleep fragmentation, altered dream phenomena and hallucinations/illusions in PD should be considered distinct but often overlapping behaviors. Goetz et al. (2005), in a prospective longitudinal study focused in the relationship between hallucinations and sleep disorders in PD, concluded that hallucinations and global sleep disorders progress differently. The authors considered that hallucinations and sleep disorders are separate behavioral abnormalities and that sleep alterations are not necessarily harbingers of hallucinations. Contrarily, it has been reported an association between visual hallucinatory experiences and the use of sleep medications (Davidsdottir et al., 2005) and other authors identified sleep disturbances as an independent factor predicting the hallucination in PD (de Maindreville et al., 2005).

Hallucinations in PD are generally more frequent in the evening and during the night, a feature shared by other forms of hallucinosis (eg. peduncular hallucinosis and the Charles Bonnet syndrome) (Sanchez-Ramos et al., 1996; Fenelon et al., 2000). Although this finding may be related to poor visual acuity during darkness, daytime somnolence has been identified as an independent predictive factor for visual hallucinations (Fenelon et al., 2000) suggesting a greater importance of wakefulness (Manford and Andermann, 1998 for a review).

Polysomnographic studies suggested a link between REM sleep abnormalities and the development of hallucinations during the course of PD (Comella et al., 1993; Nomura et al., 2003). It has also been suggested that some of the features of PD patients with medication-induced psychosis may be narcoleptic in nature. In this context, the so-called "sleep attacks" of PD patients may represent REM sleep intrusions into wakefulness, and VH with psychosis may represent the dream imagery of REM sleep intruding into wakefulness (Arnulf et al., 2000). Lesions involving brainstem structures controlling sleep, especially those generating REM sleep in PD patients, seem to support this hypothesis (Manford and Andermann, 1998 for a review). Along the same lines, a study using 24-hour ambulatory polysomnography in 20 PD patients with VH showed that hallucinations were highly correlated to daytime REM sleep or nocturnal REM sleep in 33% of the instances (Manni et al., 2002) suggesting that the neural mechanisms involved in generating sleep, and particularly in dream imagery, may play a causative role in VH in PD.

Antiparkinsonian drugs

The relation between dopaminergic treatment and VH is complex. The facilitating role of dopaminergic treatment is well established and virtually all antiparkinsonian agents-

dopaminergic drugs, anticholinergics, and amantadine can induce hallucinations and other psychotic behavior in susceptible patients with PD. However, VH are not an invariable complication of treatment and rarely occur in other disorders in which DA treatment is used such as hyperprolactinaemic infertility and Ekbom's syndrome (Papapetropoulos and Mash, 2005 for a review).

The type of antiparkinsonian drug determines in part the risk of drug-induced hallucinations in susceptible PD patients. Double-blind controlled trials in de novo patients without dementia suggest that dopamine agonists are more likely to induce psychosis than L-Dopa. Among dopamine agonist, there is no difference between ergot and nonergot compounds regarding the incidence of drug-induced psychosis. The addition of monoamine oxidase-B inhibitors or catechol methyl-transferase inhibitors to enhance dopaminergic transmission may also occasionally trigger psychotic symptoms (Papapetropoulos and Mash, 2005 for a review).

Although dose reductions of dopaminergic agents may lead to resolution of psychotic symptoms, dose–response relations are more complex. When administering intravenous L-dopa infusions in PD patients with visual hallucinations Goetz et al. (1998) were not able to precipitate hallucinations by high-dose intravenous L-dopa, in contrast to prominent increases in dyskinesia during such infusions. Cross-sectional studies did not find a simple side-effect of dopaminergic treatment for explaining the occurrence of VH (Fenelon et al., 2000; Holroyd et al., 2001; Merims et al., 2004). Moreover, a recent retrospective autopsy study (Williams and Lees, 2005) found no association between levodopa dosage and VH suggesting that the pathological substrate has a greater effect on the development of VH than the drugs alone.

Ocular disorders

Visual hallucinations may occur in blind patients and in as many of 12% of cognitively normal people with poor visual acuity, a condition called the Charles Bonnet syndrome (Teunisse et al., 1996). Moreover, it has been shown that poor eyesight contributes to the severity of visual hallucinations in patients with Alzheimer's disease (McShane et al., 1995). PD patients with VH showed significantly reduced visual acuity in the best eye (Holroyd et al., 2001) and performed less well on both contrast and color discrimination test in comparison to nonhallucinating PD patients (Diederich et al., 1998). It has also been shown a correlation between contour colour perception ability and risk of visual hallucinations (Buttner et al., 1996). Moreover, ocular disorders were identified as independent factors for the onset of hallucinations in a follow-up study (de Maindreville et al., 2005). These data suggest an influence of primary visual factors in the occurrence of VH.

Other risk factors

Conflicting results have been reported for the association between the ε4 allele of the apoliprotein E gene (APOE4) and VH in PD. It has been suggested that carrying the APOE4 was a significant risk factor for the appearance of drug-induced VH and psychosis in PD (de la Fuente-Fernandez et al., 1999; Feldman et al., 2006) but other studies did not find this association (Goetz et al., 2001c; Camicioli et al., 2005). As mentioned above, the presence of VH is a risk factor for developing dementia (Aarsland et al., 2003) and some authors found a relationship between the ε4 allele and presence of dementia in PD (Parsian et al., 2002; Pankratz et al., 2006) suggesting an overlap in the genetic etiology of both manifestations.

1.2.3. Neurochemical basis of VH

Dopaminergic System

The frequent occurrence of VH in association with chronic dopaminergic treatment for PD prompted the hypothesis that VH represent a medication-induced toxic syndrome due to overstimulation of mesolimbic D3 and D4 dopaminergic receptors (Diederich et al., 2005 for a review). Moskowitz et al. (1978) postulated a pharmacological kindling model to suggest enhanced sensitivity of dopaminergic receptors after chronic treatment. In this model, dopamine can no more be adequately stored at the presynaptic level; thus, excessive quantities of dopamine overflow onto supersensitive receptors, inducing psychotic signs. Several studies reported a significant compensatory up-regulation of striatal DA receptors in MPTP-treated monkeys as well as in PD patients (Papapetropoulos and Mash, 2005 for a review). However, although the relative DAergic overactivity due to stimulation of supersensitive receptors by replacement therapy may provide a permissive environment for drug-induce psychosis, several observations change this hypothesis of VH as simple dopaminergic intoxication. There were reports of hallucinations in PD patients before dopaminergic drugs became available, indicating that the illness itself may play some role in generating psychosis (Fenelon et al., 2006). The daily dose of levodopa is no different between hallucinators and non hallucinators (Fenelon et al., 2000) and use of levodopa was not associated with VH in patients with PD (Williams and Lees, 2005). Moreover, genetic polymorphism comparisons between PD subjects with chronic hallucinations and subjects without hallucinations have not revealed differences for the dopamine transporter (Goetz et al., 2001c; Goldman et al., 2004).

Despite these data, DA dosage lowering or withdrawals usually improve the psychotic symptoms (Lieberman, 1998; Wint et al., 2004). The atypical neuroleptic clozapine which preferentially blocks D3 and D4 mesolimbic DA receptors and 5HT2 receptors showed clear efficacy in treating PD-related VH. Quetiapina, a strong 5HT2 receptor antagonist but also a moderate D2 receptor antagonist, showed efficiency in treating drug-induced psychosis in PD patients (Wint et al., 2004). A second line of evidence linking VH directly to the

dopaminergic system is that all dopaminergic drugs are associated with their induction or exacerbation. L-dopa and dopamine agonists, as well as catechol methyltransferase (COMT) inhibitors and monoamine oxidase (MAO) inhibitors when used with L-dopa are associated with VH. This evidence strongly suggests that dopaminergic pharmacology is involved in the PD related VH (Diederich et al., 2005).

Cholinergic system

Greater reductions in choline acetyltransferase activity in the temporal lobe have been associated with a higher prevalence of hallucinations in Parkinson's disease, PDD and DLB (Perry et al., 1991). After effectively treating hallucinations by reducing anticholinergic and/or dopaminergic agents, Goetz et al. (1982) postulated that acetylcholine blockade might induce PD-related hallucination. Lack of balance between cholinergic and DAergic system has been advocated as an explanation for VH, because VH can also be triggered by anticholinergic medication. Imbalance of cholinergic/serotoninergic system with lower levels of cholinergic markers and relative preservation of serotoninergic markers in the temporal or parietal cortex has been suggested as a possible neurochemical explanation for psychosis in DLB. Post-mortem neurochemical studies also found cholinergic deficits associated with VH in patients with AD and DLB. It has been proposed that cortical acetylcholine normally enhances neuronal signal to noise ratio, and when levels are reduced, irrelevant intrinsic and sensory information normally processed in parallel at subconscious level enters conscious awareness in the form of VH (Diederich et al., 2005 for a review). Finally, the efficacy of cholinesterase inhibitors in several small open-label studies to treat psychosis in demented PD patients would support this hypothesis (Reading et al., 2001; Bergman and Lerner, 2002; Bullock and Cameron 2002; Fabbrini et al., 2002).

Serotonergic System

Serotonin, a monoamine neurotransmitter, is also thought to play a role in producing psychotic symptoms. Several findings point to the role of serotonin in VH. Lesions of serotonergic neurons of the raphe nuclei or serotonin depletion induce apparent VH as well as disinhibition of phasic rapid eye movement (REM) processes in cats. Dopaminergic drug treatment depresses already low cerebral serotonin levels in PD resulting in dopamine–serotonin ratios reductions to approximately 20% of normal values. Based on these findings, serotonin augmentation in PD patients with VH seems to be a logical approach, and it has been documented that the serotonin precursor, L-tryptophan, alleviated the intensity and/or diminished the frequency of visual paranoid hallucinations in PD patients (Diederich et al., 2005 for a review). Finally, atypical antipsychotic agents such as clozapine and quetiapine have shown efficacy in the treatment of psychosis in PD. These have been found to have a greater affinity for serotonin (5-HT2) than dopamine (D2) receptors (Papapetropoulos and Mash, 2005 for a review).

1.2.4. Neuropsychological studies in PD patients with VH

Few studies have examined the specific role of cognitive dysfunction in the genesis of hallucinations in PD patients. Given that hallucinations are mainly visual, the early studies explored complex visual performance and special aspects of visual memory and imagery in PD patients with VH versus PD patients without VH (Barnes et al., 2001; 2003). The authors found that PD patients with VH were particularly impaired on tests of recognition memory for faces and object recognition (silhouette identification) as measured by the VOSP (Visual object and space perception battery). The subjects with VH were unable to resolve ambiguities in stimuli by sensory bottom-up processing but seem to be guided by top-down knowledge about the objects were likely to be. The performance of these patients on the VOSP's spatial subtest was preserved. Hallucinating PD patients also showed a greater propensity to report imaged stimuli as percept, which means that patients with hallucinations believed that the mental image triggered by a word acquisition phase was a real picture (a phenomenon known as difficulty with source or reality monitoring). The authors proposed that the failure to extract correct information from the stimulus ("visual silhouette agnosia") caused aberrant release of previously stored schemas being played out in the form of internal images, thus linking VH to hypothesized unconscious memory substitution. Because of the deficits in source monitoring, they suggested that PD patients become unable to decide if images are internally or externally generated. This dilemma may lead to confusion not only between imagination and perception but also between previously imagined material and previously perceived material. The authors proposed a multi-factorial model for the occurrence of hallucinations; the combination of degraded visual information about the environment, plus impaired and perhaps fluctuating source monitoring, together with failing memory and an over-reliance on previously stored schemas, which on occasion "fill in" for missing detail, provide the basis for visual hallucinations.

Grossi et al. (2005) compared non-demented PD patients with and without hallucinations on several neuropsychological tasks: verbal fluency (semantic and phonological), verbal learning (Rey's Auditory Verbal learning Test), and abstract non-verbal reasoning (Raven's Progressive Matrices). They found that patients with hallucinations scored significantly lower than patients without hallucinations only on verbal learning-immediate recall tasks, and semantic and phonological fluency tasks. They concluded that the reduced fluency, verbal learning and learning efficiency in the hallucinating patients (in presence of normal delayed recall) may be ascribed to a relative dysfunction of controlling and monitoring (executive) functions subtended by pre-frontal cortex. In contrast to the selective impairment found in both previously described studies, Sinforiani et al., 2006 (in press) reported that PD patients are characterized by several cognitive deficits. They found that hallucinating PD patients showed deficits affecting logical memory (Babcock's Story Recall Test; verbal long-term

memory), spatial short-term memory (Block Tapping Test) and nonverbal logical abilities measured by Raven's Progressive Matrices Test.

The main limitations of these studies are that patients with and without VH showed different duration of the illness (Barnes et al., 2003) which could influence the neuropsychological scores given the progressive deterioration during the illness course of some cognitive functions such as frontal, visuoperceptive and visuospatial functions (Levin et al., 1991; Azuma et al., 2003). Moreover, in the study of Sinforiani et al. (2006 in press) some of the hallucinating PD patients could be diagnosed as affected by dementia according to DSM-IV criteria; the presence of dementia could explain why these authors found impairment in non verbal logical abilities measured by Raven's Progressive Matrices Test meanwhile Grossi et al. (2005) found this function preserved.

1.2.5. Neuroimaging studies of VH

Functional neuroimaging studies have shown abnormalities on visual pathways in PD patients with VH. The earliest SPECT study evaluated rCBF by regions of interest (ROI) in PD patients with medication induced hallucinations (some of them with cognitive impairment). The authors documented significantly lower cerebral blood flow in the left temporal lobe and temporo-occipital region among hallucinating PD subjects compared to those without hallucinations. The authors suggested that hypometabolism in temporal cortices might reflect degeneration of mesolimbic or mesocortical pathway predisposing to occurrence of VH (Okada et al., 1999). Recently, Oishi et al., 2005 explored changes in rCBF associated with non psychotic VH (VH no related to acute change of DAergic medication) in non-demented PD patients. This study showed significantly lower rCBF in the right fusiform gyrus and higher rCBF in the right middle and superior temporal gyri in hallucinating patients compared to non-hallucinating PD patients, suggesting a dysfunction in the ventral visual pathway associated with the presence of this symptom. Only one study has explored the relationship between regional changes in brain perfusion and changes in severity of hallucinations. O'Brien and co-workers (2005) evaluated a sample composed by demented PD patients and subjects with DLB and found an association between decrease in hallucinations score and increased perfusion in the midline parietal area encompassing the posterior cingulate, precuneus and superior parts of cuneus. It was suggested that the increase in posterior cingulate/precuneus perfusion could be the result of increased general attention to visual stimuli associated with the patient experiencing decreased frequency of hallucinations.

There is only one PET study investigating brain metabolic abnormalities associated with VH in PD patients (Nagano-Saito et al., 2004b). The authors found that the decrease of relative regional cerebral glucose metabolic rate (rCMRglc) in the posterior areas was 24% greater in VH than in non-VH patients. As regards NCs, VH patients showed a lower rCMRglc on

lingual gyrus and inferior parietal lobe. Comparing to non VH, hallucinating PD patients had greater rCMRglc in the left superior frontal gyrus. The authors concluded that a pattern of relative hypermetabolism in the frontal cortex with relative hypometabolism in the posterior areas is probably a metabolic feature of VH in PD patients.

During a visuoperceptive paradigm using fMRI, Stebbins et al. (2004) found that among hallucinating PD subjects, visual stimuli did not activate regions of posterior cortex (occipital, temporal, parietal) involved in the perception of visual stimuli and motion to the same extent as seen in non hallucinating patients. They also found increased activation in anterior cortical regions (frontal cortex), and subcortical structures (caudate nucleus). The authors concluded that a disruption in the attentional modulation of visual perception may play a role in the pathophsysiology of VH in PD.

Functional neuroimaging studies of VH in patients with DLB or AD have shown changes in cerebral perfusion, measured by single photon emission computed tomography (SPECT), or changes in regional cerebral glucose metabolic rate (rCMRglc) measured by PET. Specifically, VH in AD have been associated with hypoperfusion of parietal lobe (Kotrla et al., 1995) while DLB patients with VH showed decreased glucose utilization in the primary visual cortex with a relatively preserved metabolism in the right temporoparietal association cortex (Inamura et al., 1999). Finally, as regards structural MR studies, occipital atrophy has been associated with VH in AD (Holroyd et al., 2000) but a study performed in hallucinating PD patients searching for occipital lobe or deep white matter lesion in the visual pathways did not detected systematic changes (Kraft et al., 1999). Structural whole brain changes associated with VH in non-demented PD patients have not been investigated.

1.2.6. Clinicopathological associations of VH in neuropathological studies

The anatomical substrate of hallucinations is under debate and there are very few neuropathologic studies of VH in parkinsonian disorders. The first study investigated cases meeting neuropathological criteria for DLB (Gomez-Tortosa et al., 1999) but did not find a relationship between regional distribution of LB and presence of hallucinations. Later, Harding et al. (2002a) analyzed a large cohort of cases with LB pathology (patients with DLB, PDD and Parkinson's disease without dementia) and reported that cases with hallucinations had significantly more LB/field on average than those without hallucinations in the parahippocampus and the amygdala. The second study performed by the same authors studied non-demented Parkinson's disease and age-sex matched NCs (Harding et al., 2002 b). There was a significant increase in the density of LB in the basolateral amygdaloid nucleus (nearly double) in Parkinson's patients suffering from hallucinations compared with Parkinson's patients who did not report them. Likewise, the proportion of neurones containing LB was also nearly double in those with hallucinations. The authors suggested that increased

density of LB in the basolateral amigdaloid nucleus could disrupt the ability of the amygdale to integrate coordinated behavioral responses between the ventral stream cortical visual system and the extrageniculostriate (colliculo-thalamo-amygdala) visual system. This, in association with dopamine replacement therapies might precipitate the visual hallucinations experienced by patients with PD. The most recent neuropathological study reported high LB densities across the amygdala in PD patients with VH compared to non hallucinating PD patients but also found an involvement of frontal (BA 9) and parietal lobes (BA 39) (Papapetropoulos et al., 2006 in press).

II. APPROACH AND OBJECTIVES

II. APPROACH AND GENERAL OBJECTIVES OF THE THESIS

Cognitive impairment of different degrees and hallucinations are common complications of chronic Parkinson's disease (PD) (Aarsland et al., 2001b; Aarsland et al., 2003; Williams and Lees, 2005). The pathogenesis, pathophysiology, and relationship between cognitive deficits and presence of hallucinations are not fully understood but both impact severely on overall disability and quality of life of PD patients (Factor et al., 2003; Williams and Lees, 2005). Cognitive impairment and dementia are the most frequently reported risk factors for visual hallucinations in PD (Aarsland et al., 1999b; Fenelon et al., 2000; Barnes and Davis, 2001; Holroyd et al., 2001; Williams and Lees 2005). Similarly, most studies have found a greater prevalence of psychosis in demented versus non-demented patients with PD (Papapetropoulos et al., 2005). However, although the relationship between VH and cognitive dysfunction is well established, it seems that the emergence of VH is not caused directly by the presence of general cognitive impairment because not all PD patients with dementia experienced VH (Fenelon et al., 2000) and association studies reported several risk factors for the development of this symptom supporting a multicausal nature of this phenomenon (Diederich et al., 2005 for a review). The data presented in this thesis intend to give some clues towards a better understanding of the cerebral basis and cognitive deficits associated with dementia and visual hallucinations in Parkinson's disease patients.

The general aims of the studies carried out in this thesis were:

1) To study *in vivo* structural brain changes associated with dementia and visual hallucinations in Parkinson's disease patients.

2) To cognitively characterize a group of non-demented PD patients with VH in a cross-sectional and longitudinal study.

III. METHODS

III. METHODS

This thesis consists of five studies examining cognitive functions and structural brain characteristics in PD patients using neuropsychological and MRI methods. The first and the second investigations evaluated a sample of PD patients with and without dementia. The three last studies were carried out with non-demented PD patients with and without visual hallucinations.

Our first study was a cross-sectional MRI investigation in PD patients with and without dementia using a volumetric technique. Post-mortem studies have reported LB pathology and hippocampal and amygdalar atrophy in demented and non-demented PD patients but *in vivo* amygdalar changes have not been investigated. The objective of the first study was to quantify amygdalar and hippocampal reductions in PD patients with and without dementia using a volumetric analysis and to relate the volume of these brain structures with global status and memory performance (Chapter 4.1). With regard to structural brain changes observed in PD patients, several cross-sectional investigations reported atrophic features in demented and non-demented PD patients but there are not longitudinal studies investigating gray matter changes in specific brain areas. The second study aimed to characterize the pattern of brain changes and cognitive decline over time in demented and non-demented PD patients using voxel-based-morphometry (Chapter 4.2).

To assess whether the presence of hallucinations is associated with a specific pattern of cognitive impairment and structural gray matter reductions we designed three studies in non-demented PD patients who suffer from VH. Brain abnormalities have been reported in PD patients with VH using neuropathological and functional MRI techniques but there are no studies investigating *in vivo* structural brain changes in these patients. The objective of our third study was the cross-sectional characterization of cerebral changes in PD patients with VH using the voxel-based-morphometry technique. The fourth study comprised the neuropsychological assessment of a hallucinating PD sample focalizing in the temporo-parieto-occipital functioning. Finally, given that the presence of hallucinations has been associated with a more rapid cognitive decline assessed by general cognitive tests screening, the aim of our fifth study was to evaluate changes over a one-year period in the cognitive domains assessed in the cross-sectional study. A comprehensive description of study samples and methods used can be found in chapter four.

IV. RESULTS

IV. RESULTS

4.1. BRAIN VOLUMETRIC REDUCTIONS IN PARKINSON'S DISEASE WITH DEMENTIA

4.1.1. INTRODUCTION

Parkinson's disease (PD) is a widespread degenerative illness affecting the central, peripheral, and enteric nervous system. The underlying pathological process progresses slowly but relentlessly and involves multiple neuronal systems. The disease is the consequence of changes in the neuronal cytoskeleton developing in particularly susceptible types of nerve cells. Components of the limbic and motor systems have been shown to be particularly vulnerable to degeneration. The most frequently affected limbic sites include the entorhinal region, the second sector of Ammon's horn, and important subnuclei of the amygdala (Braak and Braak, 2000). Neuropathological investigations have found amygdalar and hippocampal degeneration in PD patients with dementia (de la Monte et al., 1989; Cordato et al., 2000). In addition, the degree of cognitive impairment correlates with the density of Lewy neurites in the CA2 hippocampal field, raising the possibility that the disruption of the connection between the dentate gyrus, entorhinal cortex, septal nuclei, hypothalamus and the CA1 field contributes to dementia in PD (Churchyard and Lees, 1997). PD patients without dementia exhibit similar pathological changes in the hippocampus and the amygdala, including atrophy and Lewy body formation. In one study, total amygdalar volume was reduced by 20%, due to neuronal loss and neuronal shrinkage (Harding et al., 2002b).

Magnetic resonance (MR) volumetric analysis allows quantification *in vivo* of regional cerebral atrophy. Reductions in hippocampal volume are observed in PD patients with and without dementia (Laakso et al., 1996; Camicioli et al., 2003). To our knowledge, amygdalar volume has not been quantified *in vivo* in PD patients. This study investigated possible amygdalar and hippocampal reductions in PD patients with and without dementia and related these structural changes to global cognitive status and memory performance.

4.1.2. METHODS

Sample

Forty-eight subjects between 54 and 84 years of age participated in the study. The patient sample comprised 16 subjects with an initial diagnosis of idiopathic PD who met criteria for dementia (PDD) in later years and 16 PD patients who did not. Patients were recruited from an outpatient movement disorders clinic (PD and Movement Disorders Unit, Department of Neurology, Hospital Clinic, Barcelona). Some of these patients had participated in previous studies (Summerfield et al., 2002; Summerfield et al., 2005). The healthy control group

consisted of 16 subjects matched to patients by age and education without any history of psychiatric or neurological disorder.

The diagnosis of Parkinson's disease was made using UK Brain Bank Criteria (Daniel and Lees, 1993). The severity of parkinsonian symptoms was assessed by subscale III of the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn et al., 1987). The stage of the disease was estimated according to the Modified Hoehn and Yahr scale (Jankovic et al., 1990). Depression was evaluated by means of the Hamilton scale (Hamilton, 1960). Dementia was assessed using two standardized instruments: the DSM-IV-TR (American Psychiatric Association, 2003), and the Mini-Mental State Examination (MMSE) (Folstein et al., 1975). Patients with MMSE scores below 23 and with DSM-IV-TR criteria for dementia were considered as PDD. Clinical and demographic characteristics of the sample are displayed in Table 4.1.1.

All subjects were neuropsychologically assessed using Folstein's Mini-Mental State Examination to evaluate global cognitive dysfunctions and a modified version of the Rey Auditory-Verbal Learning Test (RAVLT) (Lezak et al., 2004) to assess memory functions. For the RAVLT we recorded learning (the sum of 1-5 presentations), and forgetting (% of memory loss after 20 minutes of interference).

The study was approved by the local ethics committee. Written informed consent was obtained from the patients or their caregiver after full explanation of the procedures involved in the study.

Data analysis

Statistical analysis was carried out using SPSS 11.0. For normally distributed variables with homogeneity of variance, we used an analysis of variance (ANOVA) and post-hoc Bonferroni test. For non-normally distributed variables or in the case of non-homogeneity of variance, we used the non-parametric Kruskal-Wallis test, which provides a chi-square statistic.

Magnetic Resonance Image acquisition and analysis

Magnetic resonance imaging (MRI) was obtained in all subjects using a 1.5T GE Nvi/Cvi 8.4 machine (GE, Milwaukee, WI). A strict imaging protocol was used, including a 3-D IR Prep SPGR sequence of the entire brain in the axial plane, and the following parameters: repetition time (TR) = 17; echo time (TE) = 5; inversion time (TI) = 300; 1.5 mm thickness; field of view (FOV) =24x24; 256x256; and 1 number of excitations (NEX).

Images were displayed and measured using MRIcro (Nottingham, UK) software. MRIcro permits the manual tracing of a region-of-interest (ROI) and gives an automatic estimation of

its volume. Measurements were carried out by an investigator blind to the patients' group (PDD, PD or control). All structures were measured twice in order to obtain intra-rater reliability. The values reported represent the mean of these two measurements. The brain structures measured included hippocampus and amygdala. Estimations of global gray and white matter volume and cerebrospinal fluid (CSF) volume were also obtained after the automatic brain segmentation procedure carried out by statistical parametric mapping (SPM).

Hippocampus. The hippocampus was measured as described previously (Aylward et al., 1999) (A detailed description is available online at http://pni.med.jhu.edu/). Briefly, the procedure is as follows: (1) locate the fornix in the coronal slice; (2) follow the gray matter of the hippocampus posteriorly until it can no longer be seen; (3) begin tracing from the most posterior point, including the subiculum, moving anteriorly until the hippocampus can no longer be distinguished from the amygdala; and (4) perform a correction in the sagittal plane. Briefly, the lateral boundary of the hippocampus was set at the inferior temporal horn of the lateral ventricle or temporal lobe white matter. Boundaries of the hippocampus were traced manually, with the white matter of the parahippocampal gyrus as the inferior boundary; the alveus or lateral ventricle as the superior boundary and the amygdala as the anterior boundary. In slices in which a clear demarcation between hippocampus and amygdala was not seen, the gray matter superior to the lateral ventricle was not sampled.

Amygdala. It is often difficult to distinguish the amygdala from the surrounding gray matter, and various protocols have been described to estimate amygdalar volume. We manually traced the amygdala posteriorly-inferiorly in the coronal plane, with subsequent correction in sagittal and axial views. Hippocampus and amygdala were separated through visualization of the alveus. The amygdala was bordered medially by the entorhinal cortex and gray matter of the parahippocampal gyrus, and laterally by the temporal horn of the lateral ventricle and temporal lobe white matter. The choroid plexus was excluded.

Intrarater reliability for all measures was high, with kappa scores for all structures of more than 0.90. The ROIs measured were corrected by the total intracranial volume (sum of gray matter, white matter and cerebrospinal fluid) and multiplied by 10^3 to obtain corrected values.

4.1.3. RESULTS

The demographic variables (age, gender, and years of education) of samples were similar. Clinical variables in the two patient groups did not differ statistically in years of disease evolution, scores on Scale IIII of the Unified Parkinson's Disease Rating Scale or depression, although the PDD group showed a more advanced stage of illness on the Hoehn and Yahr scale. Neuropsychological testing showed significant differences between the groups in MMSE and RAVLT scores (see Table 4.1.1.).

	Controls	PD	PDD	Test statistics	*p*-value
Age (yr)	71.3 ± 7.5	72.9 ± 4.4	70.1 ± 7.9	1.46[a]	0.482
Gender (Men: Women)	5:11	6:10	5:11	0.19[b]	0.91
Education (yr)	10.2 ± 5.2	9 ± 5.2	6.6 ± 4.5	2.09[c]	0.135
Hamilton score	0.7 ± 1.2	1.7 ± 2.1	2.9 ± 4.6	3.44[a]	0.179
Disease evolution (yr)	-	11.3 ± 6.8	13.3 ± 5.3	2.59[a]	0.108
Hoehn and Yahr	-	2.7 ± 0.7	3.4 ± 1.1	4.11[a]	0.042*
UPDRS III	-	25.6 ± 13.5	36 ± 13.2	4.19[c]	0.051
MMSE	29.4 ± 1.1	28.6 ± 1.0	17.3 ± 5.5	33.52[a]	<0.0005*†‡
RAVLT learning	36.7 ± 6	34.9 ± 6.5	15.1 ± 8	45.08[c]	<0.0005*‡
RAVLT forgetting	3.1 ± 4	7.9 ± 6.2	15.1 ± 12.2	12.59[a]	0.002*†‡

Table 4.1.1. *Demographic, clinical, and neuropsychological variables. Values are mean ± SD. [a] Indicates calculated using Kruskal-Wallis test; [b] Indicates calculated using the χ2 test; [c] Indicates calculated using analysis of variance (ANOVA) test. * Differences between PD and PD; † Differences between controls and PD; ‡ Differences between controls and PDD.*

Regarding the MRI volumetric analysis, the PD group showed decreased volume in both structures (amygdala, 11%; hippocampus, 10%), although the reductions did not reach statistical significance. Compared with controls, demented patients showed an amygdalar volume reduction of 21% and a hippocampal volume reduction of 20%.

ANOVA showed a significant group effect for both direct and corrected measures (see Table 4.1.2.). Post-hoc analysis revealed significant differences in corrected amygdala ($p = 0.008$) and corrected hippocampus ($p = 0.004$) between the PDD and control group. In nondemented patients, both structures had values between those of demented patients and controls (see Figure 4.1.1.).

	Controls	PD	PDD	F statistic	*p*-value
Amygdala[a]	2485 ± 397.7	2,231.3 ± 476.9	2,043.7 ± 540.1	3.48	0.039*
Hippocampus[a]	5571 ± 767	5,130.5 ± 839.6	4,638.3 ± 993.8	4.58	0.015*
Amygdala corrected[b]	1.6 ± 0.3	1.4 ± 0.3	1.3 ± 0.3	5.10	0.010*
Hippocampus corrected[b]	3.6 ± 0.7	3.2 ± 0.4	2.9 ± 0.6	6.0	0.005*

Table 4.1.2. *MRI volumetric results. Values are mean ± SD. [a] Raw volumes (mm^3; .[b] Measures corrected by total brain volume (structure volume in mm^3/total brain volume in mm^3) x 1000.* Differences between controls and PDD.*

The MMSE correlated with the amygdala ($r = 0.39$; $p < 0.01$) and hippocampus ($r = 0.35$; $p < 0.01$) in the whole sample. Memory also showed significant correlations with both

structures. RAVLT learning correlated with amygdala (r = 0.38; p < 0.01) and hippocampus (r = 0.54; p < 0.01). In demented PD patients we found a significant correlation between RAVLT delayed recall and hippocampal volume. Because PDD patients had longer disease duration than PD patients (by around 2 years), we carried out correlations of this variable with volumetric MRI data. No significant correlations were found for either the whole sample or the separate groups.

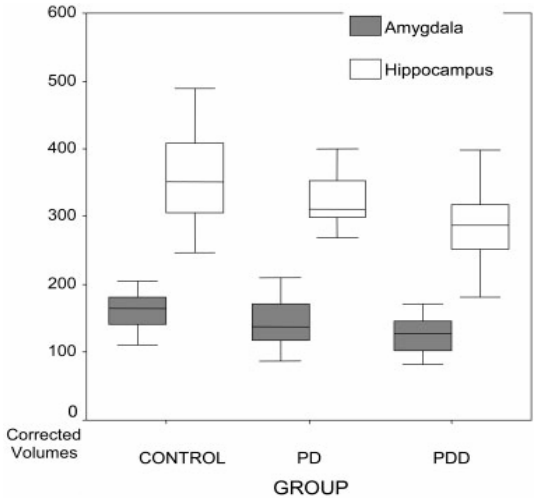

Figure 4.1.1. *Box plot showing amygdalar and hippocampal ratios of the groups*

4.1.4. DISCUSSION

In agreement with previous postmortem volumetric studies (de la Monte et al., 1989; Cordato et al., 2000) our results showed significant reductions in the amygdala and hippocampus in PD patients with dementia. These reductions may reflect neuropathological changes in these structures (Mattila et al., 1998, 1999).

We provide the first *in vivo* evidence of a reduction in amygdalar volume in PD patients with dementia. Atrophy of the amygdala is subtle and is not detected easily either visually or using quantitative single-section area analysis (Harding et al., 2002b). Three-dimensional volumetric post-mortem studies of regional brain atrophy in demented PD have reported amygdalar reductions of 18% (de la Monte et al., 1989) and 29% (Cordato et al., 2000) compared with that in age-matched normal controls. Our results in PDD patients were similar (a 21% reduction). With regard to NDPD, only one volumetric study has been published on postmortem amygdalar atrophy. In a well-selected sample of nondemented, levodopa responsive-PD, a neuropathological study revealed a 20% global amygdalar volume reduction compared with controls (Harding et al., 2002b). In our sample, the volume reduction was only 10% compared to the control sample. The low level of reduction in our study in comparison with post-mortem studies could be attributed to years of evolution from onset, and it is

possible that amygdalar degeneration occurs during the course of the disease (Braak et al., 1994; Del Tredicci et al., 2002).

The amygdala is a cerebral structure involved in emotional processes such as recognition of facial expressions and evocation of emotional responses (Phan et al., for a review 2002; Yang et al., 2002). Functional imaging data revealed abnormal amygdala responses in non-demented PD patients during a paradigm that involved perceptual processing of fearful stimuli (Tessitore et al., 2002). The atrophy of this structure could contribute to deficits in recognition of emotional expression of faces (Jacobs et al., 1995b) and emotional prosody (Benke et al., 1998) documented in PD patients.

We also observed hippocampal volumetric loss in demented and nondemented Parkinson's patients compared with controls. Hippocampal volumetric atrophy in PD has been reported on previously using MRI (Laakso et al., 1996; Camicioli et al., 2003) and in a postmortem study (Cordato et al., 2000). Histopathological studies have described Lewy bodies and Alzheimer'stype changes in the hippocampus in demented PD patients, both of which probably contribute to cognitive loss (Mattila et al., 1998; Apaydin et al., 2002). Lewy bodies and Lewy neurites are observed mainly in the CA2 and CA3 fields and fibrillar tangles in the CA1 sector of the hippocampus (Churchyard and Lees, 1997; Mattila et al., 1999). Demented PD patients have increased neurofibrillary tangles in the CA1 sector of the hippocampus (Apaydin et al., 2002). Churchyard and Lees (1997) stressed the impact of hippocampal degeneration on the process of dementia in PD. These authors suggest that the pathological process associated with Lewy neurite formation in CA2 disrupts the hippocampal function, and hence cognition, by interfering with inputs to the CA1 field. In that study, Lewy neurites density in the CA2 field of the hippocampus was related to the severity of dementia.

In a previous study using voxel-based morphometry (VBM) in the same sample of demented patients (Summerfield et al., 2005) we also observed hippocampal atrophy in PDD compared with controls, but we did not obtain significant results for the amygdala. These discrepancies were also observed by Good et al. (2002) in a study with Alzheimer's disease patients. In their study, the ROI analyses seemed more sensitive to volume loss in the amygdala whereas VBM seemed more sensitive to regional hippocampal volume loss.

In summary, we found amygdalar and hippocampal volume reductions in PD patients with dementia. MRI is sensitive to the limbic involvement in PD, and limbic atrophy seems to present a continuum between demented and nondemented patients. Although MRI volumetric studies are presently of limited clinical utility for the individual diagnosis of dementia, they may help to increase our knowledge of the *in vivo* neuropathological bases of cognitive and emotional deficits associated with PD.

4.2. LONGITUDINAL EVALUATION OF CEREBRAL MORPHOLOGICAL CHANGES IN PARKINSON'S DISEASE WITH AND WITHOUT DEMENTIA

4.2.1. INTRODUCTION

In the last few years cognitive impairment of variable degrees has been increasingly recognized in patients with Parkinson's disease (PD) (Dubois and Pillon, 1997 for a review; Goldman et al., 1998). There have been several cross-sectional studies in which prevalence of dementia in PD was reported to range from 18-41% (Mayeux et al., 1992; Aarsland et al., 1996), although a recent longitudinal study in a community-based population has suggested a cumulative incidence of about 80% (Aarsland et al., 2003).

The pathological findings observed in post mortem studies of PD with dementia (PDD) are Lewy body-type degeneration in limbic and cerebral cortical areas and Alzheimer-type changes of variable degree. Studies using alpha-synuclein antibodies to identify Lewy pathology support the view that dementia is closely correlated with the presence and density of neocortical and limbic Lewy bodies and neurites (Hurtig et al., 2000; Mattila et al., 2000; Apaydin et al., 2002; Calopa et al., 2002). Other studies have also suggested that the coincident Alzheimer-type pathology is an important contributor to dementia in PD (de Vos et al., 1995; Burn, 2004).

Structural imaging studies using the technique of voxel-based morphometry (VBM) have shown differences in gray-matter volume between demented PD patients and controls in cortical and subcortical cerebral regions. Specifically, Burton and et al. (2004) reported reduced gray matter volume in PDD patients compared with controls in the temporal lobe bilaterally, including hippocampus and parahippocampal gyrus, in the occipital lobe, the frontal and parietal lobes, and some subcortical regions. In a previous voxel-based morphometry study performed by our group we found that PDD compared to NCs showed gray volume reductions affecting frontal (anterior cingulate), limbic (hippocampus and parahipocampal gyrus), and subcortical regions (thalamus, putamen, bilateral accumbens and hypothalamus). Non-demented PD patients had higher hippocampal volumes compared to PDD but they showed atrophic changes in hippocampus and anterior cingulate in comparison with NCs (Summerfield et al., 2005).

The technique of VBM has been shown to be useful in characterizing regional brain decreases across time in degenerative diseases such as Alzheimer's disease (Matsuda et al., 2002) and in patients with cognitive impairment without dementia (Karas et al., 2004). To our knowledge, there are no published studies on the progression of regional volume loss in PD using VBM. One longitudinal study, in which a technique for the quantification of absolute brain changes was used, showed that non-demented PD patients had significant reductions in whole brain volume compared with controls over a two-year follow-up period (Hu et al., 2001). The present study

aimed to determine the pattern of brain atrophy across time in PD patients with and without dementia using the VBM technique.

4.2.2 METHODS

Sample

Patients were recruited from an outpatient movement disorders clinic (Parkinson's disease and Movement Disorders Unit, Department of Neurology, Hospital Clinic, Barcelona). All of them fulfilled the UK Brain Bank criteria for PD (Daniel and Lees, 1993). The patients were part of a previously-studied initial sample of 29 patients: 13 PD and 16 PD with dementia (Summerfield et al., 2005). They were invited by telephone for a follow-up assessment. From the original PD sample without dementia, one subject declined to participate and another was demented at follow-up. Concerning the original PD sample with dementia, four subjects died, while in another four patients it was impossible to perform magnetic resonance imaging owing to severe motor impairment. Thus, eleven patients with PD and eight patients with PD with dementia were included in the follow-up evaluation. The average follow-up period was 25 months (SD=5.2), similar to that reported in the only previous longitudinal study in PD (Hu et al., 2001).Written informed consent was obtained for all subjects. The ethics committee of our hospital approved the study.

The follow-up assessment included a history provided by the patient and the caregiver, a neurological (Unified Parkinson's Disease Rating Scale (UPDRS) [Fahn and Elton, 1987]; Hoehn and Yahr Rating Scale [Jankovic et al., 1990]) and neuropsychological examination, and MRI. The diagnosis of dementia at follow-up was made by the neurologist based on an interview with the patient and a caregiver using the DSM IV-TR (American Psychiatric Association, 2003) as a guide, along with administration of the Mini-mental State Examination (MMSE) (Folstein et al., 1975). Subjects needed a MMSE score of 23 or lower and DSM-IV-TR items to fulfill dementia criteria. Presence of hallucinations was assessed by a structured interview developed in our hospital. The scale comprised items covering the type (visual, auditory, tactile and olfactory) and temporal aspects of the hallucinations (time of day, frequency and duration). A quantitative score for the VH was computed using the *"Hallucination"* item from the *Neuropsychiatric Inventory (NPI)* (Cummings et al., 1994). Depression was rated using the Hamilton scale (Hamilton, 1960).

Neuropsychological assessment

Subjects were tested individually in a well-lit, quiet room by a neuropsychologist experienced in testing neurologically impaired individuals. The neuropsychological assessment included test of memory, and of visuoconstructive and frontal lobe functions. The Rey Auditory Verbal Learning Test (RAVLT) assesses immediate memory span, new learning and delayed recall (Lezak et al., 2004). It consists of 15 words read aloud for five consecutive trials, each trial being followed by

a free recall test. After a 20-min. delay period, each subject is again required to recall the words in the list. The Digit Span forward and backward subtest of the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III, Wechsler, 2001) was used to assess attention and working memory. Here, subjects have to recall a series of digits in the same order and in reverse order. The WAIS Block Design subtest was used to examine visuospatial and visuoconstructive abilities. We used the reduced version (four blocks) without registering the execution time. Letter fluency was used to test prefrontal functioning (Lezak et al., 2004). Individuals were given 1 minute to generate words starting with F, A, and S, excluding proper nouns and numbers.

Data analysis

Statistical analysis was carried out using SPSS 11.0. For clinical and demographic variables, we used the Mann-Whitney U-test for independent samples. The neuropsychological measures at both sessions were analyzed using the non-parametric Wilcoxon test for related samples.

Magnetic Resonance Image acquisition and analysis

MRI acquisitions were performed using a 1.5 Tesla Signa Nvi/Cvi 8.4 General Electric (Milwaukee, USA). The imaging protocol included axial 3D IR Prep SPGR (Inversion Recovery Prepared Spoiled Gradient-echo) sequence of the entire brain and the following parameters: TR (Repetition time) = 17; TE (Echo time) = 5; TI (Inversion time) = 300; 1.5 mm thickness; FOV (Field of view) = 24x24; 256x256; 1 NEX (Number of excitations).

Images were analyzed with MATLAB 6.5 (MathWorks, Natick, MA) and SPM2 (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, London, UK). Original MR Images registered in DICOM format (one two-dimensional file per slice) were organized into three-dimensional files (volumes) by means of MRIcro software (University of Nottingham, UK) and saved in ANALYZE 7.5 format compatible with SPM2. Images were aligned along the anterior-posterior commissure (AC-PC) line. Application of the optimized voxel-based morphometry (VBM) procedure (Good et al., 2001), as well as details of our acquisition protocol and analyses are described elsewhere (Summerfield et al., 2005). Paired *t*-tests using SPM2 were undertaken to compare base-line vs. follow-up gray matter volumes within each group. VBM analysis was thresholded at voxel level p uncorrected < 0.001. Only the significant clusters of more than 20 contiguous voxels were considered in the analysis. We only interpreted clusters with a p corrected < 0.05.

4.2.3. RESULTS

Both groups were comparable in terms of age, sex and years of education. There were no differences in disease duration or stage of the illness, although the PDD group did show a higher score on Part III of the Unified Parkinson's Disease Rating Scale. Both PD groups differed in the

degree of mental impairment assessed by Mini-Mental State Examination in both evaluations: baseline and follow-up (see Table 4.2.1.).

	PD	PDD	Test statistics	*p*-value
Age (yr)	74.5 ± 4.6	70.3 ± 10.1	37.00[a]	0.559
Gender (men/women)	7/4	5/3	0.003[b]	0.960
Years of education	7.7 ± 4	7.6 ± 5.8	39.00[a]	0.671
Disease duration (yr)	12.4 ± 6.6	13.5 ± 5.7	38.00[a]	0.619
Hoehn and Yahr stage	3.2 ± 0.9	3.9 ± 1.0	27.00[a]	0.145
UPDRS III	21.1 ± 6.3	42.4 ± 18.6	20.00[a]	0.047*
Hamilton score	4.3 ± 5.4	3.1 ± 2.6	43.50[a]	0.968
MMSE baseline	28.6 ± 1	20 ± 2.4	0.001[a]	<0.0005*
MMSE follow-up	27.6 ± 1.4	15.5 ± 5.7	1.00[a]	<0.0005*

Table 4.2.1. *Demographic and clinical characteristics of the sample at the follow-up. Values are mean ± SD.* [a] *Indicates calculated using Mann-Whitney U-test;* [b] *Indicates calculated using the χ2 test. * denotes significant (p < 0.05) differences between PD and PD.*

Table 4.2.2. shows the clinical progression and the proportion of PD patients with hallucinations. We did not find any difference statistically significant regarding the progression of clinical severity evaluated by Hoehn and Yahr or by the UPDRS scale. None of the PD patients without dementia showed hallucinations, but this symptom occurred in all demented patients at baseline evaluation. Complex visual hallucinations (VH) were the most common type of hallucinatory phenomena. These were persistent in 6 of 8 cases. The severity of VH measured by the Neuropsychiatric Inventory (NPI) did not correlate with gray matter volume in temporal and occipital regions neither at baseline nor at the follow-up evaluation.

	Group	Time 1	Time 2	*z-value* Wilcoxon test (Time 1 vs.Time 2)	*p*-value
Hoehn and Yahr stage	**PD**	2.9 ± 0.8	3.2 ± 0.9	-1.32	0.187
	PDD	3.2 ± 0.9	3.9 ± 1.0	-1.76	0.078
UPDRS III	**PD**	22.3 ± 11.7	21.1 ± 6.3	-0.31	0.759
	PDD	32.0 ± 6.3	42.4 ± 18.6	-1.12	0.262
Presence of hallucinations	**PD**	-	-	-	-
	PDD	8/8	6/8	-	-

Table 4.2.2. *Clinical results at baseline (Time 1) and follow-up (Time 2) in PD samples. Values are mean ± SD.*

Results of the neuropsychological assessment are presented in Table 4.2.3. Across time the PD group showed a decreased performance on several tests, but only the scores in digit forward reached statistical significance. The raw scores of the group with dementia decreased on all tests, and the RAVLT learning score reached significance.

Task	Group	Time 1	Time 2	*z-value* Wilcoxon test (Time 1 vs.Time 2)	*p*-value
RAVLT Learning	**PD**	35 ± 6.1	30.6 ± 5.9	-1.94	0.052
	PDD	20.6 ± 6.1	13.9 ± 5.2	-2.37	0.018*
RAVLT Forgetting	**PD**	3.4 ± 1.9	2.1 ± 4.4	-1.24	0.215
	PDD	2.3 ± 2.7	1.7 ± 1.5	-0.43	0.670
Digit forward	**PD**	7.4 ± 2	6.2 ± 1.2	-2.01	0.045*
	PDD	5.6 ± 1.0	5.4 ± 1.4	-0.37	0.713
Digit backward	**PD**	3.9 ± 1.8	3.7 ± 1	-0.49	0.623
	PDD	2.3 ± 1.4	1.6 ± 1.3	-1.09	0.276
Block design	**PD**	16.7 ± 5.6	14.6 ± 5.5	-1.27	0.205
	PDD	5.1 ± 7.2	3.4 ± 4.8	-0.74	0.461
Letter fluency (FAS)	**PD**	8.5 ± 4	7.5 ± 3.6	-1.38	0.168
	PDD	4.3 ± 5	3.2 ± 2.5	-1.33	0.183

Table 4.2.3. *Cogntive results at baseline (Time 1) and follow-up (Time 2) in PD samples. Values are mean ± SD. RAVLT: Rey Auditory-VerbalLearning Test; RAVLT Learning: Sum of words correctly recalled of Trial 1 to 5; RAVLT Forgetting: Number of lost words after the 20-minute delay; FAS: Sum of all admissible words for the three letters divided by three.* denotes significant score decreased in the follow-up*

VBM results are described in Table 4.2.4. and illustrated in Figs. 4.2.1. and 4.2.2. When compared with baseline, the group without dementia showed significant clusters of reduced gray matter volume in the right anterior and posterior cingulate gyrus, bilateral temporo-occipital region, bilateral insula, right hypothalamus and nucleus accumbens, and left hippocampus. The PDD group showed a decrement in gray matter volume in the right fusiform gyrus, right parahippocampal gyrus and hippocampus, right temporo-occipital region, and right medial anterior temporal gyrus

Cerebral region	*Cluster*		*Voxel*			
	Number of voxels	***p corrected***	**Z value**	**Talairach's coordinates**		
				x	**y**	**z**
Decreases in gray matter volume in PD group in the follow-up						
Right anterior cingulate gyrus	8482	<.0005	4.72	1	31	19
Right temporo occipital region	6179	<.0005	4.41	44	-65	0
Left insula	3241	<.0005	4.29	-32	2	9
Right insula	1612	0.002	4.18	37	-6	0
Right posterior cingulate gyrus	1614	0.002	4.11	11	-49	30
Left temporo occipital region	982	0.021	1.01	-37	-62	12
Right hypothalamus / Nucleus accumbens	1314	0.006	3.98	1	-9	-5
Left hippocampus	921	0.026	3.44	-22	-19	-11
Decreases in gray matter volume in PD group in the follow-up						
Right fusiform gyrus / Right Hippocampus and parahippocampal gyrus	4773	<.0005	4.58	26	-56	-8
Right temporo occipital region	1059	0.018	4.04	40	-56	6
Right medial anterior temporal gyrus	781	0.050	3.93	42	-18	-6

Table 4.2.4. *Results from the analysis of decreases in gray matter volume in PD groups * Each reported anatomical location exceed a voxelwise statistical threshold of p<0.001 uncorrected level. The cerebral regions are referred to the location of the cluster. The Tailarach coordinate refers to the location of the most statistically significant voxel in the cluster*

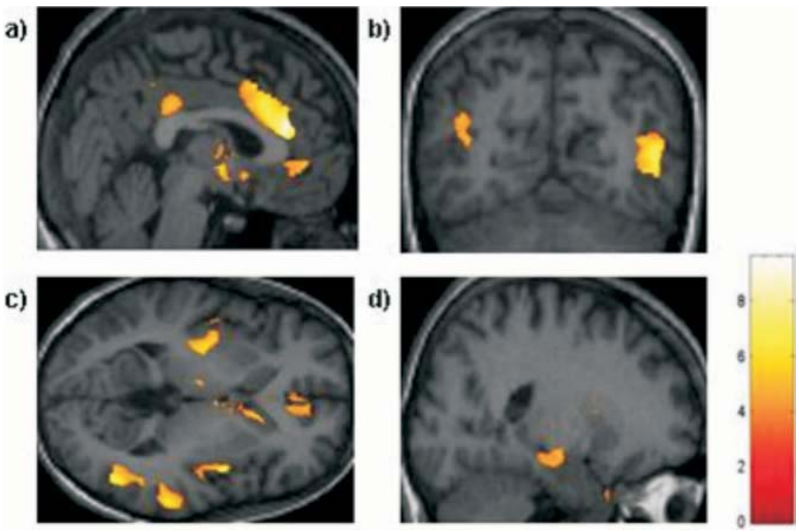

Figure 4.2.1. *Results of the comparison between initial and follow-up MRI in non-demented PD patients. Voxels reaching significance at the uncorrected p < 0.001 level are rendered on T1 image. Clusters of gray matter loss are seen in a) right anterior and posterior cingulate gyrus, right hypothalamus and nucleus accumbens (b) bilateral temporo occipital region (c) bilateral insula, right anterior cingulate, and right temporal region (d) left hippocampus.*

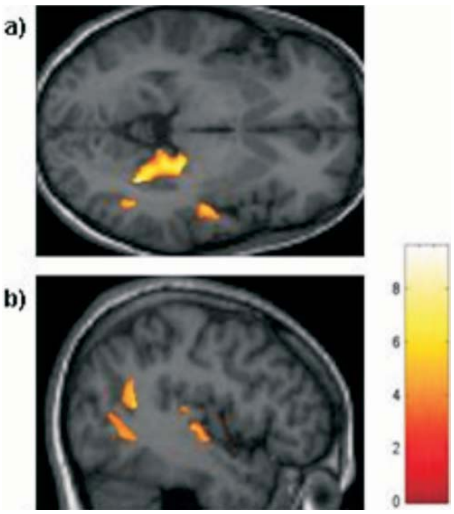

Figure 4.2.2. *Gray volume loss in demented PD patients.Voxels reaching significance at the uncorrected p < 0.001 level are rendered on T1 image. Clusters of volume difference are observed in (a) right fusiform gyrus, hippocampus and parahippocampal areas and (b) right temporo occipital region and right medial anterior temporal gyrus.*

To investigate the relationship between cognitive decline and brain volume loss, we performed an analysis of covariance (ANCOVA) using the neuropsychological scores that achieved statistical significance or a trend towards it in the base-line vs. follow-up conditions. Specifically, for the PDD patients we included the RAVLT learning scores and for the PD patients the RAVLT learning and digit forward scores. When entered into the analyses the above mentioned covariates, the gray matter differences between pre and post MRI acquisitions lost significance. This suggested that cognitive decline is related to gray matter volume loss.

4.2.4 DISCUSSION

The present research provides the first *in vivo* documentation using VBM of progressive gray matter loss in PD with disease progression. Patients with and without dementia showed volume reductions in neocortical and limbic structures. In PD patients without dementia the brain loss broadly involved the paralimbic regions (anterior and posterior cingulate and insular cortex) along with other limbic structure such as the hippocampus. Gray matter loss in the associative temporo-occipital neocortex also occurred. In demented patients limbic volume loss was only observed in the hippocampus and the neocortical decrement tissue involved regions in temporal and occipital lobes.

In the non-demented PD group we observed a clear paralimbic and limbic involvement. This is consistent with post-mortem data showing neuronal loss and Lewy body pathology in insular cortex and cingulate gyrus in PD (Braak et al., 2003). Moreover, hypoperfusion of insular region in a group of non-demented advanced PD has been reported previously (Kikuchi et al., 2001). We also observed a progressive volume loss of hippocampus. Using manual volumetric analysis comparing PD patients with and without dementia, Camicioli et al. (2003) found a pattern in

hippocampal reduction. Non-demented patients showed hippocampal volume value between those of demented patients and controls suggesting progressive hippocampal loss in PD.

Old age, advanced stage of the disease, and impairment in verbal memory have been identified as risk factors to the development of dementia (Levy et al., 2002a; Levy et al., 2002b). Our PD sample is old, shows an advanced H & Y stage, a trend to memory decline, and a significant hippocampal reduction, but they have not developed dementia in two years of follow-up. Longer longitudinal studies would be necessary to identify possible evolution to dementia. In this way, Aarsland and et al. (2003) found that more than three quarters of their PD cohort developed dementia in an 8-year study period.

In our demented PD sample the volume loss involved several neocortical areas. This is consistent with single-photon-emission CT studies in which marked perfusion deficits were described in posterior associative regions (Kawabata et al., 1991; Tachibana et al., 1993) and with neuropathological studies which suggest a relationship between the presence of dementia and cortical pathology (LB-type degeneration [Apaydin et al., 2000; Hurtig et al., 2000; Mattila et al., 2000; Calopa et al., 2002; Burn, 2004]; or and Alzheimer-Type pathology [De Vos et al., 1995; Burn, 2004]). Our results with VBM neuroimaging support the concept that the neocortex is a substrate for dementia in PD, in addition to limbic (Braak and Braak, 2000) and subcortical structures (Perry et al., 1985; de la Monte et al., 1989; Zweig et al., 1993).

The cortical volume loss in the sample of patients with dementia included a marked decrease volume in the fusiform gyrus with disease progression. The volume reduction of this cerebral region could be related to high densities of Lewy bodies in temporal inferior regions (Harding et al., 2002a). The progressive tissue loss that we found might influence in the persistence and progressive nature of hallucinations in PD (Goetz et al., 2001b; Factor et al., 2003). However, we found no correlation between gray matter volume in temporo-occipital areas including fusiform gyrus and presence of visual hallucinations either in baseline or in the follow-up evaluation. So, although volume reduction of this cerebral region might be partially related to visual hallucinations, additional factors as neurochemical deficits reported in these patients seems to be necessary for the presence of this symptom (see Diederich et al., 2005 for a review).

Surprisingly, the progressive volume loss in PD patients without dementia was widespread and marked. These results could reflect the different regional involvement with disease progression in agreement with the neuropathological staging reported by Braak et al. (2003). These authors described the topographic extent of PD-related brain lesion (Lewy neurites/bodies) in progressive stages. According to this study, limbic and paralimbic degeneration (Stage 4) precede neocortical degeneration (Stage 5 and 6). The demented patients are probably in a more advanced neuropathological stage in which degeneration of the limbic and paralimbic regions may be less

active. This interpretation could explain why patients without dementia showed a widespread gray matter loss. In fact neuropathological (Fearnley and Lees, 1991) and neuroradiological (Staffen et al., 2000; Kaasinen et al., 2003; Nurmi et al., 2003) studies suggest that a slower progression occurs at more advanced stages of the disease.

The small sample size and the high number of decreased brain areas are points against carrying out a classical correlation analysis. However, when considering the cognitive scores of PD samples as covariates, the gray matter differences between pre and post MRI acquisitions lost significance. This suggests a relationship between cognitive status and gray matter loss across time.

One limitation of the study is the small sample tested in the follow-up. However, our sample is comparable in term of size to that reported by Hu et al. (2001) and we studied well matched groups in terms of disease duration. Additionally, in the present report we used a quantitative and automatic approach which contributes a novel and complementary analysis not performed until now.

A methodological consideration to bear in mind is that we considered the statistic maps threshold at $p < 0.001$ uncorrected for multiple comparisons. A comparison without a priori hypothesis of the brain regions that may have been affected by the progression of the disease in both groups should have been addressed using a p corrected value for multiple comparisons (for instance at $p < 0.05$). However, owing to the preliminary nature of this investigation since no previous data using VBM in longitudinal studies are available, as well as the small size of our samples we decided to use a less stringent cut-off.

Another limitation is the absence of a control group. Previous evidence from MRI studies showed an age-related loss of brain tissue. Using VBM, Good et al. (2001) found that normal ageing is associated with a linear decline in gray matter with an accelerated loss in parietal and frontal areas and with a relative preservation of medial temporal lobe structures. Prominent tissue loss in frontal and parietal areas as compared to temporal and occipital areas have also been found in a longitudinal study performed using semi-automated techniques for a quantitative analysis of MR volumes of normal cognitively older adults (Resnick et al., 2003). In this way the temporal and occipital loss found in PD samples could be more related to the neurodegenerative process than to the age effect given that these structures are relative spared with ageing. However, in a recent study using VBM, Tisserand et al. (2004) reported decreases in gray matter density in various frontal regions but also in the temporal lobes in elderly subjects without cognitive decline. Brain volume changes in our PD groups could partially be explained by the age effect but the time between the first and the second assessment was the same for both groups examined, therefore the pattern of cerebral changes due to ageing should be similar.

In summary, this is the first study using VBM which found that both demented and non-demented PD patients show progressive gray matter loss in several cerebral regions. The neocortical gray matter decrease in demented patients suggests that cortical involvement play an important role in dementia in Parkinson disease. In the future, it will be essential to perform prospective longitudinal studies involving longer follow-up with a larger number of subjects and including healthy elderly people.

4.3 REGIONAL CEREBRAL ATROPHY IN PARKINSON'S DISEASE PATIENTS WITH VISUAL HALLUCINATIONS

4.3.1. INTRODUCTION

Visual hallucinations (VH) occur in approximately fifty per cent of patients with Parkinson's disease (PD) (William and Lees, 2005). The feature most consistently associated with this symptom is the presence of cognitive impairment or dementia although other risk factors have been identified including depression, disease severity, long disease duration, old age, sleep alterations and antiparkinsonian treatment. The dopaminergic and cholinergic systems (and possibly the serotoninergic system) may play a role in their development, but the exact pathophysiology of hallucinations in PD is unknown (Papapetropoulos and Mash, 2005).

Few studies have investigated the neural substrate of VH. In a post-mortem study of patients with PD, dementia with Lewy bodies and a history of VH, Harding et al. (2002a) reported an association between VH and the presence of Lewy bodies in medial and inferior temporal areas including amygdala, parahippocampus and inferior temporal cortices.

Functional neuroimaging studies showed abnormalities in the cerebral activity of several associative areas. Using [^{18}F] fluorodeoxyglucose positron emission tomography, Nagano-Saito et al. (2004) found that PD patients with VH showed a hypermetabolism in the superior frontal gyrus. The results of a SPECT study concluded that VH in PD are associated with hypoperfusion of the right fusiform gyrus and hyperperfusion in the right superior and middle temporal gyri (Oishi et al., 2005). Using the fMRI technique during a visual stroboscopic and kinematic paradigm, Stebbins et al. 2004 also found that hallucinating PD patients had increased activation in the superior and inferior frontal gyrus. Moreover, PD patients with VH showed decreased activation in regions of the posterior cortex (occipital, temporal, parietal).

To the best of our knowledge no studies of structural gray matter abnormalities in non-demented PD patients with VH have been conducted. The aim of our study was, therefore, to investigate the pattern of cerebral atrophy in Parkinson's disease patients with VH using whole-brain voxel based morphometry. Given that neuropathological and functional data showed abnormalities in brain areas involved in the processing of visual stimuli, we predicted that PD patients with VH will show structural changes affecting these cerebral regions.

4.3.2. METHODS

Sample

Thirty-eight people suffering from idiopathic PD and 21 controls gave their informed consent to take part in the study. Participants were recruited from an outpatient movement disorders

clinic (PD and Movement Disorders Unit, Department of Neurology, Hospital Clinic, Barcelona). The local ethics committee approved the study. All patients were diagnosed by an expert neurologist as having idiopathic PD according to UK Brain Bank criteria (Daniel and Lees, 1993). Exclusion criteria for all subjects were clinical depression and dementia. For the diagnosis of dementia we used the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Revised Fourth Edition (DSM-IV-TR) and the Mini-Mental State Examination score (normal score ≥24) (Folstein et al., 1975). Patients with VH were included in the study whether they had experienced VH in the previous year. The group of patients with VH comprised 18 patients. To avoid including patients with dementia with Lewy bodies we excluded subjects with symptoms such as transient loss of consciousness, neuroleptic sensitivity or VH within 5 years after the initial motor symptoms (McKeith et al., 2005).This sample was compared with 20 patients with idiopathic PD but without any history of VH. The healthy control group comprised 21 spouses of PD patients who were matched to patients by age and education and who had no history of psychiatric or neurological disorders.

The severity of parkinsonian symptoms was assessed by subscale III of the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn et al., 1987). The stage of the disease was estimated using the modified Hoehn and Yahr scale (Jankovic et al., 1990). Depression was evaluated by means of the Hamilton scale (Hamilton, 1960). The Folstein Mini-Mental State Examination (MMSE) was used as a general cognitive screening test. Clinical and demographic variables in the three groups were analyzed by an analysis of variance (ANOVA test) and post-hoc Bonferroni comparisons with exception of gender analysis, in which a Chi-Square test was used. Clinical variables in both Parkinson's groups were analyzed by non-parametric Mann-Whitney test.

Though we tried to match PD patients with and without VH in all relevant clinical variables, the assessment showed that PD patients with VH had a higher Hamilton score and a more advanced stage of the illness (graded by H & Y scale) compared to non-VH patients. Moreover, although hallucinating PD patients had MMSE scores > 24 and no patient fulfilled the DSM-IV-TR for dementia, general cognitive status was lower in PD patients with VH than in normal controls and non hallucinating PD patients (See Table 4.3.1.).

The first VH were experienced by our PD patients within 11.2 ± 4.7 years of the initial motor symptoms. A Spanish version of the Neuropsychiatric Inventory (NPI) (subscale hallucinations) was used to quantify the severity of hallucinations (Cummings et al., 1994). The mean scores (± SD) for the total NPI was 6.61 ± 2.3 (range 2 to 12). The hallucinations in our sample occurred in normal state of consciousness without delirium. All patients had complex VH which were fully formed images of people, faces or animals. The VH disappeared after levodopa reduction in eight cases (44.4%), while three patients (16.7%)

needed antipsychotic medication and four (22.2%) required both interventions. Medication did not need to be modified in the remaining patients because the hallucinations were well tolerated. At the time of scanning 6 cases (33.3%) had active hallucinations.

	PD+VH n = 18	PD without VH n = 21	Controls n =20	Test statistic	*p*-value
Age (years)	74.5 ± 5.6	72.8 ± 5.8	72.7 ± 6.5	0.523 [a]	NS
Gender (men/women)	7:11	8:12	9:12	0.069[b]	NS
Education (years)	7.6 ± 3.7	7.5 ± 3.4	7.9 ± 4.6	0.047[a]	NS
Hamilton score	6.7 ± 4.7	3.6 ± 2.8	2.9 ± 3.1	5.94[a]	0.005*†
MMSE	27.0 ± 2.1	29.1 ± 1.4	29.4 ± 2.3	8.256[a]	0.001*†
Disease duration (years)	12.6 ± 5.6	10.6 ± 4.3	-	140.0[c]	NS
UPDRS III 'on' state	29.3 ± 11.7	24.5 ± 14.0	-	135.5[c]	NS
Hoehn and Yahr stage	3.2 ± 1.0	2.5 ± 0.7	-	103.5[c]	0.021*
Levodopa daily dose (mg)	723.6 ± 249.5	647.5 ± 387.2	-	117.5[c]	NS

Table 4.3.1. *Demographic and clinical, variables. Values are mean ± SD; [a] Indicates calculated using analysis of variance (ANOVA) test; [b]Indicates calculated using the Pearson χ2 test; [c]Indicates calculated using U Mann-Whitney test; * Significant differences between PD+VH patients and PD patients without VH; †Significant differences between PD+VH patients and controls.*

Magnetic Resonance Image acquisition and analyses

MRI was obtained in all subjects using a 1.5 Tesla GE Signa scanner (General Electric, Milwaukee, WI, USA). Whole brain T1-weighted 3D SPGR date sets were acquired in the axial plane, and according to the following parameters [TR (repetition time) = 12 ms, TE (echo time) = Min, TI (inversion recovery time, prep time) =300ms, 256x192 matrix, 1.5 mm slice thickness, flip angle = 20 º, FOV (field of view) = 24 cm.

Analysis was performed using MATLAB 6.5 (MathWorks, Natick, MA) and SPM2 (Statistical Parametric Mapping, Welcome Department of Imaging Neuroscience, London, UK). An optimized voxel-based morphometry analysis was performed according to previously described methods (Good et al., 2001). Briefly, the processing steps outlined by this protocol are (1) the creation of a customized anatomical T1-weighted template as well as a customized gray matter template from all participants. (2) Segmentation of the original structural MRI images into gray matter, white matter and cerebrospinal fluid images in native space. (3) Normalization of the segmented gray matter images extracted to our gray matter template, and reapplication of the optimized normalization parameters to the original whole-brain structural images (in native space) (4) Segmentation of the normalized whole-brain images into gray matter, white matter and cerebrospinal partition (5) Modulation of the gray matter images applying the Jacobian determinants derived from the spatial normalization step

which makes it possible to compensate for the possible volume changes due to the spatial normalization procedure. (6) Smoothing of modulated images using a 12-mm full width at half maximun (FWHM) Gaussian Kernel.

Gray matter volume changes were assessed by analysis of the modulated data. We performed the following analysis:

1. ANCOVA analysis including total intracranial volume (TIV) as a covariate to remove any variances due to differences in head size. An estimation of TIV was calculated from the addition of global gray, white, and cerebrospinal fluid volume obtained after the automatic brain segmentation carried out by SPM. The objective of this analysis was to explore the pattern of gray matter reductions in hallucinating PD patients without excluding the influence of clinical variables that usually coexist with the presence of VH.

2. ANCOVA model that incorporated TIV, MMSE, Hamilton, and Hoehn and Yahr scores as confounding variables in order to study the structural brain changes associated with the presence of VH in PD patients independently of the influence of these variables. We first performed an exploratory analysis using a threshold of $p < 0.001$ uncorrected for multiple comparisons. Secondly, in order to search for gray matter abnormalities in posterior visual associative areas (parieto-occipital) that were previously found to be functionally abnormal in PD patients with VH, we used a small volume correction (SVC). This specific SVC gives the optimal correction for multiple comparisons available in this VBM study. This optimized SVC was centered on the Tailarach coordinate of the most statistically significant voxel in the cluster and defined by spheres of 10.0-mm radius.

4.3.3. RESULTS

ANCOVA analysis including only TIV as covariate

PD patients with VH vs. Controls

Relative to controls, patients with VH showed several areas of gray matter volume loss (See Table 4.3.2. and Figure 4.3.1.). The clusters of major volume of gray matter loss were localized on the right medial frontal gyrus [Brodmann area (BA) 8], left anterior superior temporal gyrus (BA 38), left insula, and the superior parietal lobe (BA 7) bilaterally. Although less marked, gray matter volume decreases were also observed on the middle frontal gyrus bilaterally (BA 6, 9, 10, 46) and on the right superior and inferior frontal gyrus bilaterally (BA 6, 44). Temporo-occipital associative visual areas were also involved [left fusiform gyrus, right lingual gyrus (BA 18), and left superior occipital gyrus (BA 19)]. Subcortical areas showing significant volume reductions included the caudate nuclei bilaterally.

Cerebral region	*Cluster*		*Voxel**			
	Number of voxels	***p corrected***	***t* value**	**Talairach's coordinates**		
				x	**y**	**z**
Right medial frontal gyrus (BA 8)	9261	<0.0001	5.17	1	38	37
Left anterior superior temporal gyrus (BA 38)/ insula	7927	<0.0001	5.67	-46	19	-14
Right superior parietal lobe (BA 7)	7317	<0.0001	5.33	21	-72	37
Left superior parietal lobe (BA 7)	2507	<0.0001	4.90	-26	-69	48
Right middle frontal gyrus (BA 10)	719	<0.0001	3.85	35	56	18
Right middle frontal gyrus (BA 9/46)	656	<0.0001	4.29	39	24	23
Left fusiform gyrus (BA 18)	630	<0.0001	3.83	-26	-88	11
Right middle frontal gyrus (BA 6)	629	<0.0001	3.79	44	5	51
Left middle frontal gyrus (BA 9)	554	0.001	3.72	-26	40	28
Right lingual gyrus (BA 18)	554	0.001	3.96	2	-75	10
Left inferior frontal gyrus (BA 44)	518	0.002	4.21	-54	14	24
Left caudate	494	0.003	3.52	-8	9	9
Left superior occipital gyrus (BA 19)	480	0.004	3.57	-30	-73	29
Left inferior parietal lobe (BA 40)	462	0.005	3.75	-53	-39	44
Right inferior frontal gyrus (BA 44)	419	0.01	4.14	54	16	23
Right caudate	382	0.018	3.64	9	11	6
Right superior frontal gyrus (BA 6)	378	0.019	3.62	20	8	62
Left middle frontal gyrus (BA 9)	554	0.001	3.72	-26	40	28

Table 4. 3. 2. *Clusters of gray matter volume decrease on PD+VH patients compared with controls*
*Total intracranial volume was introduced in the analysis like covariable; BA: Brodmann area; Results are listed by cluster size; x y z are the coordinates in Talairach space. These coordinates represent the location of the voxelwith the highest significance; *Each reported anatomical location exceeds a voxelwise statistical threshold of p <0.001 uncorrected level.*

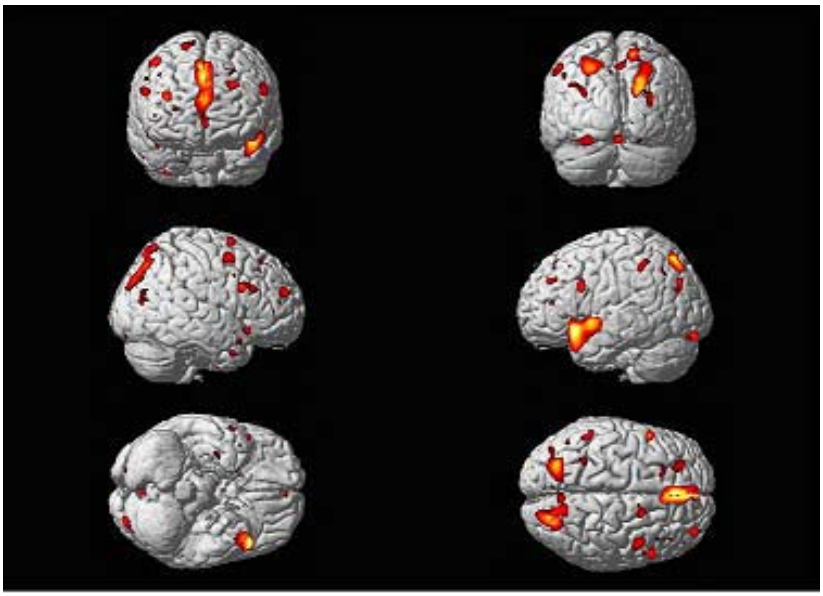

Figure 4.3.1. *Gray matter volume loss in PD+ VH relative to healthy controls projected onto a standard 3D SPM brain (p uncorrected < 0.001)*

PD patients with VH vs. PD patients without VH

Comparison of the two PD groups demonstrated that Parkinson's disease patients with VH showed gray matter reductions in the left anterior superior temporal gyrus (BA 38), left insula and in the left superior and inferior parietal lobe (BA 7, 40). Several frontal areas also showed significant reductions [left medial and middle frontal gyrus (BA 10/32), and inferior frontal gyrus bilaterally (BA 9, 44)]. Less marked changes according to the cluster size were observed in the right superior temporal gyrus (BA34) and in the uncus (BA 28) (See Table 4.3.3. and Figure 4.3.2.).

Region	*Cluster*		*Voxel**			
	Number of voxels	***p corrected***	***t* value**	**Talairach's coordinates**		
				x	**y**	**z**
Left anterior superior temporal gyrus (BA 38)/ insula	2024	<0.0001	4.29	-41	12	-7
Left superior parietal lobe (BA 7)	915	<0.0001	4.29	-29	-67	52
Left medial frontal gyrus (BA 10/32)	871	<0.0001	3.53	-3	41	-10
Right inferior frontal gyrus (BA 9)	866	<0.0001	4.50	52	15	23
Left inferior parietal lobe (BA 40)	618	0.001	3.72	-58	-40	44
Left middle frontal gyrus (BA 10)	490	0.003	4.01	-45	51	-6
Right inferior frontal gyrus (BA 44)	452	0.006	3.63	47	13	5
Right superior temporal gyrus (BA 34) / Uncus (BA 28)	422	0.010	3.81	19	7	-31
Left inferior frontal gyrus (BA 9)	351	0.029	3.91	-52	12	20

Table 4.3.3. *Clusters of gray matter volume decrease on PD+VH patients compared with PD patients without VH. Notes as for table 4.3.2.*

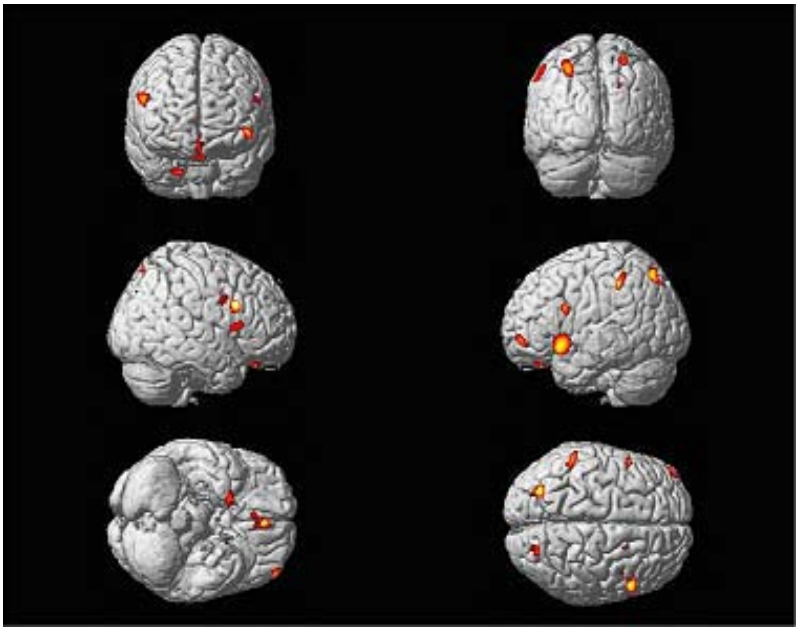

Figure 4.3.2. *Gray matter volume loss in PD+VH relative to PD patients without VH projected onto a standard 3D SPM brain. (p uncorrected < 0.001).*

PD patients without VH vs. Controls

Compared with controls, non-hallucinating PD patients had gray matter volume reduction affecting the right superior frontal gyrus (BA 6) and the left anterior superior temporal gyrus (BA 38) (See Table 4.3.4.).

Cerebral region	*Cluster*		*Voxel**			
	Number of voxels	***p corrected***	***t* value**	**Talairach's coordinates**		
				x	**y**	**z**
Right superior frontal gyrus (BA 6)	751	<0.0005	4.34	7	5	68
Left anterior superior temporal gyrus (BA 38)	360	0.016	3.91	-47	20	-18

Table 4.3.4. *Clusters of gray matter volume decrease on PD patients without VH patients compared with controls Notes as for table 4.3.2.*

High PD+VH patients vs. low PD+VH patients

To further establish a relationship between hallucinations and regional grey matter volume decrease, we divided the PD+VH sample into two groups according to the score on *Hallucinations* subscale of the NPI inventory. Patients with a score from 1 to 6 were classified as low PD+VH (N=8) while those scoring 7 to 12 were classified as high PD+VH (N=10). There were no differences for any demographical or clinical variables between these two samples with VH. Compared with the low PD+VH group, the high PD+VH subjects showed greater grey matter volume reduction bilaterally in the medial frontal gyrus (BA 6/8) and the temporal pole (BA 38) (See Table 4.3.5.).

Cerebral region	*Cluster*		*Voxel**			
	Number of voxels	***p corrected***	***t* value**	**Talairach's coordinates**		
				x	**y**	**z**
Left anterior temporal pole (BA 38)	2416	<0.0001	7.21	-32	16	-39
Right medial frontal gyrus (BA 6/8)	554	<0.0001	6.30	31	18	29
Right anterior temporal pole (BA 38)	689	<0.0001	5.98	34	20	-35
Right medial frontal gyrus (BA 6/8)	323	0.018	4.98	-32	20	29

Table 4.3.5. *Clusters of gray matter volume decrease on PD patients without VH patients compared with controls Notes as for table 4.3.2.*

ANCOVA analysis including TIV, MMSE, H&Y and Hamilton scores as covariates

PD patients with VH vs Controls

By comparing the control group to patients with VH, the exploratory analysis ($p < 0.001$, uncorrected for multiple comparisons) revealed several areas of gray matter volume reduction (Table 4.3.6. and Figure 4.3.3.). The clusters of major gray matter volume loss were located on the superior parietal lobe [Brodmann area (BA)] (BA 7) bilaterally, right medial frontal

gyrus (BA 8), right lingual gyrus (BA 18) and left inferior parietal lobe (BA 39). Occipital associative visual areas were also involved [left inferior and right middle occipital gyrus (BA 18)]. Although less marked, a gray matter volume decrease was also observed in the middle frontal gyrus (BA 6, 10). By performing the SVC we have observed a significant grey matter volume decrease ($p < 0.05$ corrected for multiple comparisons) located in the same parieto-occipital regions.

Anatomical region	**Number of voxels**	***T* value**	**Coordinate**		
			x	***y***	***z***
*Results for the whole brain **					
Bilateral superior parietal lobe (BA 7)	14487	5.71	-26	-69	48
		5.13	27	-69	55
Right medial frontal gyrus (BA 8)	9038	5.04	4	41	37
Right lingual gyrus (BA 18)	2691	4.94	1	-76	-11
Left inferior parietal lobe (BA 39)	1850	5.02	-43	-77	33
Left inferior occipital gyrus (BA 18)	1505	4.29	-28	-91	-11
Right middle occipital gyrus (BA 18)	1168	4.38	29	-70	15
Right middle frontal gyrus (BA 6)	642	4.19	44	6	51
Right middle frontal gyrus (BA 10)	438	3.81	33	41	23
Right superior occipital gyrus (BA 18)	324	3.89	21	-90	-10
*Small volume correction***					
Left superior parietal lobe (BA 7)	2427	5.71	-26	-69	48
Right superior parietal lobe (BA 7)	3076	5.13	27	-69	55
Right lingual gyrus (BA 18)	2136	4.94	1	-76	-11
Right middle occipital gyrus (BA 18)	1137	4.38	29	-70	15
Left inferior occipital gyrus (BA 18)	1261	4.29	-28	-91	-11

Table 4.3.6. *Clusters of gray matter volume reduction on PD+VH patients compared with controls*
BA = Brodmann Area. x y z are the coordinates in Tailarach space. The Tailarach coordinates refer to the location of the most statically significant voxel in the cluster.
** $p < 0.001$ uncorrected for multiple comparisons.*
*** $p < 0.05$ corrected for multiple comparisons.*

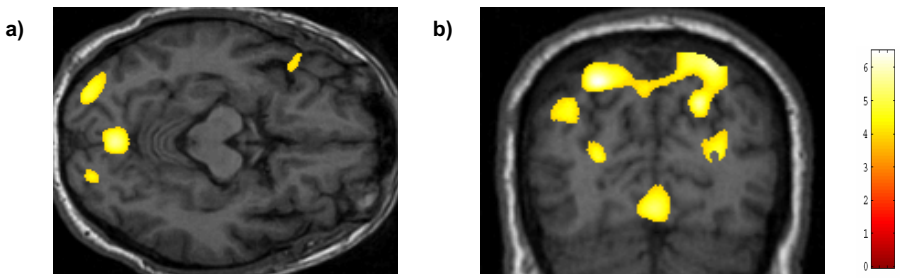

Figure 4.3.3. *Gray matter volume reductions in PD+VH patients compared to controls subjects. Voxels reaching significance at the uncorrected p < 0.001 level are rendered on a normal T1-weighted image. The greatest cluster of grey matter volume differences are observed in (a) left inferior occipital gyrus (BA 18), right lingual gyrus, (BA 18) and right superior occipital gyrus (BA 18) (b) superior parietal lobe bilaterally (BA7), left inferior parietal lobe (BA 39), right middle occipital gyrus (BA 18) and right lingual gyrus (BA 18).*

PD patients with VH vs PD patients without VH

On direct statistical comparison between the two PD groups ($p < 0.001$, uncorrected for multiple comparisons), Parkinson's disease patients with VH showed significantly more atrophy in the left lingual gyrus (BA 18) and bilaterally in the superior parietal lobe (BA 7) (Table 4.3.7. and Figure 4.3.4.). Using the SVC ($p < 0.05$ corrected for multiple comparisons), volume differences were found in the same areas.

Anatomical region	Number of voxels	*T* value	Coordinate		
			x	*y*	*z*
*Results for the whole brain **					
Left lingual gyrus (BA 18)	5921	5.00	-1	-70	-12
Right superior parietal lobe (BA 7)	1972	4.41	25	-70	57
Left superior parietal lobe (BA 7)	1889	5.04	-26	-73	49
*Small volume correction***					
Left lingual gyrus (BA 18)	2259	5.00	-1	-70	-12
Left superior parietal lobe (BA 7)	1624	5.04	-26	-73	49
Right superior parietal lobe (BA 7)	1374	4.41	25	-70	57

Table 4.3.7. *Clusters of gray matter volume reduction on PD+VH compared with PD patients without VH. Notes as for table 4.3.6*

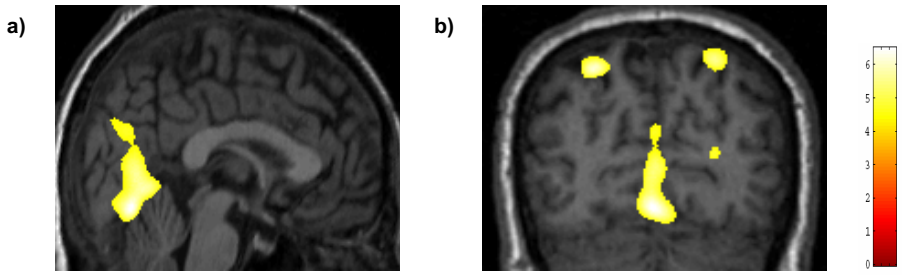

Figure 4.3.4. *Gray matter volume reductions in PD+VH patients compared to PD patients without VH. Voxels reaching significance at the uncorrected p < 0.001 level are rendered on a control healthy subject T1-weighted image. The greatest cluster of gray matter volume differences are observed in a) left lingual gyrus (BA 18), (b) superior parietal lobe bilaterally (BA7) and left lingual gyrus (BA 18)*

4.3.4. DISCUSSION

This study aimed to identify structural brain changes in PD patients with VH using the technique of VBM. When we compared hallucinating PD patients with healthy controls the cortical regions most affected were medial frontal gyrus, anterior superior temporal gyrus /insula and parietal lobe. In the comparison between hallucinating PD patients and those without VH, the region with the most significant volume reduction in hallucinating patients was a cluster including the anterior superior temporal gyrus and insula. The ANCOVA analysis, which includes mood score, severity of the illness and global cognitive performance as confounding variables, revealed that, in comparison to both healthy controls and the non-

hallucinating PD group, PD patients with VH had gray matter volume decrease involving mainly the lingual gyrus and superior parietal lobe.

In the analysis performed including only TIV as covariate, the most consistent finding distinguishing PD patients with hallucinations from PD patients without VH and from healthy controls was a reduction in volume of the anterior temporal superior gyrus (BA 38). Moreover, within the PD+VH group, the severity of hallucinations was associated with a higher grey matter reduction in the temporal pole. The anterior temporal lobe has been implicated in semantic processing (McClelland and Rogers, 2003) and MRI structural studies have shown a significant atrophy focused in this area in patients with semantic dementia (Mummery et al., 2000). Furthermore, several structural studies using VBM in PD patients have shown a clear volume reduction of this cerebral area in both demented and non demented samples (Burton et al., 2004; Summerfield et al., 2005; Nagano-Saito et al., 2005). Visual hallucinations have not been reported in patients with semantic dementia (Garrard and Hodges, 2000) and it is unlikely that a focal reduction in this area alone would be sufficient to cause them. Nevertheless, an atrophy of the region which has been implicated in higher level integration of semantic information could exacerbate pre-existing reported deficits in other cognitive domains such as a visuoperception and visual memory (Barnes et al., 2001, 2003).

The ANCOVA analysis eliminating potential confusion variables provided the first in vivo evidence of gray matter volume reduction in hallucinating PD patients affecting visual associative areas such as lingual gyrus (BA 18) and superior parietal lobe (BA7). In human studies, lingual gyrus has been implicated in the visual processing at different levels of complexity. Electrical cortical stimulation and lesional studies in humans show that this area has an important role in color perception, visual discrimination and visual attention (Lee et al., 2000; Gallant et al., 2000). In addition, fMRI studies showed that the lingual gyrus increases its activity during face and picture recognition, (Stern et al., 1996; Clark et al., 1998; Gorno-Tempini et al., 1998, Wiser et al., 2000) and also when subjects encode complex visual scenes (Rombouts et al., 1999). In animal studies, not exact homology was found between high order visual areas in monkeys and humans (Tootell et al., 2003; Orban et al., 2004). However, some authors claimed that there is a correspondence between lingual gyrus and fusiform gyrus and macaque area TEO (posterior inferior temporal cortex) (Kanwisher et al., 1997). This area maintains reciprocal connections with other visual areas such as V2, V3 and V4 (Gattass et al., 2005) and it has been implicated in the processing of color, faces and movement (Dubowitz et al., 2001). The dysfunction of lingual gyrus could lead to visuoperceptive impairment which has been pointed as important causal factor for the presence of VH (Barnes et al., 2003; Collerton et al., 2005).

In addition to atrophic changes of the lingual gyrus the hallucinating PD group was characterized by a consistent volume loss involving the superior parietal lobe. These area, corresponding to BA 7, receives visual input from PO (parieto-occipital areas), which receives inputs from V1, V2 and V3 (Rizzolatti and Matelli, 2003). Functional MRI studies have implicated the superior parietal lobe in visuo-spatial working memory (Newman et al., 2003), mental imagery (Lambert et al., 2004; Mechelli et al., 2004) and in conjunction with frontal lobe, with spatial and non spatial visual attention tasks (Kastner et al., 1999; Coull and Frith, 1998). Attentional deficits have been identified as an important factor in the causal models of VH (Collerton et al., 2005). Additionally, abnormalities in the brain pattern of attentional visual response have been reported in hallucinating PD patients, with greater frontal and subcortical activation and lower parietal and temporo-occipital cortical activation than non-VH PD subjects (Stebbins et al., 2004). The volume reduction of the superior parietal lobe may lead to a disruption in the visual attention pathways leading to the incorporation of stereotyped form-objects into the visual field and predisposing to VH (Collerton et al., 2005).

We cannot establish the cause of volume reduction in occipital and parietal regions without neuropathological confirmation, though a contribution of primary cortical degenerative changes could be suggested. Neuropathological post-mortem studies investigating brain changes associated with VH have reported a clear role of Lewy body pathology. Harding et al, 2002a reported that cases with VH have more Lewy bodies than those without hallucinations in the amygdala and parahippocampus, and cases presenting hallucinations early in the disease course have more LB within the temporal cortex (parahippocampus and inferior temporal cortex), indicating that LB pathology in medial temporal regions predisposes to hallucinations. Several patients in this study were demented and indeed the cortical changes may be more related to dementia than hallucinations per se. However, in a recent study with a well-matched sample of PD with and without hallucinations and without dementia, Lewy body densities were higher across the amygdala and the cortical areas studied in PD patients with VH (Papapetropoulos et al., 2006, in press).

The structural changes observed in our non-hallucinating PD sample in comparison to normal controls were located in frontal regions. This finding corroborates those of other MRI-VBM studies investigating regional differences in non-demented PD patients (Burton et al., 2004; Nagano-Saito et al., 2005; Summerfield et al., 2005). For their part, studies with demented PD patients showed that dementia in PD is associated with gray matter volume reductions affecting mainly the temporo medial and occipital regions (Burton et al., 2004; Nagano-Saito et al., 2005; Summerfield et al., 2005). Our non-demented hallucinating PD group showed an involvement of occipital areas but a preservation of medial temporal structures. Although the overlap between cognitive impairment and presence of VH in PD patients is well known, our

design does not allow us to conclude whether the atrophic changes in occipital areas are also a preclinical marker of developing cognitive impairment. Longitudinal studies are required to clarify this issue.

In conclusion, patients with VH had cerebral gray volume reductions affecting mainly parieto-occipital regions. Although it is unlikely that a behavioral pattern as complex as VH will be determined by a dysfunction of a single brain areas, we suggest that atrophic local changes in visual associative areas may contribute to the presence of this symptom.

4.4 NEUROPSYCHOLOGICAL DEFICITS IN PARKINSON'S DISEASE PATIENTS WITH VISUAL HALLUCINATIONS

4.4.1. INTRODUCTION

Visual hallucinations (VH) belong to the most frequent neuropsychiatric symptoms of Parkinson's disease (PD), affecting 22 to 50% of patients (Fenelon et al., 2000; Williams and Lees, 2005). Although they have been associated with the presence of cognitive impairment or frank dementia (Fenelon et al., 2000; Williams and Lees, 2005), only few studies have addressed specific neuropsychological deficits in nondemented PD patients with VH. Barnes et al. (2001, 2003) found that hallucinating PD patients showed deficits in object perception and visual recognition memory in comparison with both nonhallucinating PD patients and healthy controls. Cognitive deficits related to executive functions have also been reported in hallucinating PD patients (Grossi et al., 2005). In terms of the underlying brain mechanisms, neuroimaging and neuropathological studies found an association between temporal and frontal cerebral abnormalities and VH in PD patients (Okada et al., 1999, Harding et al., 2002a; Stebbins et al., 2004). Our study investigates the potential relationship between VH in PD and deficits in different neuropsychological domains, with a particular emphasis on testing of temporal lobe function.

4.4.2. METHODS

Sample

Participants were recruited from the Parkinson Disease and Movement Disorders Unit, Hospital Clinic Universitari, Barcelona, Spain. The sample comprised 24 PD patients who had experienced VH in the previous year, 21 PD patients who never suffered from VH, and 21 healthy elderly controls. The controls comprised spouses of PD patients and community volunteers without any history of psychiatric or neurological disorders who were matched with patients for age and education. All subjects gave informed consent to participate in this study, which was approved by the local Ethics Committee.

The details of the diagnostic criteria and clinical assessment are described elsewhere (Ramírez-Ruiz et al., 2005). Patients who fulfilled DSM-IV-TR criteria for dementia or presented clinical depression (Hamilton score $\geq$ 15) were excluded. All patients passed a visual acuity test consisting of reading from a distance of approximately 40 cm.

The demographic and clinical characteristic of the sample (PD+VH; PD; Controls) are, respectively, as follows: age (74.7 ± 5.4; 73.3 ± 6.1; 73 ± 6.7), sex distribution ([males/females] 10/14; 9/12; 9/12), years of education (7.3 ± 3.4; 7.7 ± 3.4; 7.9 ± 4.6), and visual acuity (0.5 ± 0.2; 0.6 ± 0.2; 0.7 ± 0.2). None of these variables differed significantly

among the samples. PD patients with VH obtained a lower MMSE (26.7 ± 2.1) and a higher Hamilton scores (6.5 ± 4.6) than both non-VH PD patients (MMSE = 29.2 ± 1.4; Hamilton = 3.6 ± 2.7) and healthy controls (MMSE = 29.9 ± 1.6; Hamilton = 2.7 ± 2.6) ($p < 0.0005$; $p < 0.05$, respectively). Concerning clinical differences between both PD groups, hallucinating PD patients presented similar motor severity as assessed by the UPDRS motor scale (30.6 ± 14.5) but a more advanced Hoehn and Yahr stage (3.3 ± 1.1) compared to nonhallucinating PD patients (UPDRS = 24.9 ± 13.7; H&Y = 2.5 ± 0.7) ($p = 0.21$; $p = 0.015$ respectively). No differences in levodopa daily dose were found between PD groups with and without VH ($p = 0.071$).

The VH in our PD sample consisted of well-formed images of people, faces or animals. Insight into the hallucinatory nature of the phenomenon was maintained in 63% of the patients. Associated delusions were present in 33% of the patients. These delusions were primarily paranoid in type and involved elementary misbelieves concerning infidelity or theft. All hallucinating PD patients but one was on dopaminergic treatment at the time of evaluation. A modification of the antiparkinsonian treatment preceding the onset of VH was recorded in 33% of the patients. The VH disappeared after dopaminergic drug dosage reduction in eleven cases (45.8%), whereas five patients (20.8%) needed antipsychotic medication and five (20.8%) required both interventions. In the remaining patients, medication was not modified because the hallucinations were well tolerated.

Neuropsychological assessment

General intellectual ability was assessed by the Information and Similarities subtests from WAIS-III. Language was evaluated by a verbal comprehension test (Token Test) and a picture naming tests (Boston Naming Test) and frontal functions by phonological and semantic fluency tests. A modified version of the Rey's Auditory Verbal Learning Test (RAVLT) was used to assess verbal learning, delayed recall, and recognition. To assess visuoperceptive functions, we used the Benton Facial Recognition Test (BFRT) and the standard drawing and multiple-choice version of the Benton Visual Form Discrimination Test (VFDT) (Benton et al., 1994). Finally, we evaluated visual memory functions using the subtest Memory for Faces from Warrington's Recognition Memory Test. All tests were administered and scored according to conventional procedures (Spreen and Strauss, 1998).

Data analysis

Statistical analysis was carried out using SPSS 11.0. Sex distribution was compared with Pearson-$\chi 2$ tests. For normally distributed quantitative variables with homogeneity of variance, we used an analysis of variance (ANOVA test) and the post-hoc Bonferroni test. For non-normally distributed variables, and/or in the case of no equality of variance between the groups, we used the nonparametric Mann-Whitney *U* test. Finally, we performed an analysis

of covariance (ANCOVA) using MMSE, Hoehn and Yahr stage and Hamilton scores to determine whether differences between the two PD groups on cognitive tests persisted after controlling for these variables.

4.4.3. RESULTS

The results of the neuropsychological assessment are shown in Table 4.4.1. The groups did not differ in general intellectual ability as evaluated with the Similarities (p = 0.343) and Information (p = 0.777) subtests from WAIS-III. However, the analysis of variance showed group differences in the other domains assessed: language, memory, frontal and visuoperceptive functions. The post hoc test revealed poorer performance in PD patients with VH than in healthy controls in all neuropsychological measures except RAVLT- recognition. Patients with VH were more impaired than those without VH on language assessed by Token and Boston Naming Tests (p = 0.034 and p = 0.032 respectively), verbal learning (p < 0.0005), semantic fluency (p = 0.022) and visuoperceptive functions evaluated by Benton Facial Recognition (p < 0.0005) and Visual Form Discrimination (p = 0.042). The only significant difference between PD patients without VH and healthy controls was observed in visual memory (p = 0.001).

	PD with VH	PD without VH	Controls	*P* Value[a]	*P* Value[b]
General intellectual ability					
Similarities (WAIS-III)	11.7 ± 4.8	12.7 ± 6.0	14.0 ± 5.1	NS	-
Information (WAIS-III)	11.5 ± 6.9	12.4 ± 6.1	12.9 ± 7.3	NS	-
Language					
Token Test	27.8 ± 4.4	30.6 ± 2.8	31.9 ± 3.0	<0.05**	NS
Boston Naming Test	47.3 ± 7.0	51.8 ± 4.3	52.5 ± 5.4	<0.05**	NS
Verbal Memory					
RAVLT- Learning	24.8 ± 7.2	38.8 ± 7.0	41.9 ± 7.2	<0.0005**	<0.0005
RAVLT- Memory loss	8.4 ± 10.8	3.7 ± 4.4	3.0 ± 2.7	0.043*	-
RAVLT- Correct recognition	12.5 ± 2.1	12.8 ± 2.1	13.7± 1.4	NS	-
RAVLT- False recognition	2.4 ± 2.3	1.3 ± 1.3	0.9 ± 0.8	0.007*	-
Executive Functions					
Phonological fluency (P)	7.4 ± 4.5	9.7 ± 3.7	12.7 ± 6.1	0.002*	-
Semantic fluency (animals)	9.4 ± 4.5	13.3 ± 4.7	17.1 ± 5.1	<0.05**	NS
Visuoperceptive Functions					
Benton Facial Recognition Test	43.7 ± 4.5	49.0 ± 4.3	49.4 ± 2.9	<0.0005**	<0.05
Visual Form Discrimination Test	26.4 ± 3.8	28.8 ± 3.1	30.4 ± 2.0	<0.05**	NS
Visual Memory					
Warrington's Recognition Test	31.1 ± 5.6	33.5 ± 6.5	40.4 ± 5.6	<0.005*	-

Table 4.4.1. *Demographic and clinical, variables. Values are mean ± SD; [a] Indicates calculated using analysis of variance (ANOVA) test; [b] Analysis of covariance between PD groups using MMSE, Hoehn and Yahr and Hamilton scores as covariates. * Significant difference between PD patients with VH and controls; ** Significant difference between PD patients with VH and controls and between PD patients with VH and PD patients without VH.*

WAIS-III, Wechsler Adult Intelligence Scale; RAVLT- Learning, Sum of words correctly recalled from Trial 1 to 5; RAVLT- Memory loss, Percentage of memory loss: percentage of words loss after 20 min of interference; RAVLT- Correct recognition, Number of words correctly recognized from the original list; RAVLT- False recognition, Number of words falsely recognized from the original list;

Given that the specific neuropsychological deficits may be related to the global cognitive performance (MMSE score) and to the differences in illness stage (Hoehn and Yahr scale) and mood (Hamilton scale), we performed an analysis of covariance (ANCOVA) between the two PD groups using these clinical variables as covariates. After removing the effect of these variables, differences in RAVLT-verbal learning ($p < 0.0005$) and in Benton Facial Recognition Test ($p = 0.013$) remained significant.

4.4.4 DISCUSSION

PD patients with VH showed several cognitive deficits affecting not only visuoperceptive performance, as previously reported, but also language and verbal memory domains. This suggests that cerebral dysfunction in PD with VH extends beyond the subcortical-frontal circuits typically described in PD.

On test of verbal memory, PD patients with VH demonstrate the classical PD pattern, consisting of deficits in free recall but normal recognition (Pahwa et al., 1998, for a review). However, our patients with VH showed also deficits in long term retention (RAVLT-memory loss) and the presence of false intrusions. These findings could reflect an involvement of limbic and temporal cortex, as suggested by neuropathological studies (Harding et al., 2002a), in addition to a disruption of nigro-striato-thalamo-cortical circuitry.

The differences on Benton's Facial recognition Test in the hallucinating patients are in agreement with the neuropsychological (Barnes et al., 2003) as well as neuroimaging findings suggesting involvement of visual associative areas in patients with VH (Okada et al., 1999, Stebbins et al., 2004). These differences are not likely to be caused by a lower visual acuity, although we cannot exclude a faulty visual input due to primary visual deficits commonly seen in PD, such as reduced color and contrast discrimination (Diederich et al., 2005). Differences in BFRT remained significant after controlling for MMSE. In contrast, the differences between hallucinating and non hallucinating PD patients on the VFDT lost significance after such covariation. The performance on VFDT, in addition to visuoperceptive skills involved in BFRT, requires additional visuospatial functions. This finding could explain why this test depends to a higher degree on the general cognitive status.

Regarding the face recognition memory, our results are partially in agreement with those reported by Barnes et al., 2003 that found a significant impairment in PD patients with and without VH vs. healthy controls. Nevertheless, we did not observe significant statistical differences on the Warrington Facial Recognition Test between hallucinating and nonhallucinating groups, although PD patients with VH scored lower than those without this symptom. Longitudinal studies can clarify the relevance of visual memory impairment on cognitive decline associated with the presence of hallucinations.

In addition to complex visual dysfunction, we observed deficits on language comprehension. The poor performance on the Token Test could be related to an impairment in sentence processing (Grossman et al., 2002), which has been associated with a reduced activation of anteromedial prefrontal cortex and posterolateral temporal regions (Grossman et al., 2003). Additionally, the reduced performance on the Token Test could also be related to visual attention impairment, as alterations of parieto-frontal connections associated primarily with the attentional modulation of visual perception have been implicated in the pathophysiology of VH (Stebbins et al., 2004).

The recruitment of inferior frontal and ventral temporal regions has been observed during confrontation naming and semantic fluency tasks in healthy subjects (Henry et al., 1998; Vitali et al., 2005). The deficits found in these cognitive domains in our hallucinating patients, therefore, could reflect dysfunction in these brain areas. From the clinical point of view, naming impairment has been related to the level of general cognitive dysfunction in PD (Pahwa et al., 1998 for a review) and prospective studies have identified deficits in verbal fluency as predictors of the development of dementia (Jacobs et al., 1995a). This is consistent with our finding that the differences between the PD groups in naming and category fluency lost significance once the effects of general cognitive status were removed from the analysis. The reduced efficiency in language and semantic fluency in our PD patients with VH could reflect the starting point of the more general cognitive decline which might later lead to dementia.

In conclusion, hallucinating PD patients were characterized by a wide range of impairments affecting several cognitive domains. The presence of such extensive deficits may escape the compensatory processes and, thus, favor the perception of VH. Given the well-documented relationship between dementia and hallucinations, it remains to be shown in longitudinal studies whether visuoperceptive and memory impairments found in our hallucinating PD sample are the earliest symptoms of a progressive cognitive decline.

4.5 COGNITIVE CHANGES IN PARKINSON'S DISEASE PATIENTS WITH VISUAL HALLUCINATIONS. A FOLLOW-UP STUDY

4.5.1 INTRODUCTION

Hallucinations, mainly of visual nature, affect about 50% of patients with Parkinson's disease (Williams and Lees, 2005). Cross-sectional studies have found that hallucinating PD patients show greater neuropsychological impairment than those without this symptom. The deficits are varied, affecting several cognitive domains such as verbal fluency (Grossi et al., 2005; Ramírez-Ruiz et al., in press); verbal memory (Grossi et al., 2005; Sinforiani et al., 2006 in press; Ramírez-Ruiz et al., in press); language (Ramírez-Ruiz et al., in press); non-verbal logical abilities (Sinforiani et al., 2006 in press); visuoperceptive functions and visual memory (Barnes et al., 2003;) and visuo-spatial functions (Sinforiani et al., 2006 in press).

The presence of hallucinations in PD has been identified as a significant predictor of dementia (Aarsland et al., 2003) and has been associated with a more rapid cognitive decline as assessed by mini mental state examination (MMSE) (Aarsland et al., 2004). However, the global nature of this test does not allow identification of specific neuropsychological deficits. The aim of this study was to evaluate the difference in cognitive performance over one-year period in a range of neuropsychological functions in PD patients with history of VH, and to compare it with PD patients without VH and control subjects.

4.5.2 METHODS

Sample

PD patients who met the diagnostic criteria of idiopathic Parkinson's disease (Daniel and Lees, 1993) were recruited from an outpatient movement disorders clinic (PD and Movement Disorders Unit, Department of Neurology, Hospital Clinic, Barcelona). The healthy control group comprised spouses of PD patients or community volunteers who had no history of any psychiatric or neurological disorder or of drug or alcohol abuse. The participants were part of a previously-studied sample made up of 24 nondemented PD patients with current VH or history of them in the previous year, 21 PD patients without any history of VH and 21 normal elderly controls (NCs). All subjects were invited by phone to participate in a second assessment one year later. Of the original PD sample with VH, two died and two other patients declined to participate. Of the original PD sample without VH, one subject refused to take part in the study, as did three from the healthy group. Thus, 20 PD patients with VH, 20 PD without VH and 18 NCs were included in the final follow-up evaluation. The average follow-up period was 13 months (SD = 1.4). Written informed consent was obtained for all subjects. The study was approved by the local Ethical Committee.

Clinical evaluation

Patients were clinically assessed with the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn et al., 1987) and the severity of the disease was graded according to Hoehn and Yahr staging scale (Jankovic et al., 1990) The global cognitive state was measured by Folstein Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and the Hamilton scale (Hamilton, 1960) was administered to assess mood. All patients passed a visual acuity test consisting of reading at a distance of approximately 40 cm.

Neuropsychological assessment

The initial and follow-up neuropsychological examination comprised of the same battery examining 6 cognitive domains: language, verbal memory, frontal, visuoperceptive functions and visual memory. Language was evaluated with the Token Test and the Boston Naming Test which measures verbal comprehension and word-finding ability respectively. We also administered the Similarities subtest from WAIS-III which assesses verbal abstraction. To examine verbal memory a modified version of the Rey Auditory-Verbal learning Test (RAVLT) was used. The measures retained were number of words recalled over five acquisition trials (learning), delayed recall and recognition. Frontal functions were evaluated using a phonological fluency task (the numbers of words beginning with "P" produced in one minute) and a category fluency task (the number of animals names produced in one minute). Visuoperceptive function was tested using the Benton Facial Recognition Test (Benton et al., 1994) and the standard drawing and multiple-choice version of the Benton Visual Form Discrimination Test (Benton et al., 1994) which measure visuoperceptive and visuospatial components. Finally, to evaluate visual memory we used the Warrington Recognition Memory for Faces (RMF). All tests were administered and scored in accordance with conventional procedures (Spreen and Strauss, 1998).

Data analysis

Statistical analysis was carried out using SPSS 11.0. Gender distribution was compared with $\chi 2$ tests. The between-groups analysis for clinical and cognitive variables at baseline and during follow-up was performed using analysis of variance (ANOVA test) or a T-test for independent samples in the case of variables normally distributed with homogeneity of variance. For non-normally distributed variables, and/or in the case of no equality of variance, we used the non-parametric Mann-Whitney *U* test. The Spearman correlation coefficient evaluated the association between a variation in dopaminergic medication and a change in cognitive measures at baseline and after follow-up. Finally, the general linear mixed model (GLM) was used to test whether the performance on neuropsychological measures at both examinations differed over time in the different groups.

4.5.3 RESULTS

Initial evaluation

Clinical and neuropsychological characteristics of the samples at baseline evaluation

Characteristics of the patients who completed the follow-up at baseline are presented in Table 4.5.1. There were no significant between-group differences in age, gender or education. In comparison to the non-VH group and NCs, hallucinating PD subjects showed a higher Hamilton score and a lower MMSE score; however, none of the VH patients met criteria for clinical depression or dementia. The PD groups had similar scores in the UPDRS motor subscale, but the VH group showed a more advanced Hoehn and Yahr stage.

At baseline evaluation, 25% of the hallucinating PD patients experienced were currently VH whereas 75% of the sample reported history of VH in the last 12 months. The VH in our PD sample were well-formed images of people, faces or animals. All PD VH patients but one were receiving dopaminergic treatment at the time of the initial evaluation. The treatment for VH was: dopaminergic drug dosage reduction in nine cases (45%), antipsychotic medication in four patients (20%) and a combination of both in the other four patients (20%). Medication was not modified in the remaining patients because the hallucinations were well tolerated.

	Group	Time1	Time 2
Age (years)	**PD with VH**	74.8 ± 5.3	-
	PD non VH	73.4 ± 6.2	-
	Control	72.6 ± 6.9	-
Gender (men/women)	**PD with VH**	9/11	-
	PD non VH	8/12	-
	Control	7/11	-
Education (years)	**PD with VH**	7.0 ± 3.7	-
	PD non VH	7.6 ± 3.5	-
	Control	8.3 ± 4.7	-
Visual acuity	**PD with VH**	0.5 ± 0.2 [a]	0.5 ± 0.2
	PD non VH	0.6 ± 0.2	0.6 ± 0.2
	Control	0.7 ± 0.2	0.6 ± 0.1
MMSE	**PD with VH**	25.7 ± 2.3[ab]	23.2 ± 4.5[ab]
	PD non VH	28.1 ± 1.8[c]	27.7 ± 2.4[c]
	Control	28.5 ± 2.4[c]	28.6 ± 2.2[c]
Hamilton scores	**PD with VH**	6.6 ± 4.5[ab]	7.7 ± 5.1[a]
	PD non VH	3.6 ± 2.8[c]	5.3 ± 5.2
	Control	3.1 ± 3.3[c]	2.0 ± 2.3[c]
PD onset	**PD with VH**	61.4 ± 7.4	-
	PD non VH	62.7 ± 7.4	-
Disease duration (years)	**PD with VH**	13.3 ± 5.7	-
	PD non VH	10.7 ± 4.3	-
Hoehn and Yahr stage	**PD with VH**	3.3 ± 1.1[b]	4.0 ± 1.2[b]
	PD non VH	2.5 ± 0.7[c]	2.9 ± 0.7[c]
UPDRS III 'on'	**PD with VH**	32 ± 14.5	41.8 ± 16.4[b]
	PD non VH	25.4 ± 13.9	29.0 ± 12.8[c]
Levodopa daily dose (mg)	**PD with VH**	885 ± 340.5	936.3 ± 278.5
	PD non VH	818.8 ± 473.8	941.5 ± 347.7

Table 4.5.1. *ANOVA comparisons, demographic and clinical variables between groups at baseline and at follow-up (1 year). Values are mean ± SD; [a] $p < 0.05$ versus healthy controls; [b] $p < 0.05$ versus PD patients without VH; [c] $p < 0.05$ versus PD patients with VH.*

Regarding the neuropsychological differences between groups at first evaluation, the hallucinating PD patients performed significantly worse than PD patients without VH and NCs on several cognitive measures, including: language (Token and Boston Tests), verbal memory (learning score), frontal, and visuoperceptive measures (Table 4.5.2.). The only significant difference between PD patients without VH and healthy controls was observed in visual memory ($p < 0.0001$).

	Group	Time1	Time 2
Language			
Similarities (WAIS-III)	**PD with VH**	11.4 ± 4.9	9.7± 5.2[a]
	PD non VH	12.5 ± 6.1	12.3 ± 4.9
	Control	14.7 ± 5.2	15.8 ± 5.7
Token Test	**PD with VH**	28.1 ± 3.8[ab]	26.2 ± 4.9[ab]
	PD non VH	30.8 ± 2.6[c]	30.6 ± 1.8[c]
	Control	32.2 ± 2.1[c]	32.3 ± 2.1[c]
Boston Naming Test	**PD with VH**	46.8 ± 7.2[ab]	45.3 ± 8[ab]
	PD non VH	51.7 ± 4.3[c]	50.9 ± 5.4[c]
	Control	53.4 ± 4.5[c]	53.2 ± 4.6[c]
Verbal memory			
RAVLT- Learning	**PD with VH**	25 ± 7.8[ab]	22.6 ± 9[ab]
	PD non VH	39.1 ± 7[c]	42.1 ± 9.3[c]
	Control	41.6 ± 8.1[c]	46.1 ± 8.6[c]
RAVLT- Delayed Recall	**PD with VH**	-6.8 ± 9.3	-11.3 ± 11.1[ab]
	PD non VH	-3.4 ± 4.6	-3.7 ± 5.2[c]
	Control	-3.5 ± 3.3	-2.4 ± 3.1[c]
RAVLT- False recognition	**PD with VH**	2.2 ± 1.8	3.8 ± 3.2[ab]
	PD non VH	1.3 ± 1.3	0.9 ± 0.9[c]
	Control	0.9 ± 0.9[c]	0.7± 0.7[c]
Frontal function			
Phonological fluency (P)	**PD with VH**	7.9 ± 4.5[ab]	6.0 ± 3.1[ab]
	PD non VH	9.4 ± 3.6[c]	10.0 ± 4.7[c]
	Control	13.6 ± 6.2[c]	13.6 ± 6.4[c]
Semantic fluency (animals)	**PD with VH**	10.0 ± 4.6[ab]	8.8 ± 4.4[ab]
	PD non VH	12.9 ± 4.5[c]	14.2 ± 4.7[c]
	Control	17.6 ± 5.1[c]	16.8 ± 5.9[c]
Visuoperceptive function			
Benton Facial Recognition Test	**PD with VH**	43.3 ± 4.4[ab]	42.6 ± 4.6[ab]
	PD non VH	49.0 ± 4.2[c]	47.6 ± 4.3[c]
	Control	49.4 ± 2.6[c]	50.2 ± 2.4[c]
Visual Form Discrimination Test	**PD with VH**	26.5 ± 3.7[ab]	24.2 ± 4.5[ab]
	PD non VH	29.3 ± 2[c]	30.4 ± 1.8[c]
	Control	30.6 ± 1.7[c]	31.3 ± 1.2[c]
Visual Memory			
Warrington's Recognition Test	**PD VH**	31 ± 5.6[a]	26.9 ± 3.9[ab]
	PD non VH	33 ± 6.3[a]	34.6 ± 6.5[c]
	Control	40.9 ± 5.2	41.3 ± 5[c]

Table 4.5.2. A*NOVA comparisons neuropsychological scores between groups at baseline and at follow-up (1 year); Values are mean ± SD;* [a] *$p < 0.05$ versus healthy controls;* [b] *$p < 0.05$ versus PD patients without VH;* [c] *$p < 0.05$ versus PD patients with VH; WAIS-III = Wechsler Adult Intelligence Scale; RAVLT- Learning = Sum of words correctly recalled from Trial 1 to 5; RAVLT- Delayed recall = Percentatge of number of words lost from Trial 5 to Trial 8; RAVLT- False recognition = Number of words falsely recognized from the original list.*

Follow-up evaluation

Clinical and neuropsychological characteristic of the samples at second evaluation

None of the PD patients without history of VH at the time of the initial examination developed hallucinations during the one-year follow-up period. Among the patients with history of VH at the initial evaluation, four patients (25%) had developed active hallucinations by the time of second evaluation whereas ten (50%) had not. Five patients (20%) who were currently experiencing VH at baseline continued to do so in the follow-up and only one patient who had hallucinated at study entry did not experienced VH at follow-up.

There were no differences in clinical and cognitive variables between PD patients with current VH vs PD patients with history of this symptom either at baseline or follow-up evaluation. In the subsequent analysis we therefore considered all patients with history of VH as one group (VH) and compared them with the PD patients who had never hallucinated (non-VH).

The VH group differed significantly from the non-VH group in all clinical measures except the Hamilton score. Final dosage of DA treatment did not differ between hallucinating and non hallucinating PD patients (Table 4.5.1.). Regarding neuropsychological measures, the cognitive performance comparison between groups (see Table 4.5.2.) revealed that PD subjects with VH showed significantly lower scores on verbal (delayed recall and false recognition) and visual memory measures compared to non-hallucinating PD patients; these differences were not observed in the initial evaluation.

Clinical and cognitive differences across time between groups

There was no significant change in Hamilton scores over one year period in any group. The decrease in MMSE score was: 0.4 points for PD patients without VH; 2.5 points for hallucinating PD patients, and 0.05 for NCs. This decline was statistically significant only for PD patients with VH ($F = 4.8$; $p = 0.01$). Forty (40%) of the hallucinating sample met dementia criteria at follow-up evaluation (DSM-IV-TR criteria and MMSE $\leq$ 23). The percentage of change in the Hoehn and Yahr stage and in the motor subscale of UPDRS was calculated for both PD group as follows:

$$\frac{\text{baseline score - follow up score}}{\text{baseline score}} \times 100$$

Inter-group analysis using the Mann-Whitney test showed that the percentage of motor worsening (change in UPDRS score) and illness progression (difference in H&Y stage) were comparable for VH (UPDRS = 45.1 ± 15.1; H&Y = 23.6 ± 9.2) and non VH groups (UPDRS = 51.9 ± 26.6; H&Y = 17.9 ± 6.5). The change in levodopa dosage between initial and follow-

up evaluation was calculated using the same formula. Only PD patients without VH received a higher levodopa dosage than at the base-line evaluation ($Z = -2.29$; $p = 0.022$).

To test whether the performance on neuropsychological measures at the two examinations differed across time in the three groups, a general linear mixed model (GLM) was used. The GLM analysis of variance for repeated measures revealed significant interaction between changes over time and group in the cognitive functions assessed. The significant interaction was caused by the PD group with VH who showed a steeper cognitive decline over time than non-hallucinating PD patients and NCs (See Table 4.5.3.). In comparison with non-VH and NCs, the hallucinating PD group had a significant progressive decline in language (comprehension), verbal memory (RAVLT- False recognition), visual form discrimination and visual memory. Hallucinating PD patients also showed a progressive impairment of frontal functions (phonological fluency) compared to non-VH PD patients.

	Interaction Group x Time (p-value)*	**Post-hoc comparison (p-value)†**	
		PD+VH > PD non VH	**PD+VH > NCs**
Language			
Token Test	0.05	0.048	0.025
Verbal memory			
RAVLT-False recognition	0.002	0.001	0.004
Frontal function			
Phonological fluency (P)	0.068	0.026	0.099
Visuoperceptive function			
Visual Form Discrimination Test	<0.0005	<0.0005	0.001
Visual memory			
Warrington's Recognition Test	0.001	<0.0005	0.004

Table 4.5.3. *General Lineal Mixed Model of cognitive decline of the samples from one year follow-up. *A significant interaction of Group x Time indicates differential rates of changes in a test score as a function of group; †Post-hoc comparison is testing the differences in slope of cognitive decline in the mentioned several neuropsychological measures over time; RAVLT- False recognition = Number of words falsely recognized from the original list.*

Finally, in order to determine the extent of the deterioration in the hallucinating PD group in different cognitive domains, a percentage of cognitive decline was calculated for each domain according to the formula:

$$\frac{\text{baseline score - follow up score}}{\text{baseline score}} \times 100$$

In the case of the following cognitive domains several indexes were combined to form a composite score: language (Boston and Token tests); frontal (phonological and semantic verbal fluencies); verbal memory (RAVLT learning, delayed recall and false recognition measures). The composite score was calculated as the algebraic sum of the average percentage change in each cognitive test or measure, divided by the number of test or measures. The cognitive domain with the largest degree of deterioration was visual memory, followed by complex visual form discrimination and frontal functions (Figure 4.5.1.). There was not association between changes in cognitive performance and changes in dopaminergic dosage or motor impairment assessed by UPDRS motor subscale. Figure 4.5.2. shows a copy of the MMSE interlocking pentagon at the initial and follow-up examination performed by a hallucinating PD patient with active hallucinations at baseline and at follow-up. We observed severe visuoconstructive disintegration at second evaluation.

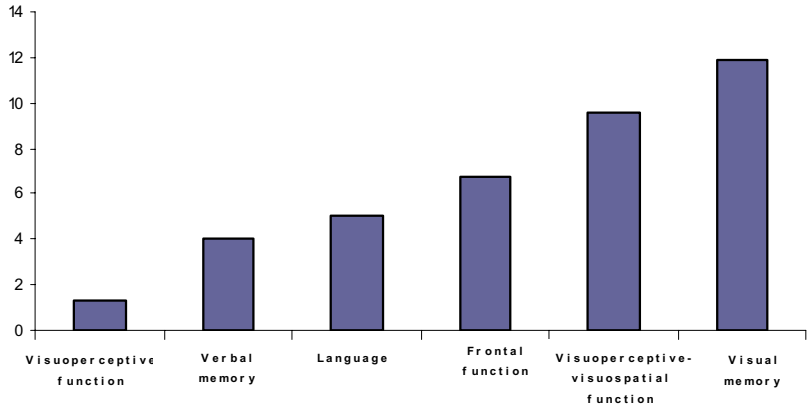

Figure 4.5.1. *Percentage of cognitive decline in PD patients with VH*

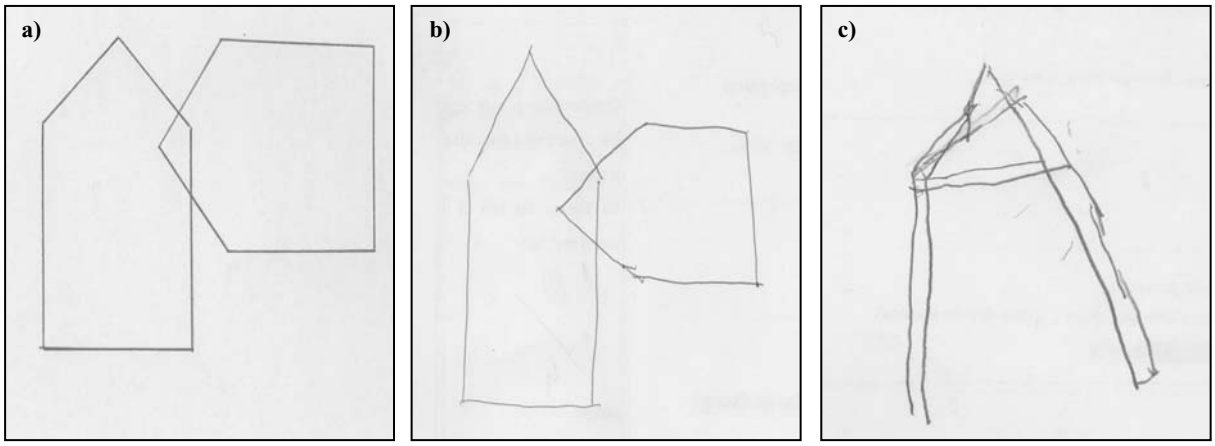

Figure 4.5.2. *a) MMSE interlocking pentagons to be performed; b) baseline copy; c) follow-up copy*

4.5.4 DISCUSSION

To the best of our knowledge, this is the first study to investigate changes in neuropsychological performance over time in PD patients with visual hallucinations. The cognitive impairment over time in our hallucinating PD subjects was severe in comparison with the non hallucinating PD group, and forty per cent of hallucinating PD sample were considered clinically demented at follow-up assessment. The hallucinating PD patients showed progressive decline, which affected mainly visual memory and visuoperceptive functions. Significant though less marked deficits were also observed in frontal and language functions. These results supported those of other studies with longer follow-up periods (Aarsland et al., 2003; Factor et al., 2003) that using cognitive screening instruments identified the presence of visual hallucinations as a risk factor for mental decline in PD patients.

The most pronounced cognitive decrease was observed in visual memory. The impairment over time in visual memory could be related to progressive deficits in the cerebral network involved in visual encoding. These deficits could be related to progressive extension of LB pathology, particularly in areas involved in face encoding and recognition memory such as medial temporal, fusiform and prefrontal regions (Rapsack, 2003 for a review). Neuropathological and neuroimaging studies have found pathological changes in these areas in VH patients. Specifically, Harding et al. (2002a) found high density of LB affecting temporal cortices (parahippocampus) in cases with hallucinations (PD patients with and without dementia and subjects with DLB). Using SPECT, Oishi et al. (2005) observed an association between visual hallucinations in PD and hypoperfusion in the right fusiform gyrus. Unfortunately, no longitudinal studies are available to confirm this hypothesis.

Regarding visuoperceptive functions, the performance on the Benton Facial Recognition Test was impaired in hallucinating PD patients compared to non-hallucinating and NCs; however, the scores in this task did not change significantly over time. In contrast, we observed a progressive impairment in Visual Discrimination Test in VH patients. This task involve two visual functions: visuoperceptive (complex visual shape discrimination) and visuospatial (spatial localization) (Rao et al., 2003). Visuoperceptive impairment has been reported in PD patients with VH (Barnes et al., 2003; Ramírez-Ruiz et al., in press) but the results for visuospatial functions are contradictory. Barnes et al. (2003) did not observe greater deficits in hallucinating PD patients on the spatial perception subtest of VOSP (Visual object and space perception battery) than in non hallucinating PD patients. However, others authors found an association between hallucinatory experiences and difficulty estimating spatial relations (Davidsdottir et al., 2005) and visuo-spatial learning (Sinforiani et al., 2006 in press). The continuous deterioration on the Visual Form Discrimination Test in our

hallucinating PD patients would suggest a visuospatial progressive decline in addition to a visuoperceptive dysfunction.

The pathological basis for the impairment in complex visual functions in PD patients with VH remains unclear but they may well be caused by both combined peripheral visual factors and cortical changes. Regarding primary visual functions, the impairments observed in the higher order visual tests are probably not caused by a lower visual acuity because there were no differences between VH and non-VH patients. However, other primary visual deficits such as reduce contrast discrimination mediated by disruption of dopaminergic processes in the retina (Diederich et al., 1998) and loss of useful field of view (Uc et al., 2005) could be responsible for a faulty visual input which may interfere with the initial processing of the stimulus.

As far as brain cortical abnormalities are concerned, the impairment on Benton Facial Recognition Test in our hallucinating PD patients is in agreement with neuropathological and neuroimaging findings that suggest dysfunctions of ventral visual pathway (Harding et al., 2002a; Stebbins et al., 2004; Oishi et al., 2005). However, the progressive decline in Visual Form Discrimination Test, suggests a greater involvement of parieto-occipital regions. Abnormalities in parieto-occipital areas in hallucinating PD patients have been described in recent studies. Nagano-Saito et al. (2004b) found that VH patients showed hypoperfusion in occipital regions (lingual gyrus) compared with NCs. In a post-mortem clinico-pathological study, high LB densities in parietal cortex were observed associated with the presence of VH in PD patients (Papapetropoulos et al., 2006 in press). Thus, the decline in Visual Form Discrimination Test observed in our hallucinating PD patients may be related to dysfunctions of parietal occipital and cortices.

In our initial cross-sectional study (Ramírez-Ruiz et al., in press), the impairment in the complex visual form discrimination task in our VH sample was related to the general mental status. General cognitive impairment and the presence of VH in PD have been associated with cortical cholinergic depletion (Bosboom et al., 2004 and Papapetropoulos and Mash, 2005 for reviews). Moreover, acetylcholine is one of the specific neurotransmitter that modulate the visuospatial function (Wezenberg et al., 2005). In this way, the impairment in the Visual Form Discrimination Test in our hallucinating sample may also be related to a progressive cholinergic depletion in these patients.

The deficits in visuoperceptive functions and visual memory observed in our hallucinating sample support the current models of VH in which the combination of degraded visual information from the environment (Barnes et al., 2003; Collerton et al., 2005; Diederich et al., 2005) and failing visual memory (Barnes et al., 2003) are important causal factors for the occurrence of VH. Dysfunction in cerebral temporal medial areas, in addition to progressive

dysfunction in dorsal visual areas, could be related to the observed decline in complex visual form discrimination and visual memory functions. There is only one SPECT longitudinal study investigating the neural correlates associated with changes in VH in demented PD patients and subjects with DLB. The authors found a significant relationship between decreases in hallucination score an increased perfusion in the midline parietal area encompassing the posterior cingulate, precuneus and superior part of the cuneus (O'Brien et al., 2005). Future studies are needed to elucidate whether brain metabolic changes are associated with visuoperceptive and visual memory decline in hallucinating PD patients.

The decline observed in phonological fluency, but not in semantic fluency, suggests a frontal lobe involvement. The frontal/executive dysfunction has been extensively described in PD and it has been attributed to disruption of frontostriatal circuitry (Zgaljardic et al., 2003 for a review). Cognitive deficits associated with frontal functions have also been described in hallucinating PD patients (Barnes et al., 2003; Grossi et al., 2005) and abnormalities in the functioning of several frontal areas have been reported in functional imaging studies in PD patients with VH (Nagano-Saito et al., 2004b; Stebbins et al., 2004).

Finally, we observed a progressive impairment in verbal comprehension in our hallucinating PD. Although classically the PD neuropsychological profile did not include aphasic characteristics, there is evidence of language-related symptoms in non-demented PD patients (Zgaljardic et al., 2003 for a review). Deficits in verbal comprehension have been reported and attributed to grammatical difficulties (Ullman et al., 1997), working memory dysfunction (Grossman, 1999), cognitive resource limitations (Grossman et al., 2000) and deficits on information processing speed (Lee et al., 2003). Moreover, a recent fMRI study found differences in the activation of the brain network involved in linguistic aspects of sentence pre-processing in PD compared with healthy controls. The authors found that in comparison with healthy controls, PD patients showed a lesser recruitment of striatal, anteromedial prefrontal (BA32/10) and posterolateral temporal cortical regions (BA 21/22/39) (Grossman et al., 2003).

Few researchers have followed the progress of neuropsychological changes in PD. Significant cognitive decline was observed over eight years and longer (Hughes et al., 2000; Aarsland et al., 2003) but, over shorter periods of time cognitive decline is slow or negligible (Burton et al., 2005; Firbank et al., 2005). Our hallucinating PD patients showed a faster cognitive decline not associated with changes in dopaminergic medication or motor impairment. The decline was observed in cognitive functions associated with later diagnosis or progression to dementia in PD, such as visuospatial functions (Levin et al., 1991), verbal memory (Levy et al., 2002a; Wood and Troster, 2003) and letter fluency (Jacobs et al., 1995; Levy et al., 2002a). Moreover, forty per cent of hallucinating patients met criteria of clinical dementia at

follow-up. The rol of Lewy body, Alzheimer-type neuropathology and dopaminergic and nondopaminergic lesions in the cognitive decline in hallucinating PD patients remain to be investigated by clinico-pathological studies.

V. GENERAL DISCUSSION

V. GENERAL DISCUSSION

This thesis comprises five studies examining cognitive functions and structural brain changes associated with the presence of dementia and visual hallucinations (VH) in Parkinson's disease (PD) patients. The first two studies investigated the neural substrate of dementia in PD patients, while the following three explored the cognitive and structural brain changes in non-demented PD subjects with and without VH.

Our first study was a cross-sectional MRI investigation examining amygdalar and hippocampal volumes in Parkinson's disease patients with and without dementia. Demented PD patients (PDD) showed a statistically significant amygdalar and hippocampal volume reduction (21% and 20% respectively) compared to normal controls (NCs). A similar, albeit less pronounced volume reduction (amygdala, 11%; hippocampus, 10%) was observed in non-demented patients but it did not reach statistical significance. However, in both demented and non demented PD groups, hippocampal and amygdalar volumes correlated with verbal learning as measured by RAVLT. While two previous studies reported hippocampal atrophy in PDD patients (Laakso et al., 1996; Camicioli et al., 2003), our study is the first in vivo evidence of *amygdalar* volume reduction in this patient group. Similarly, our study is the first to document an association between amygdalar volume and verbal learning in PD, a relationship previously established between hippocampal atrophy and verbal memory (Riekkinen et al., 1998; Camicioli et al., 2003). The functional importance of amygdala has been emphasized by recent studies postulating its modulatory influence (basolateral nucleus) on distinct memory processes mediated by the hippocampus and dorsal striatum (Poldrack and Packard, 2003 for a review). Our MRI volumetric results are also in keeping with post-mortem volumetric studies which found significant reductions in the amygdala and hippocampus in PD patients with and without dementia (de la Monte et al., 1989; Cordato et al., 2000) The reductions observed may reflect the presence in these structures of Lewy bodies (LB) (Mattila et al., 1999; Cordato et al., 2000; Harding et al., 2002b) or/and Alzheimer's disease (AD) neuropathological changes (Mattila et al., 1998).

The second study examined the pattern of cognitive and structural brain changes in Parkinson's disease with and without dementia over 2 years-period using the voxel-based morphometry technique. All PD patients, irrespective of the presence or absence of dementia showed a decline of cognitive functions and progressive brain atrophy on longitudinal follow-up. However, the pattern of gray matter reduction was different in PDD and NDPD groups. The most marked gray matter reduction in NDPD subjects was found in the anterior cingulate gyrus. In contrast, in the PDD group the greatest gray matter decrease involved visual associative areas (right fusiform gyrus). Both PD groups showed progressive hippocampal atrophy and gray matter reductions affecting temporo-occipital associative areas. Our study is

the first longitudinal investigation of PD patients with and without dementia using VBM. The finding of progressive volume loss in the hippocampus in PD patients with and without dementia has not been previously reported although several cross-sectional studies showed atrophy of this structure compared to NCs (Laakso et al., 1996; Riekkinen et al., 1998; Camicioli et al., 2003; Bruck et al., 2004; Nagano-Saito et al., 2005). Likewise, although perfusion deficits in temporal and occipital associative regions has been documented by cross-sectional single-photon emission CT studies in non-demented (Abe et al., 2003; Osaki et al., 2005) and demented PD patients (Antonini et al., 2001; Mito et al., 2005), our study is the first to demonstrate a progression of atrophic changes in these areas.

The widespread progressive volume loss observed in the NDPD group, including subcortical structures (hypothalamus, accumbens), hippocampus, insula, cingulate gyrus and temporo-occipital regions, might at first appear surprising. However, the progression of atrophy with increasing involvement of temporal mesocortex and extension to the adjacent neocortical areas is in keeping with the recent staging of PD pathology as postulated by Braak et al. (2003). The atrophy in our NDPD sample is likely to be of functional relevance since the gray matter volume loss was accompanied by a significant reduction in attentional functions (Digit forward-WAIS) and a nearly significant ($p < 0.052$) progressive impairment in verbal learning (RAVLT). Mild cognitive impairment of this type, in conjunction with concomitant hippocampal and neocortical atrophy, might provide a presymptomatic marker for the risk of dementia.

The PDD group was characterized by a marked volumed decrease in the right fusiform gyrus, not observed in NDPD. Atrophic changes affecting this area in PDD have been reported in a cross-sectional study (Burton et al., 2004) but until now it has not been demonstrated longitudinally. The pathological changes in visual associative areas may contribute to the existence (Laatu et al., 2004; Mosimann et al., 2004) and progression (Levin et al., 1991) of visual impairment in cognitively deteriorated PD patients. Additionally, the hypoperfusion in fusiform gyrus has been associated with visual hallucinations in PD patients (Oishi et al., 2005). The clinical evaluation of our demented PD sample showed that at time of follow-up evaluation, nearly all our PDD patients (8/10) showed persistent complex visual hallucinations. We did not find any correlation between gray matter volume in temporo-occipital regions and fusiform gyrus and severity of VH measured by Neuropsychiatrc Inventory (NPI) in the cross-sectional or the follow-up period. However, it is likely that the lack of association can be explained by the low variability in NPI scores in our demented PD patients.

To fully understand the atrophic changes associated with VH it is necessary to analyze PD cases without dementia. Hence, the aim of our third study was to investigate regional

structural changes in non-demented patients with VH and to compare them with NDPD without VH and with NCs. Despite of our best attempts it was not possible to find perfectly matched PD patients with and without VH. The clinical assessment revealed that our hallucinating PD patients showed a higher Hamilton score and a more advanced stage of the illness (graded by H&Y scale) compared to non-VH PD patients. Although all hallucinating PD patients had MMSE score>24 and no patient fulfilled the DSM-IV-TR criteria for dementia, the general cognitive status evaluated by this cognitive screening test revealed significant differences between hallucinating patients, non-VH PD patients and NCs. The VBM MRI analysis revealed that hallucinating PD patients in comparison to non VH subjects showed a gray matter reduction affecting mainly insula and superior temporal gyrus (BA 38). Less severe gray matter losses were observed in parietal (BA 7) and frontal areas (BA 9, 10, 32). Within the PD+VH group the severity of hallucinations was associated with a higher grey matter reduction in the temporal pole. To study the structural brain changes associated with the presence of VH in PD patients independently of the influence of the mood score (Hamilton scale), severity of the illness (H&Y stage) and global cognitive performance (MMSE score) we performed and ANCOVA analysis including these variables as covariates. The analysis revealed that in comparison with NCs and non-VH PD subjects, hallucinating PD patients showed atrophic changes affecting lingual gyrus (BA 18) and superior parietal lobe (BA 7).

Our results provide the first in vivo evidence of gray matter reduction in hallucinating PD patients. The reductions were observed in visual areas such as lingual gyrus (BA 18) and superior parietal lobe (BA7). In human studies, the lingual gyrus has been implicated in the visual processing at different levels of complexity. Electrical cortical stimulation and lesional studies in humans show that this area has an important role in color perception, visual discrimination and visual attention (Lee et al., 2000; Gallant et al., 2000). In addition, fMRI studies showed that the lingual gyrus activation with face and picture recognition, (Stern et al., 1996; Clark et al., 1998; Gorno-Tempini et al., 1998, Wiser et al., 2000) and with encoding of complex visual scenes (Rombouts et al., 1999). In animal studies, no exact homology was found between higher order visual areas in monkeys and humans (Tootell et al., 2003; Orban et al., 2004). However, some authors claimed that there is a correspondence between lingual gyrus and fusiform gyrus and macaque area TEO (posterior inferior temporal cortex) (Dubowitz et al., 1997). This area maintains reciprocal connections with other visual areas such as V2, V3 and V4 (Gattass et al., 2005) and it has been implicated in the processing of color, faces and movement (Dubowitz et al., 2001). The dysfunction of lingual gyrus could lead to visuoperceptive impairment which has been pointed as important causal factor for the presence of VH (Barnes et al., 2003; Collerton et al., 2005).

In addition to atrophic changes of the lingual gyrus the hallucinating PD group was characterized by a consistent volume loss of superior parietal lobe. This area, corresponding to BA 7, receives visual input from PO (parieto-occipital areas), which receive inputs from V1, V2 and V3 (Rizzolatti and Matelli, 2003). Functional MRI studies have implicated the superior parietal lobe in visuo-spatial working memory (Newman et al., 2003), mental imagery (Lambert et al., 2004; Mechelli et al., 2004) and in conjunction with frontal lobe, with spatial and non spatial visual attention tasks (Kastner et al., 1999; Coull and Frith, 1998). Attentional deficits have been identified as an important factor in the causal models of VH (Collerton et al., 2005). Additionally, abnormalities in the brain pattern of attentional visual response have been reported in hallucinating patients, with greater frontal and subcortical activation and lower parietal and temporo-occipital activation than non-VH PD subjects (Stebbins et al., 2004). The volume reduction of the superior parietal lobe may lead to a disruption in the visual attention pathways leading to the incorporation of stereotyped form-objects into the visual field predisposing to VH (Collerton et al., 2005).

Several factors might contribute to the volume reduction in occipital and parietal regions. Firstly, it could have been caused by primary cortical changes, specifically LB pathology. Neuropathological post-mortem studies investigating brain changes associated with VH have reported a clear role of Lewy body changes. Harding et al, 2002a found that cases with VH have more Lewy bodies than those without hallucinations in the amygdala and parahippocampus, and cases presenting hallucinations early in the disease course have more LB within the temporal cortex (parahippocampus and inferior temporal cortex), indicating that LB pathology in medial temporal regions predisposes to hallucinations. Several patients in this study were demented and indeed the cortical changes may be related more to dementia than hallucinations per se. However, in a recent study with a well-matched sample of PD with and without hallucinations and without dementia, Lewy body densities were higher across the amygdala and the cortical areas studied in PD patients with VH. (Papapetropoulos et al., 2006, in press). Secondly, the atrophy might be precipitated by a functional disconnection caused by damage to subcortical structures. The compact zone of the substantia nigra gives off efferents to the striatum (Nakano, 2000) and there is evidence supporting the connection of the basal ganglia and visual association cortex. Specifically, studies in monkeys demonstrated that extensive destruction of the caudate head and dorsal portions of the striatum was followed by impairment in spatial processing. In contrast, lesions in the caudate tail and ventral portions of the striatum resulted in deficits in visual discrimination (Ruiz-Sanchez de Leon and Fernandez-Guinea, 2005 for a review). The loss of nigrostriatal neurons could cause deafferentation of cortico-striatal projections and lead to a dysfunction and neuronal death in cortical visual areas.

Our fourth and fifth study focused on cognitive differences between VH and non VH patients. The fourth study applied a cross-sectional, the fifth a longitudinal design. In cross-sectional comparison of hallucinating and non hallucinating PD patients, the VH group manifested a wide range of cognitive dysfunctions affecting several cognitive domains: verbal learning (Rey's auditory verbal learning test -RAVLT-), language (Boston Naming Test and Token Test), executive functions (semantic fluency) and visuoperceptive functions (evaluated by Benton Facial Recognition Test –BFRT- and Visual Form Discrimination Test –VFDT-). Only the neuropsychological deficits affecting verbal learning and visuoperceptive functions (BFRT) were independent of the stage of the PD, mood and general mental status measured by MMSE. At the follow-up evaluation 40% of the hallucinating PD patients fulfilled clinical criteria of dementia whereas no PD patients without VH or healthy subjects showed significant cognitive impairment. The cognitive domains in which the slope of decline was more severe in PD patients with VH were: visual memory for faces, followed by complex visual form discrimination, frontal functions, language and verbal memory.

The most pronounced decline on the follow-up evaluation of the VH group was observed on the Warrington Recognition Memory Test for faces. Interestingly, on the cross-sectional study there was no significant difference between PD patients with and without VH, although both PD groups performed worse than NCs. The impairment over time in visual memory could be related to progressive deficits involved on visual encoding and underlie the progressive extension of LB pathology in areas involved in face encoding and recognition memory such as medial temporal, fusiform and prefrontal regions (Rapsack, 2003 for a review). With respect to visuoperceptive functions we found that compared to non-hallucinating and NCs subjects, the VH PD sample showed impairment on Benton Facial Recognition Test in the cross-sectional as well as in the follow-up evaluation. However, while the scores on this visuoperceptive task did not deteriorate significantly over time, we observed a progressive impairment in complex visual form discrimination assessed by VFDT in VH patients. This task involves two visual functions: visuoperceptive (complex visual shape discrimination) and visuospatial (spatial localization) (Rao et al., 2003). Visuoperceptive impairment has been reported in hallucinating PD patients (Barnes et al., 2003) but the results for the visuospatial functions are contradictory. Barnes et al. (2003) did not observe greater deficits in PD patients with VH in the spatial perception subtest of VOSP (Visual object and space perception battery) compared to non hallucinating PD patients. In contrast, other authors found an association between hallucinatory experiences and difficulty estimating spatial relations (Davidsdottir et al., 2005) and impairment on visuo-spatial learning (Sinforiani et al., 2006, in press). The decline in Visual Form Discrimination Test in our hallucinating PD patients would suggest a progressive visuospatial decline in addition to visuoperceptive dysfunction.

The deficits in visuoperceptive functions and visual memory observed in our hallucinating sample support the current models of VH in which the combination of degraded visual information from the environment (Barnes et al., 2003; Collerton et al., 2005; Diederich et al., 2005) and failing visual memory (Barnes et al., 2003) are important causal factors for the occurrence of VH. The impairments observed in the higher order visual tests are not likely to be caused by a lower visual acuity because there were no differences between our VH and non VH groups. However, other primary visual deficits such as reduce contrast discrimination mediated by disruption of dopaminergic processes in the retina could interfere with the initial processing of the stimulus (Diederich et al., 2005 for a review). Turning to cortical abnormalities associated with visuoperceptive deficits, the impairment on BFRT in hallucinating patients is in keeping with neuropathological and neuroimaging findings suggesting dysfunctions of ventral visual pathway (Harding et al., 2002b; Stebbins et al., 2004; Oishi et al., 2005). However, the progressive decline in VFDT suggests a greater involvement of parieto-occipital regions. This hypothesis is supported by our structural MRI study that showed a significant gray matter reduction affecting parietal lobe (BA7) and lingual gyrus (BA18) in the hallucinating PD patients. Finally, the impairment over time in the VFDT could be associated with a progressive cholinergic depletion. Acetylcholine is an important neurotransmitter in the modulation of visuospatial functions (Wezenberg et al., 2005) and cortical cholinergic deficits have been pointed as neurobiochemical deficit associated with presence of VH in PD (Papapetropoulos and Mash, 2005 for a review). Moreover, several small-scale open-label trials have used cholinesterase inhibitors to treat VH in PDD patients with relative success (Papapetropoulos and Mash, 2005 for a review). It has been proposed that cortical acetylcholine normally enhances neuronal signal to noise ratio, and when the levels are reduced, irrelevant intrinsic sensory information, normally processed in parallel at subconscious level, enters conscious awareness in the form of VH (Diederich et al., 2005 for a review).

Nevertheless, our neuropsychological and neuroimaging results suggest that the occurrence of VH cannot be explained sufficiently by a visual dysfunction alone. In addition to the visual impairment, we observed in our hallucinating PD group cognitive deficits indicative of frontal and, more importantly, temporal dysfunction. Firstly, we found deficits in two language-related tests: the Token Test and Boston Naming Test. Although the performance on the Token Test can be influenced by visual attention impairment, recent evidence suggested that a primary syntactic dysfunction is not uncommon in PD patients if sufficiently sensitive test are being used (Ullmann et al., 1997; Grossman et al., 2000). Hovewer, neither attentional nor syntactic dysfunction is likely to explain the deficits observed on Boston Naming Test in the cross-sectional and longitudinal study, suggesting “a deterioration acces to semantic field”, as postulated by Frank et al. (1996). These neuropsychological results are in keeping with the findings of our MRI VBM study which documented a consistent gray matter reduction

affecting the anterior temporal superior gyrus (BA 38) in hallucinating PD patients compared to non VH patients and in PD patients with high severity of VH. This area has recently attracted a lot of attention because of its crucial role in the semantic integration (McClelland and Rogers, 2003 for a review). Interestingly, some previous studies have observed atrophic changes in BA 38 in PD patients, alghough the authors did not comment on its possible functional significance (Nagano-Saito et al., 2005; Summerfield et al., 2005). Secondly, we observed deficits affecting verbal memory. Impairment in tests of verbal memory performance in hallucinating PD patients has been reported by Grossi et al. (2005) and interpreted in terms of frontal dysfunction. However, in the follow-up evaluation of our hallucinating PD patients we detected, in addition to encoding deficits, impairment in verbal long term retention (RAVLT-Memory loss) and a progressive impairment in verbal recognition. These findings suggest a neural substrate extending beyond the fronto-striatal circuits (Higginson et al., 2003) and involving limbic and temporal cortex , as suggested by recent neuropathological studies (Harding et al., 2002a; Harding et al., 2002b; Papapetropoulos et al., 2005)

In conclusion, our results are in keeping with the current interpretation of the nature of cognitive deficits in PD. Since the emergence of the concept of subcortical dementia in the 1970-ies (Albert et al., 1974) the cognitive symptoms in PD were mainly interpreted in terms of fronto-striatal dysfunction. However, recent neuroimaging studies documented hypoperfusion affecting posterior cortical areas (Abe et al., 2003; Mito et al., 2005; Osaki et al., 2005) while neuropathological studies documented the presence of LB in temporal and parietal cortices (Harding et al., 2002a; Papapetropoulos 2006 in press). In this context our finding of temporal, parietal and occipital atrophy toghether with the deficits in visuospatial function and language stresses the importance of the posterior cortical structures in the explanation of dementia and VH in PD patients.

VI. CONCLUSIONS

VI. CONCLUSIONS

The objective of this thesis was to investigate cognitive deficits and structural brain changes associated with the presence of dementia and VH in PD. Before presenting the main conclusions, we would like to summarize briefly the main findings resulting from this thesis:

1. Our first volumetric MRI study, focusing on the evaluation of medial temporal regions, demonstrated hippocampal and amygdalar volume loss, which was more pronounced in demented than non-demented PD patients. Moreover, a significant relationship was found between verbal learning and amygdalar and hippocampal volume in both demented and non-demented PD patients. These findings underline the importance of both temporal medial structures in the cognitive deficits in PD patients.

2. The second investigation (follow-up study using VBM) showed that all PD patients irrespective of the presence or absence of dementia showed a decline of cognitive functions and progressive brain atrophy on longitudinal follow-up. However, the pattern of gray matter reduction was different in PDD and NDPD groups. The most marked gray matter reduction in NDPD subjects was found in the anterior cingulate gyrus and was accompanied by a significant reduction in attentional functions. In contrast, in the PDD group the greatest gray matter decrease involved visual associative areas (right fusiform gyrus). Both PD groups showed progressive hippocampal atrophy and gray matter reductions affecting temporo-occipital associative areas.

3. The third study, investigating regional structural changes in hallucinating and non hallucinating PD patients showed that visual hallucinations in NDPD patients were associated with gray matter volume reductions affecting cortical areas involved in visuoperceptive and attentional visual functions, specifically lingual gyrus (BA 18) and superior parietal lobe (BA 7). In addition, we observed in our hallucinating PD patients atrophic changes in posterior structures previously associated with PD dementia, such as left anterior superior temporal gyrus (BA 38) and left superior occipital lobe (BA 19).

4. Our fourth and fifth study focused on cognitive differences between VH and non VH patients. In terms of neuropsychological functions, hallucinating PD patients were characterized by visuoperceptive deficits and a progressive decline in visual memory and visuospatial functions. Moreover, VH patients were impaired in naming and verbal comprehension with the latter showing a further deterioration

on the follow-up evaluation. The cognitive decline in our PD patients with VH over 1 year period was marked and 40% of hallucinating PD patients who were not demented at initial evaluation fullfilled criteria for clinical dementia at the second evaluation. In contrast, a similar decline was not observed in PD patients without VH.

The main conclusions reached through our work are:

1. The pattern of cerebral atrophy found in demented PD and PD patients with VH extends well beyond the frontostriatal circuits traditionally described to be reponsible for cognitive symptoms in PD. Our findings of temporal, parietal and occipital atrophy stress the importance of the posterior cortical structures in the presence of cognitive impairment and VH in PD patients.

2. A close relationship was observed between the presence of hallucinations and progressive neuropsychological impairment, suggesting common neural mechanisms.

3. The cognitive impairments in hallucinating PD patients were observed in complex visual functions (visuoperceptive-visuospatial skills and visual memory) as well as semantic processing (such as interpretation of perceptual information). This neuropsychological pattern is in agreement with the atrophic changes found in our MRI study. The gray matter volume reductions involved not only secondary visual association areas but also tertiary areas implicated in the integration of semantic information.

VII. SUMMARY OF THE THESIS

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DEFICITS COGNITIVOS Y ALTERACIONES CEREBRALES ESTRUCTURALES ASOCIADAS A LA PRESENCIA DE DEMENCIA Y ALUCINACIONES VISUALES EN LA ENFERMEDAD DE PARKINSON.

Introducción

La enfermedad de Parkinson (EP) constituye uno de los trastornos neurodegenerativos más comunes en la edad avanzada (De Rijk et al., 1995). Aunque inicialmente se consideró un trastorno motor, hoy día es conocido que la enfermedad provoca una amplia variedad de sintomatología no motora como depresión, trastornos del sueño, síntomas neuropsiquiátricos y deterioro cognitivo. Los déficits neuropsicológicos asociados a la EP se presentan en funciones cognitivas tales como la atención, la memoria, funciones ejecutivas y funciones visuoespaciales (Goldman et al., 1998; Emre, 2003). Una parte de estos pacientes desarrollan un declive cognitivo progresivo evolucionando a franca demencia. La prevalencia estimada de demencia en estudios transversales va del 24 al 31% (Aarsland et al., 2005), aunque un reciente seguimiento longitudinal encontró una incidencia acumulada de aproximadamente el 80% (Aarsland et al., 2003). La presencia de demencia en la EP aumenta cuantitativamente las alteraciones cognitivas propias de esta enfermedad (Emre, 2003) observándose frecuentemente déficits relacionados con el funcionamiento de áreas corticales.

La presencia de alteraciones cognitivas en la EP ha motivado un gran número de estudios en la última década. Muchas de las investigaciones se han focalizado en la identificación de estructuras/áreas cerebrales relacionadas con la presencia de déficits neuropsicológicos y demencia. Mediante técnicas de neuroimagen estructural, se ha mostrado que pacientes con EP sin evidencia clínica de demencia muestran reducciones en estructuras subcorticales (caudado, putamen, tálamo), estructuras temporales mediales (hipocampo) y diversas áreas corticales temporales incluyendo el giro hipocampal, la ínsula y diversas áreas frontales (giro frontal inferior, medio superior y giro cingulado anterior) (Lisanby et al., 1993; Camicioli et al., 2003; Burton et al., 2004; Summerfield et al., 2005). Los estudios de neuroimagen estructural realizados en pacientes con EP y demencia han hallado que estos pacientes muestran una atrofia más pronunciada respecto a los controles sanos y enfermos de Parkinson no deteriorados cognitivamente viéndose afectadas con una especial intensidad estructuras temporales mediales (amígdala e hipocampo) y áreas corticales principalmente témporo-occipitales (Laakso et al., 1996; Burton et al., 2004; Summerfield et al., 2005). Respecto a estudios de neuroimagen que hayan evaluado la evolución de los cambios cerebrales a lo largo del tiempo en pacientes con EP con y sin deterioro cognitivo se disponen de pocos datos. A nuestro saber, sólo existe un estudio longitudinal realizado con una técnica de

corregistro serial de imágenes de resonancia magnética. Este estudio mostró que pacientes con EP no dementes presentaban una reducción de volumen cerebral anual superior a los sujetos sanos (Hu et al., 2001). Desafortunadamente, esta investigación no aportó datos sobre la localización cerebral precisa de los cambios cerebrales o el patrón de atrofia característico en pacientes con EP y demencia.

Al igual que los síntomas cognitivos en la EP, la presencia de síntomas neuropsiquiátricos y en especial la presencia de alucinaciones han despertado un gran interés recientemente. El estudio de estos pacientes ha revelado que la presencia de alucinaciones, las cuales son predominantemente de tipo visual, es uno de los factores más consistentemente asociado con el desarrollo y/o la presencia de demencia (Aarsland et al., 1999b). Los estudios neuropsicológicos llevados a cabo en pacientes con EP no demenciados con alucinaciones visuales (AV) han documentado que estos pacientes presentaban déficits visuoperceptivos, de memoria visual y una mayor tendencia a atribuir como percepciones externas imágenes que han sido creadas de una manera interna (Barnes et al., 2001; Barnes et al., 2003). Otros autores han hallado una asociación entre presencia de AV y déficits en fluencia verbal, memoria espacial a corto plazo y memoria lógica (Grossi et al., 2005; Sinforiani et al., 2006 in press). Todos los estudios cognitivos se han realizado desde una óptica transversal y ninguno ha aportado datos longitudinales sobre la progresión de estos déficits cognitivos y si estos evolucionan a un cuadro clínico final de demencia.

En la actualidad, existen pocos datos sobre la base neuroanatómica responsable de la presencia de alucinaciones y su relación con el desarrollo de demencia. Disponemos de datos de una investigación neuropatológica en la que se relacionó la densidad de cuerpos de Lewy en áreas temporales mediales y corteza inferior temporal con la presencia de AV en pacientes con EP la mayoría de los cuales presentaba demencia (Harding et al., 2002a). Estudios de neuroimagen funcional han hallado disfunciones frontales y de áreas posteriores visuales en pacientes con EP y AV (Nagano-Saito et al., 2004b; Stebbins et al., 2004; Oishi et al., 2005). Los estudios de neuroimagen estructural se han realizado en pacientes con EP que presentaban alucinaciones pero además estaban afectados de demencia imposibilitando la diferenciación de aquellos cambios relacionados con el padecimiento de alucinaciones de los asociados a la presencia de deterioro cognitivo (Nagano-Saito et al., 2005; Summerfield et al., 2005).

Objetivo de la tesis

El propósito general de esta tesis fue investigar el sustrato neuroanatómico asociado a la presencia de deterioro cognitivo y alucinaciones visuales en la enfermedad de Parkinson. Para

ello, se utilizaron diferentes instrumentos neuropsicológicos y técnicas de resonancia magnética cerebral, tanto desde una perspectiva transversal como longitudinal.

Los objetivos generales de los estudios que conforman esta tesis fueron los siguientes:

1. Estudio de los cambios estructurales cerebrales asociados a la presencia de demencia y alucinaciones visuales en la enfermedad de Parkinson
2. Caracterización cognitiva a través de un estudio transversal y de seguimiento a un grupo de pacientes con EP no dementes los cuales presentaban historia de alucinaciones visuales complejas.

Métodos

Esta tesis está compuesta de cinco estudios los cuales examinaron funciones cognitivas y características cerebrales estructurales en pacientes con EP utilizando para ello tests neuropsicológicos estandarizados y diferentes técnicas de resonancia magnética estructural. El primer y el segundo estudio evaluaron una muestra de pacientes con EP con y sin demencia. Los tres siguientes estudios fueron llevados a cabo en un grupo de pacientes con EP no dementes los cuales presentaban historia de AV complejas.

Nuestra primera investigación consistió en un estudio de resonancia magnética cerebral en el cual utilizamos una técnica volumétrica para cuantificar volúmenes hipocampales y amigdalares en pacientes con EP con y sin demencia. En dicha investigación se registró la ejecución en memoria verbal evaluada a través del Test de Aprendizaje Auditivo-Verbal de Rey a fin de correlacionarla con los datos de imagen cerebral. Nuestro segundo estudio comprendió la caracterización longitudinal de los cambios cerebrales estructurales y cognitivos en una muestra de pacientes con EP con y sin demencia. Se utilizó la técnica *"voxel-based-morphometry"* (VBM), que permite la cuantificación automática de densidad y volumen cerebral en imágenes de resonancia magnética cerebral sin la necesidad de fijar una región de evaluación a priori. La exploración cognitiva incluyó la evaluación de memoria verbal (Test de Aprendizaje Auditivo-verbal de Rey), funciones frontales (Subtests Dígitos Directos e Inversos -WAIS-III; fluencia fonética) y funciones visuo-constructivas (Subtest Cubos-WAIS-III).

A fin de responder si la presencia de alucinaciones está asociada a un patrón específico de deterioro cognitivo y reducciones de sustancia gris cerebral diseñamos tres estudios en los que se evaluó a un grupo de pacientes con EP no dementes que presentaban historia de AV complejas. El objetivo del tercer estudio consistió en la caracterización transversal de cambios cerebrales en estos pacientes utilizando de nuevo la técnica voxel-based-morphometry. En el

cuarto estudio se realizó un examen neuropsicológico de estos pacientes. La habilidad general intelectual fue evaluada a través de los subtests de Información y Semejanzas (WAIS-III). El lenguaje fue examinado a través de un test de comprensión verbal (Test de Token) y un test de denominación (Test de denominación verbal de Boston). Las funciones frontales fueron valoradas a través de una tarea de fluencia fonética y otra de fluencia semántica. Se utilizó una versión modificada del Test de aprendizaje Auditivo-Verbal de Rey para evaluar la memoria verbal. Las funciones visuoperceptivas fueron evaluadas utilizando el Test de Reconocimiento Facial de Benton y el Test de Discriminación visual de Benton. Finalmente, la memoria visual fue explorada usando el subtest de Memoria para caras perteneciente a la batería de Warrington (Warrington's Recognition Memory Test). El quinto estudio consistió en la evaluación longitudinal (1 año) de esta misma muestra mediante la bateria utilizada en la exploración inicial.

Resumen y discusión de los principales resultados obtenidos

Estudio 4.1 Reducciones volumétricas cerebrales en pacientes con EP con demencia

Nuestro primer estudio investigó volúmenes amigdalares e hipocampales en pacientes con EP con y sin demencia utilizando una técnica volumétrica de imagen de resonancia magnética cerebral. Pacientes con EP y demencia (EPD) mostraron una reducción amigdalar e hipocampal estadísticamente significativa (21% y 20% respectivamente) cuando fueron comparados con sujetos controles. Pacientes con EP no dementes (EPND) respecto a sujetos controles también presentaron disminuciones volumétricas en estas estructuras (amígdala, 11%; hipocampo, 10%), aunque dichas reducciones no alcanzaron la significación estadística. Tanto en el grupo de EP dementes como en el de los no dementes, los volúmenes amigdalares e hipocampales correlacionaron con la medida de aprendizaje verbal obtenida a través del test de Aprendizaje Verbal-Auditivo de Rey (RAVLT). Aunque investigaciones previas han hallado atrofia hipocampal en pacientes con EP y demencia (Riekkinen et al., 1998; Camicioli et al., 2003), nuestro estudio demuestra por primera vez una reducción amigdalar *"in vivo"*. De la misma manera, nuestra investigación ha documentado por primera vez una asociación entre aprendizaje verbal y volumen amigdalar en PD, dicha relación habia sido previamente establecida entre atrofia hipocampal y memoria verbal (Riekkinen et al., 1998; Camicioli et al., 2003). Nuestro datos volumétricos coinciden con los resultados de estudios volumétricos post-mortem en los que se han hallado reducciones significativas de la amígdala e hipocampo en pacientes con EP con y sin demencia (de la Monte et al., 1989; Cordato et al., 2000). Dichas reducciones podrían estar relacionadas con la presencia de cuerpos de Lewy (Lewy bodies, LB) (Mattila et al., 1999; Cordato et al., 2000; Harding et al., 2002b) y/o cambios tipo Alzheimer (Mattila et al., 1998).

Estudio 4.2. Evaluación longitudinal de cambios cerebrales morfológicos en pacientes con enfermedad de Parkinson con y sin demencia

Nuestro segundo estudio evaluó longitudinalmente cambios cognitivos y cerebrales estructurales (utilizando la técnica VBM) en un grupo de sujetos con EP con y sin demencia. Se observó que en la evaluación de seguimiento todos los pacientes con EP independientemente de la presencia o ausencia de demencia mostraron un declive cognitivo y progresiva atrofia cerebral. El patrón de cambios cerebrales fue diferente entre sujetos con EP con y sin demencia. La reducción de volumen de sustancia gris más severa en sujetos con EPND fue observada en el giro cingulado anterior. En el caso de pacientes con EPD, la disminución más marcada afectó a áreas asociativas visuales (giro fusiforme derecho). Ambos pacientes con EP mostraron atrofia progresiva hipocampal y reducción de sustancia gris en áreas asociativas témporo-occipitales.

Dicho estudio constituyó la primera investigación longitudinal utilizando la técnica de VBM en pacientes con EP con y sin demencia. El hallazgo de progresiva pérdida de volumen afectando al hipocampo en pacientes con EP con y sin demencia no había sido informado hasta ahora, aunque existían diferentes estudios transversales que mostraban atrofia de esta estructura en sujetos con EP con y sin demencia respecto a sujetos controles (Laakso et al., 1996; Riekkinen et al., 1998; Camicioli et al., 2003; Bruck et al., 2004, Nagano-Saito et al., 2005). De la misma manera, aunque déficits en perfusión cerebral utilizando la técnica de Tomografía de fotón único (SPECT) han sido hallados en regiones asociativas temporales y occipitales en pacientes con EP no dementes (Abe et al., 2003; Osaki et al., 2005), nuestro estudio es el primero en demostrar una atrofia progresiva en esas áreas.

Sorprendentemente, los EPND sufrieron una extensa progresiva pérdida de volumen cerebral que afectó a estructuras subcorticales (hipotálamo y núcleo accumbens), a hipocampo, ínsula, giro cingulado y regiones témporo-occipitales. La progresión de los cambios atróficos cerebrales, con implicación del mesocortex temporal y extensión de éstos a áreas neocorticales adyacentes estaría de acuerdo con el estadio neuropatológico descrito recientemente por Braak y cols. (2003). Dicha pérdida de sustancia gris cerebral en nuestros pacientes con EPND estuvo asociada a una disminución significativa de la atención (Dígitos directos-WAIS-III) y a un deterioro progresivo casi significativo de la memoria verbal ($p < 0.052$) (Test de Aprendizaje Auditivo-Verbal de Rey). Dicho declive intelectual unido a la concomitante atrofia neocortical e hipocampal podrían constituir marcadores presintomáticos para el riesgo de demencia.

El grupo de EPD presentó una disminución marcada de volumen cerebral afectando al giro fusiforme derecho la cual no fue observada en EPND. Cambios atróficos afectando a esta área han sido observados en pacientes con EPD (Burton et al., 2004), sin

embargo hasta ahora no se habían demostrado longitudinalmente. Estos cambios patológicos en áreas asociativas visuales podrían contribuir a la existencia (Laatu et al., 2004; Mosimann et al., 2004) y progresión (Levin et al, 1991) del deterioro de las funciones visuales complejas en EP. Por otro lado, la hipoperfusión en el giro fusiforme ha sido asociado con la presencia de AV en pacientes con EP (Oishi et al., 2005). La evaluación clínica de los pacientes con EP y demencia mostró que prácticamente la totalidad de ellos (8/10) presentaban AV complejas en el seguimiento. Sin embargo, no se observó una relación entre la severidad de las alucinaciones visuales medidas a través del cuestionario NPI (Neuropsychiatric Inventory) y volumen de sustancia gris en regiones temporales y occipitales ni en el momento inicial del estudio ni en la evaluación de seguimiento. Cabe la posibilidad que la falta de asociación esté explicada por una baja variabilidad en las puntuaciones del ítem "Alucinaciones" en los EPD.

Estudio 4.3. Atrofia regional cerebral en pacientes con EP afectados de alucinaciones visuales

A fin de estudiar los cambios atróficos asociados a la presencia de alucinaciones visuales es necesario estudiar pacientes con EP sin demencia pero con presencia de AV. Así que nuestro tercer estudio evaluó un grupo de pacientes con EP no dementes que presentaban historia de alucinaciones visuales complejas (EP+AV) y los comparó con una muestra de sujetos con EP que nunca había padecido este síntoma.

A pesar de que intentamos igualar a los grupos de pacientes con presencia de AV en las variables clínicas relevantes, la evaluación clínica mostró que los pacientes con EP+AV presentaban puntuaciones más elevadas en la escala de depresión de Hamilton, un rendimiento inferior en la prueba de screening mental MMSE y un estadio más avanzado de la enfermedad evaluado a través de la escala Hoehn and Yahr. El análisis de las imágenes de resonancia magnética cerebral a través de la técnica voxel-based morphometry mostró que los pacientes EP+AV respecto a los sujetos controles presentaban un patrón difuso de atrofia cerebral afectando especialmente la corteza frontal (BA 8, BA 10), temporal (BA 38, ínsula) y parietal (BA 7). La comparación entre pacientes con EP y AV respecto a sujetos con EP sin historia de este síntoma mostró que los EP+AV presentaban reducciones de sustancia gris cerebral localizadas principalmente en ínsula y giro temporal superior (BA 38). Reducciones volumétricas menos marcadas fueron también observadas en el lóbulo parietal superior (BA 7) y en áreas frontales (BA 9, 10, 32). En el grupo de EP+AV la severidad de las AV estuvo asociada con mayores reducciones de volumen de sustancia gris en el polo temporal. Con el propósito de estudiar los cambios cerebrales asociados a la presencia de AV independientemente de la influencia del estadio de la EP, rendimiento cognitivo global (MMSE) y humor depresivo (Hamilton) realizamos un análisis de las imágenes utilizando un modelo ANCOVA (Análisis de la covariancia) introduciendo aquéllas como covariables. Se observó que pacientes EP+AV respecto a sujetos con EP y controles sanos, mostraban reducciones de sustancia gris cerebral afectando principalmente a áreas cerebrales implicadas

en funciones visuales, concretamente a la corteza occipital (circunvolución lingual BA 18) y lóbulo parietal superior (BA 7).

Nuestros resultados constituyen la primera evidencia de reducciones de volumen de sustancia gris cerebral en pacientes con EP y AV. Las reducciones fueron consistentemente observadas en áreas visuales como la circunvolución lingual (BA 18) y el lóbulo parietal superior (BA7). En estudios con humanos la circunvolución lingual ha sido implicada en diversos procesos visuales de diferente nivel de complejidad. Estudios de estimulación eléctrica cerebral y estudios de lesiones, han asociado esta área con percepción del color, discriminación visual y atención (Lee et al., 2000; Gallant et al., 2000). Además, estudios de resonancia magnética funcional han relacionado la activación del giro lingual con el reconocimiento de pinturas y caras (Stern et al., 1996; Clark et al., 1998; Gorno-Tempini et al., 1998; Wiser et al., 2000) y con la codificación de escenas complejas (Rombouts et al., 1999). Respecto a estudios con animales, a pesar que no existe una correspondencia directa entre áreas visuales complejas entre macacos y humanos, algunos autores sostienen que habría una correspondencia entre el giro lingual y fusiforme en humanos y el área del macaco TEO (cortex temporal posterior inferior) (Kanwisher et al., 1997). Esta área mantiene conexiones recíprocas con otras áreas visuales tal como la V2, V3, V4 (Gattas et al., 2005). La disfunción del giro lingual podría conducir a déficits visuoperceptivos los que se han apuntado como uno de los factores causales en la presencia de AV (Barnes et al., 2003; Collerton et al., 2005).

Además de la atrofia afectando al giro lingual, también fue observada una consistente reducción de volumen de sustancia gris cerebral afectando al lóbulo parietal superior. Esta área corresponde al área de Brodmann 7, la cual recibe inputs de la área PO (parieto-occipital), quien a su vez recibe inputs del área V1, V2 y V3 (Rizzolati y Matelli, 2003). Estudios de resonancia magnética funcional han implicado esta área en funciones como memoria de trabajo visuoespacial (Newman et al., 2003), generación de imágenes mentales (Lamber et al., 2004; Mechelli et al., 2004), y en conjunción con el lóbulo frontal estaría relacionada con funciones atencionales visuales (Kastner et al., 1999; Coull and Frith, 1998). Déficits atencionales han sido identificados como importantes factores causales para la presencia de AV (Collerton et al., 2005). Además, alteraciones del patrón de respuesta cerebral en paradigmas de atención visual han sido documentadas en pacientes con EP+AV. Éstos pacientes respondían con mayor activación frontal y subcortical y menor activación parietal y témporo-occipital respecto a los sujetos con EP sin AV (Stebbins et al., 2004). Los cambios de tipo atróficos observados en el lóbulo parietal superior podrían conducir a una disrupción en las vías atencionales visuales conduciendo a la incorporación de proto-objetos en el campo visual y predisponiendo a la presencia de AV (Collerton et al., 2005).

Diferentes factores podrían contribuir a la reducción del volumen de sustancia gris cerebral en áreas occipitales y parietales. La primera causa, podría estar en relación con cambios corticales concretamente LB y neuritas de Lewy. Estudios neuropatológicos postmortem han asociado la existencia de AV en pacientes con EP a la presencia de patología de Lewy. Harding et al. (2002a) encontró que casos con EP y AV presentaban más LB en la amygdala y region parahipocampal respecto a aquellos sin alucinaciones. Los pacientes con AV de inicio temprano mostraron una mayor densidad de LB en el cortex temporal (region parahipocampal y cortex temporal inferior). La mayoria de los pacientes de este estudio eran dementes y de hecho los cambios corticales podrían estar mas relacionados con la demencia que con las AV per se. Sin embargo, un estudio reciente realizado en una muestra de pacientes con EP no demenciados, halló una mayor cantidad de LB en amygdala y áreas corticales (temporales, frontales y parietales) en aquellos pacientes con presencia de AV (Papapetropoulos et al., 2006 en prensa). Una segunda causa podría ser la desconexión funcional entre áreas visuales causada por daño a las estructuras subcorticales. La zona compacta de la sustancia negra mantiene conexiones con el estriado (Nakano, 2000), y hay evidencia sobre la existencia de conexiones entre ganglios basales y córtex de asociación visual. Concretamente, estudios en monos han demostrado que una destrucción extensa de la cabeza del caudado y de porciones dorsales del estriado fue seguida por un deterioro de la función visuoespacial. Por el contrario, lesiones de la cola del caudado y porciones ventrales del estriado resultaron en déficits visuoperceptivos (Ruiz-Sánchez de León y Fernández Guinea, 2005 para revisión). La pérdida de neuronas nigro-estriatales podría causar una desaferentización de las proyecciones córtico-estriatales y conducir a una disfunción y muerte neuronal en áreas corticales visuales.

Estudio 4.4. y 4.5. Déficits neuropsicológicos en pacientes con EP afectados de alucinaciones visuales

Nuestro cuarto y quinto estudio se centró en las diferencias cognitivas entre pacientes con EP con y sin AV. El cuarto estudio fue un estudio de tipo transversal, mientras que el quinto fue un diseño longitudinal. La comparación transversal entre alucinadores y no alucinadores reveló que los pacientes con AV mostraron diversos déficits cognitivos en aprendizaje verbal (Test de Aprendizaje Verbal-Auditivo de Rey), lenguaje (Test de denominación de Boston y Test de Token), funciones ejecutivas (fluencia semántica), y funciones visuoperceptivas y visuoespaciales evaluadas a través del Test de Reconocimiento Facial de Benton -BFRT- y el Test de discriminación de la forma visual de Benton –VFDT-). Sólo los déficits neuropsicológicos en aprendizaje verbal y funciones visuoperceptivas (examinados a través del BFRT) fueron independientes respecto al estadio de la enfermedad (Hoehn and Yahr), humor depresivo (puntuación en Hamilton) y status mental global (puntuación en MMSE). En la evaluación de seguimiento, 40% de los pacientes con EP+AV cumplieron criterios clínicos de demencia mientras que ningún paciente con EP sin AV o sujeto control mostró un deterioro cognitivo significativo. El declive cognitivo más severo en los pacientes con

EP+AV fue observado en memoria visual para caras. Otros dominios en los que se apreció un deterioro significativo fueron discriminación visual compleja, funciones frontales, lenguaje y memoria verbal.

La observación del declive en memoria visual para caras en pacientes con EP+AV constituyó un dato interesante puesto que en nuestro estudio transversal no hubieron diferencias significativas en dicha función entre pacientes con EP con y sin AV. El deterioro en memoria visual en los pacientes alucinadores podría ser secundario a déficits progresivos en la codificación visual y estar relacionados con patología de tipo LB en áreas implicadas en la codificación y reconocimiento de caras tales como regiones temporales mediales, giro fusiforme y áreas prefrontales (Rapsack, 2003 para revisión). En relación a las funciones visuoperceptivas, observamos que pacientes con EP y AV obtuvieron resultados inferiores en el Test de Reconocimiento Facial de Benton cuando fueron comparados con sujetos controles y EP sin AV. Sin embargo, mientras los resultados en este test no cambiaron significativamente en la evaluación longitudinal, se observó un deterioro significativo en una tarea de discriminación de formas visuales complejas (VFDT). Esta tarea implica dos funciones, visuoperceptiva (discriminación de formas) y visuoespacial (localización espacial) (Rao et al., 2003). Déficits en funciones visuoperceptivas han sido documentados en pacientes con EP+AV (Barnes et al., 2003), pero existen resultados contradictorios respecto a las funciones visuoespaciales. Barnes et al. (2003) no encontró mayores déficits en pacientes con EP+AV en los subtests de percepción espacial de la batería VOSP (Visual object and space perception battery) respecto a pacientes sin este síntoma. De manera opuesta, otros autores encuentran que los pacientes con EP+AV manifiestan más dificultades para estimar relaciones espaciales (Davidsdottir et al., 2005) y muestran deterioro en el aprendizaje visuoespacial (Sinforiani et al., 2006 en prensa). El deterioro en el test de discriminación visual en nuestros pacientes con EP+AV sugiere un progresivo declive visuoespacial además de una disfunción visuoperceptiva.

Los déficits en funciones visuoperceptivas y de memoria visual observados en nuestro grupo de sujetos con EP y AV coinciden con los actuales modelos teóricos sobre presencia de AV. Estos apuntan a la combinación de un input visual degradado y fallos de memoria visual como factores importantes para la existencia de AV (Barnes et al., 2003; Collerton et al., 2005; Diederich et al., 2005). El deterioro observado en nuestros pacientes con EP+AV en los test de funciones visuales complejas no está probablemente causado por una baja agudeza visual, puesto que no habían diferencias en dicha variable entre pacientes con EP con y sin alucinaciones. Sin embargo, otros déficits visuales primarios como disminución en la sensibilidad al contraste secundaria a una disrupción de los procesos dopaminérgicos en la retina podrían interferir con el procesamiento inicial del estímulo visual (Diederich et al., 2005 para revisión). En relación con el funcionamiento de áreas corticales visuales, los

déficits visuoperceptivos observados en el Test de Reconocimiento Facial de Benton estarían de acuerdo con los recientes hallazgos de neuroimagen y neuropatológicos que sugieren disfunciones en la vía visual ventral en pacientes con EP y AV (Harding et al., 2002a; Stebbins et al., 2004; Oishi et al., 2005). Por el contrario, el deterioro progresivo en el Test de Discriminación Visual de Formas implicaría disfunciones de regiones parieto-occipitales. Esta hipótesis estaría apoyada por nuestros datos de resonancia magnética estructural, los que muestran una significativa reducción de volumen cerebral en el lóbulo parietal superior (BA 7) y en el giro lingual (BA 18) en los pacientes con EP y AV. Finalmente, el deterioro en el VFDT también podría estar asociado a una reducción colinérgica progresiva. La acetilcolina es un importante neurotransmisor en la modulación de las funciones visuoespaciales (Wenzenber et al., 2005) y déficits corticales colinérgicos han sido apuntados como uno de los déficits neuroquímicos asociados a la presencia de AV en pacientes con EP (Papapetropoulos y Mash, 2005 para revisión). Además, diversos ensayos clínicos han mostrado la utilidad de los inhibidores de la colinesterasa para tratar AV en pacientes con EP y demencia (Papapetropoulos et al., 2005 para revisión). Se ha propuesto que la acetilcolina cortical aumenta la ratio señal neuronal/ruido, y cuando los niveles están reducidos, información irrelevante intrínseca sensorial, normalmente procesada en paralelo a nivel subconsciente, entraría en la consciencia en forma de AV (Diederich et al., 2005 para revisión).

Sin embargo, nuestros resultados de neuroimagen y neuropsicológicos sugieren que la presencia de AV no puede ser suficientemente explicada por una disfunción visual aislada. Además del deterioro en funciones visuales complejas, nuestros pacientes con alucinaciones presentaron signos de deterioro indicativo de disfunción frontal, y más marcadamente de disfunción temporal. En primer lugar, fueron observados déficits en dos test de lenguaje: Test de Token y Test de denominación de Boston. Aunque la ejecución en el Test de Token podría estar influenciada por factores atencionales, investigaciones recientes encuentran disfunciones sintácticas en la EP (Ullmann et al., 1997; Grossman et al., 2000). Sin embargo, ni funciones atencionales ni sintácticas podrían explicar los déficits observados en el Test de denominación de Boston, los que sugerirían un "deterioro en el acceso al campo semántico" tal y como ha sido postulado por Frank y colaboradores (1996). Esa hipótesis estaría apoyada por nuestros resultados de neuroimagen los que muestran una consistente reducción de sustancia gris afectando al giro superior temporal (BA 38) en pacientes con EP+AV respecto a sujetos con EP sin este síntoma, y en aquellos EP+AV con una mayor gravedad de este síntoma. Esta área ha despertado recientemente interés debido a su rol crucial en la integración semántica (McClelland y Rogers, 2003 para revisión). Es interesante que estudios previos han observado cambios atróficos en BA 38, aunque los autores no han comentado la posible relevancia funcional de este hallazgo (Nagano-Saito et al., 2005; Summerfield et al., 2005). Finalmente, fueron también observados déficits en aprendizaje verbal. El deterioro de esta función se ha

mostrado previamente en pacientes con EP y AV aunque ha sido explicado exclusivamente en términos de disfunción frontal. Sin embargo, en nuestro estudio longitudinal, fueron hallados déficits en memoria verbal demorada y un progresivo declive en reconocimiento verbal. Esos hallazgos sugieren la implicación del córtex límbico y temporal más allá de la contribución de circuitos fronto-estriatales (Higginson et al., 2003).

En conclusion, los resultados que derivan de esta tesis están de acuerdo con la actual interpretación de los déficits cognitivos en la EP. Desde la definición de demencia subcortical en los años 70 por Albert y cols. (1974), los déficits cognitivos en la EP han sido interpretados básicamente en términos de disfunción fronto-estriatal. Sin embargo, estudios recientes de neuroimagen han documentado hipoperfusión en áreas corticales posteriores (Abe et al, 2003; Mito et al., 2005; Osaka et al., 2005) y estudios neuropatológicos han hallado presencia de LB en áreas temporales y parietales (Harding et al., 2002a; Papapetropoulos et al., 2006 en prensa). En este contexto, nuestros hallazgos de atrofia temporal, parietal y occipital junto con déficits en funciones visuoespaciales y lenguaje enfatizan la importancia de estructuras corticales posteriores en la explicación de la demencia y la presencia de AV en la EP.

Conclusiones

El objetivo de esta tesis fue la investigación de los déficits cognitivos y cambios estructurales cerebrales asociados a la presencia de demencia y alucinaciones en la enfermedad de Parkinson. Antes de presentar las principales conclusiones, resumimos brevemente los principales hallazgos resultantes de esta tesis.

1. Nuestro primer estudio de neuroimagen estructural utilizando una técnica volumétrica focalizado en la evaluación de regiones cerebrales temporales mediales, demostró una reducción hipocampal y amigdalar, que fue más pronunciada en enfermos con EP con demencia respecto a aquellos sin demencia. Además, fue hallada una asociación estadísticamente significativa entre el aprendizaje verbal y los volúmenes amigdalares e hipocampales en pacientes con EP con y sin demencia. Esos hallazgos enfatizan la importancia de dichas estructuras en los déficits cognitivos presentes en la EP.

2. La segunda investigación (estudio VBM, longitudinal) mostró que todos los pacientes con EP independientemente de la presencia o ausencia de demencia mostraron un declive en las funciones cognitivas y una atrofia cerebral progresiva. Sin embargo, el patrón de reducción de volumen cerebral fue diferente entre el grupo de dementes y no dementes. La reducción de volumen cerebral más marcada en los pacientes con EP sin demencia fue encontrada en el giro cingulado anterior. Esta reducción se acompañó de

un deterioro significativo en las funciones atencionales. Por otro lado, en el grupo de EP con demencia, las reducciones más marcadas implicaron áreas asociativas visuales (giro fusiforme derecho). Ambos grupos con EP mostraron atrofia hipocampal progresiva y reducciones de volumen cerebral afectando a las áreas asociativas témporo-occipitales.

3. El tercer estudio investigó cambios estructurales cerebrales en pacientes con EP con y sin historia de alucinaciones visuales. Dicha investigación evidenció que la presencia de este síntoma estuvo asociada a un patrón de reducciones de volumen cerebral en áreas implicadas en funciones visuales atencionales y visuoperceptivas, concretamente giro lingual (BA 18) y lóbulo parietal superior (BA 7). Además en dichos pacientes fueron observados cambios atróficos en estructuras cerebrales posteriores previamente asociadas a la presencia de demencia en PD, específicamente en el giro temporal anterior superior izquierdo (BA 38) y en el lóbulo occipital superior izquierdo (BA 19).

4. Nuestro cuarto y quinto estudio se centraron en investigar las diferencias cognitivas en pacientes con EP con y sin historia de alucinaciones visuales. Los pacientes con alucinaciones visuales estuvieron caracterizados por déficits visuperceptivos y por un declive progresivo en funciones visuoespaciales y de memoria visual. Además, los pacientes con alucinaciones visuales presentaron un deterioro en denominación y comprensión verbal evidenciándose en esta última función un nivel de ejecución inferior en el estudio de seguimiento. El deterioro cognitivo al año del estudio inicial en este grupo de pacientes con EP y alucinaciones visuales fue significativo, y 40% de estos pacientes los cuales no presentaban demencia en el estudio inicial cumplieron criterios clínicos de demencia en la evaluación de seguimiento. Por el contrario, no fue observado un deterioro cognitivo similar en los pacientes con EP sin alucinaciones visuales.

Las principales conclusiones derivadas de este trabajo son:

1. El patrón de cambios estructurales cerebrales en pacientes con EP y demencia se extiende más allá de los circuitos fronto-estriatales descritos como responsables de los déficits cognitivos de la EP. Nuestros hallazgos de atrofia temporal, parietal y occipital enfatizan la importancia de las estructuras corticales posteriores en la explicación de la presencia de deterioro cognitivo y alucinaciones visuales en la EP.

2. Se observó una estrecha relación entre presencia de alucinaciones visuales y deterioro cognitivo progresivo sugiriendo mecanismos neuronales comunes.

3. El deterioro cognitivo en los pacientes con alucinaciones visuales fue observado en funciones visuales complejas y de procesamiento semántico (interpretación perceptual de la información). Este patrón neuropsicológico estaría de acuerdo con nuestros hallazgos de resonancia magnética estructural en los cuales se evidenciaron cambios cerebrales de tipo atrófico en áreas visuales secundarias y áreas terciarias implicadas éstas últimas en la integración de la información semántica.

II. REFERENCES

VII. REFERENCES

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VIII. PUBLICATIONS

Movement Disorders
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Amygdalar and Hippocampal MRI Volumetric Reductions in Parkinson's Disease With Dementia

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Abstract: Parkinson's disease (PD) involves neuropathological changes in the limbic system that lead to neuronal loss and volumetric reductions of several nuclei. We investigated possible volumetric reductions of the amygdala and hippocampus associated to PD. We carried out magnetic resonance imaging (MRI) volumetric studies in 16 patients with PD and dementia (PDD), 16 patients with PD without dementia (PD), and 16 healthy subjects. The general analysis of variance (ANOVA) showed a significant group effect (for the amygdala, $P = 0.01$; for the hippocampus, $P = 0.005$). A post-hoc test demonstrated that the differences were due to PDD and control group comparisons for the amygdala ($P = 0.008$) and for the hippocampus ($P = 0.004$). In nondemented PD subjects, we observed an 11% reduction in the amygdala and a 10% reduction in the hippocampus compared with that in controls. In summary, demented PD patients have clear amygdalar and hippocampal atrophy that remains statistically significant after controlling for global cerebral atrophy. Nondemented PD patients also showed a degree of volumetric reduction in these structures although the differences were not statistically significant. © 2005 Movement Disorder Society

Key words: Parkinson's disease; dementia; amygdala; hippocampus; MRI volumetry

Parkinson's disease (PD) is a widespread degenerative illness affecting the central, peripheral, and enteric nervous systems. The underlying pathological process progresses slowly but relentlessly and involves multiple neuronal systems. The disease is the consequence of changes in the neuronal cytoskeleton developing in particularly susceptible types of nerve cells. Components of the limbic and motor systems have been shown to be particularly vulnerable to degeneration. The most frequently affected limbic sites include the entorhinal region, the second sector of Ammon's horn, and important subnuclei of the amygdala.[1] Neuropathological investigations have found amygdalar and hippocampal degeneration in PD patients with dementia.[2,3] In addition, the degree of cognitive impairment correlates with the density of Lewy neurites in the CA2 hippocampal field, raising the possibility that the disruption of the connection between the dentate gyrus, entorhinal cortex, septal nuclei, hypothalamus, and the CA1 field contributes to dementia in PD.[4] PD patients without dementia exhibit similar pathological changes in the hippocampus and the amygdala, including atrophy and Lewy body formation. In one study, total amygdalar volume was reduced by 20%, due to neuronal loss and neuronal shrinkage.[5]

Magnetic resonance (MR) volumetric analysis allows quantification in vivo of regional cerebral atrophy. Reductions in hippocampal volume are observed in PD patients with and without dementia.[6,7] To our knowledge, amygdalar volume has not been quantified in vivo in PD patients. This study investigated possible amygdalar and

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TABLE 1. *Demographic, clinical, and neuropsychological variables*

Parameter	Controls (n = 16)	PD (n = 16)	PDD (n = 16)	χ^2/F statistic	*P*
Age (yr)	71.31 ± 7.5	72.87 ± 4.4	70.06 ± 7.9	1.46	0.482
Gender (men/women)	5/11	6/10	5/11	0.19	0.91
Education (yr)	10.19 ± 5.2	9.01 ± 5.2	6.62 ± 4.5	2.09	0.135
Hamilton depression	0.69 ± 1.2	1.67 ± 2.1	2.94 ± 4.6	3.44	0.179
Disease evolution (yr)	—	11.25 ± 6.8	13.33 ± 5.3	2.59	0.108
Hoehn and Yahr	—	2.69 ± 0.68	3.37 ± 1.1	4.11	0.042[a]
UPDRS III	—	25.64 ± 13.5	36.00 ± 13.2	4.19	0.051
MMSE	29.37 ± 1.1	28.62 ± 1.0	17.33 ± 5.5	33.52	$-< 0.0005$[a,b,c]
RAVLT learning	36.69 ± 6.0	34.87 ± 6.46	15.14 ± 7.96	45.08	< 0.0005[a,c]
RAVLT forgetting	3.05 ± 3.97	7.93 ± 6.19	15.11 ± 12.2	12.59	0.002[a,b,c]

[a]Differences between PD and PDD.
[b]Differences between controls and PD.
[c]Differences between controls and PDD.
PD, Parkinson's disease; PDD, Parkinson's disease with dementia; UPDRS, Unified Parkinson's Disease Rating Scale; MMSE, Mini-Mental State Examination; RAVLT, Rey Auditory-Verbal Learning Test.

hippocampal reductions in PD patients with and without dementia and related these structural changes to global cognitive status and memory performance.

SUBJECTS AND METHODS

Subjects

Forty-eight subjects between 54 and 84 years of age participated in the study. The patient sample comprised 16 subjects with an initial diagnosis of idiopathic PD who in later years met criteria for dementia and 16 PD patients who did not. Patients were recruited from an outpatient movement disorders clinic (PD and Movement Disorders Unit, Department of Neurology, Hospital Clinic, Barcelona). Some of these patients had participated in previous studies.[8,9] The healthy control group consisted of 16 subjects matched to patients by age and education without any history of psychiatric or neurological disorder.

The diagnosis of PD was made using UK Brain Bank Criteria.[10] Dementia was assessed using two standardized instruments: the DSM-IV, and the Mini-Mental State Examination (MMSE).[11] Patients with MMSE scores below 23 and with DSM-IV criteria for dementia were considered as PDD. Clinical and demographic characteristics of the sample are displayed in Table 1.

All subjects were neuropsychologically assessed using Folstein's Mini-Mental State Examination to evaluate global cognitive dysfunctions and a modified version of the Rey Auditory-Verbal Learning Test (RAVLT)[12] to assess memory functions. For the RAVLT we recorded learning (the sum of 1–5 presentations), and forgetting (% of memory loss after 20 minutes of interference).

The study was approved by the local ethics committee. Written informed consent was obtained from the patients or their caregiver after full explanation of the procedures involved in the study.

Magnetic Resonance Imaging Acquisition and Volumetric Analysis

Magnetic resonance imaging (MRI) was obtained in all subjects using a 1.5T GE Nvi/Cvi 8.4 machine (GE, Milwaukee, WI). A strict imaging protocol was used, including a 3-D IR Prep SPGR sequence of the entire brain in the axial plane, and the following parameters: repetition time (TR) = 17; echo time (TE) = 5; inversion time (TI) = 300; 1.5 mm thickness; field of view (FOV) = 24 × 24; 256 × 256; and 1 number of excitations (NEX).

Images were displayed and measured using MRIcro (Nottingham, UK) software. MRIcro permits the manual tracing of a region-of-interest (ROI) and gives an automatic estimate of its volume. Measurements were carried out by an investigator blind to the patients' group (PDD, PD, or control). All structures were measured twice to obtain intrarater reliability. The values reported represent the mean of these two measurements. The brain structures measured included hippocampus and amygdala. Estimations of global gray and white matter volume and cerebrospinal fluid (CSF) volume were also obtained after the automatic brain segmentation procedure carried out by statistical parametric mapping (SPM).

Hippocampus.

The hippocampus was measured as described previously.[13] (A detailed description is available online at http://pni.med.jhu.edu/). Briefly, the procedure is as follows: (1) locate the fornix in the coronal slice; (2) follow the gray matter of the hippocampus posteriorly until it

TABLE 2. *MRI volumetric results*

Region	Control (n = 16)	PD (n = 16)	PDD (n = 16)	*F*	*P**
Amygdala[a]	2,485.04 ± 397.69	2,231.31 ± 476.86	2,043.68 ± 540.06	3.48	0.039
Hippocampus[a]	5,571.04 ± 767.02	5,130.48 ± 839.58	4,638.27 ± 993.79	4.58	0.015
Amygdala corrected[b]	1.60 ± 0.28	1.42 ± 0.34	1.26 ± 0.27	5.10	0.010
Hippocampus corrected[b]	3.61 ± 0.71	3.24 ± 0.38	2.89 ± 0.61	6.0	0.005

*Differences between controls and PDD.
[a]Raw volumes (mm^3).
[b]Measures corrected by total brain volume (structure volume in mm^3/total brain volume in mm^3) × 1,000.
PD, Parkinson's disease; PDD, Parkinson's disease with dementia.

can no longer be seen; (3) begin tracing from the most posterior point, including the subiculum, moving anteriorly until the hippocampus can no longer be distinguished from the amygdala; and (4) perform a correction in the sagittal plane. Briefly, the lateral boundary of the hippocampus was set at the inferior temporal horn of the lateral ventricle or temporal lobe white matter. Boundaries of the hippocampus were traced manually, with the white matter of the parahippocampal gyrus as the inferior boundary, the alveus or lateral ventricle as the superior boundary, and the amygdala as the anterior boundary. In slices in which a clear demarcation between the hippocampus and amygdala was not seen, the gray matter superior to the lateral ventricle was not sampled.

Amygdala.

It is often difficult to distinguish the amygdala from the surrounding gray matter, and various protocols have been described to estimate amygdalar volume. We manually traced the amygdala posteriorly–inferiorly in the coronal plane, with subsequent correction in sagittal and axial views. Hippocampus and amygdala were separated through visualization of the alveus. The amygdala was bordered medially by the entorhinal cortex and gray matter of the parahippocampal gyrus, and laterally by the temporal horn of the lateral ventricle and temporal lobe white matter. The choroid plexus was excluded.

Intrarater reliability for all measures was high, with κ scores for all structures of more than 0.90. The ROIs measured were corrected by the intracranial volume (sum of gray matter, white matter, and CSF) and multiplied by 10^3. Statistical analysis was carried out using SPSS v11 (SPDD, Chicago, IL). For normally distributed variables with homogeneity of variance, we used analysis of variance (ANOVA) and post-hoc Bonferroni test. For non-normally distributed variables or in the case of inhomogeneity of variance, we used the nonparametric Kruskal-Wallis test, which provides a χ^2 statistic.

RESULTS

The demographic variables (age, gender, and years of education) of samples were similar. Clinical variables in the two patient groups did not differ statistically in years of disease evolution, scores on Scale III of the Unified Parkinson's Disease Rating Scale (UPDRS)[14] or depression, although the PDD group showed a more advanced stage of illness on the Hoehn and Yahr scale.[15] Neuropsychological testing showed significant differences between the groups in MMSE and RAVLT scores (see Table 1).

Regarding the morphometric analysis, the PD group showed decreased volume in both structures (amygdala, 11%; hippocampus, 10%), although the reductions did not reach statistical significance. Compared with that in controls, demented patients showed an amygdalar volume reduction of 21% and a hippocampal volume reduction of 20%.

ANOVA showed a significant group effect for both direct and corrected measures (see Table 2). Post-hoc analysis revealed significant differences in corrected amygdala ($P = 0.008$) and corrected hippocampus ($P = 0.004$) between the PDD and control group. In nondemented patients, both structures had values between those of demented patients and controls (see Fig. 1).

The MMSE correlated with the amygdala ($r = 0.39$; $P < 0.01$) and hippocampus ($r = 0.35$; $P < 0.01$) in the whole sample. Memory also showed significant correlations with both structures. RAVLT learning correlated with amygdala ($r = 0.38$; $P < 0.01$) and hippocampus ($r = 0.54$; $P < 0.01$). In demented patients we found a significant correlation between RAVLT delayed recall and hippocampal volume.

Because PDD patients had longer disease duration than PD patients did (by around 2 years), we carried out correlations of this variable with volumetric MRI data. No significant correlations were found for either the whole sample or the separate groups.

DISCUSSION

In agreement with previous postmortem volumetric studies,[2,3] our results showed significant reductions in the amygdala and hippocampus in PD patients with dementia. These reductions may reflect neuropathological changes in these structures.[16,17]

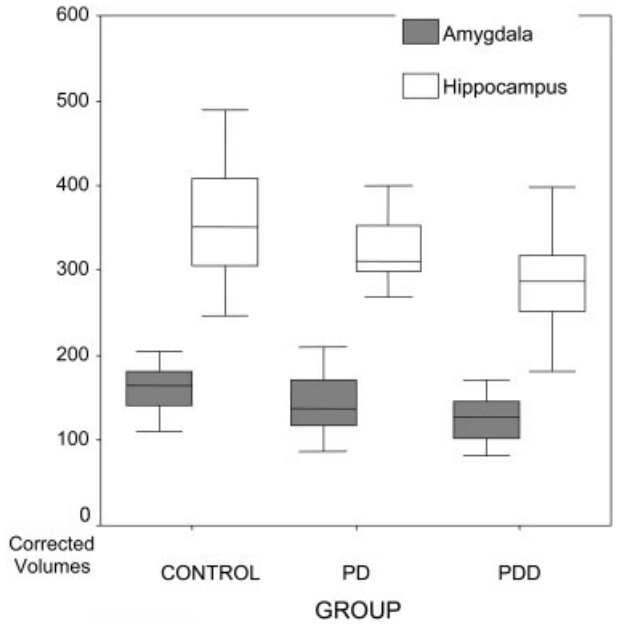

FIG. 1. Box plot showing amygdalar and hippocampal ratios of the groups. PD, Parkinson's disease; PDD, Parkinson's disease with dementia.

We provide the first in vivo evidence of a reduction in amygdalar volume in demented patients with PD. Atrophy of the amygdala is subtle and is not detected easily either visually or using quantitative single-section area analysis.[5] Three-dimensional volumetric postmortem studies of regional brain atrophy in demented PD have reported amygdalar reductions of 18%[2] and 29%[3] compared with that in age-matched normal controls. Our results in PDD patients were similar (a 21% reduction).

Only one volumetric study has been published on postmortem amygdalar atrophy in nondemented patients. In a well-selected sample of nondemented, levodopa-responsive PD, a neuropathological study revealed a 20% global amygdalar volume reduction compared with that in controls.[5] In our sample, the volume reduction was only 10% compared to the control sample. The low level of reduction in our study in comparison with postmortem studies could be attributed to years of evolution from onset, and it is possible that amygdalar degeneration occurs during the course of the disease.[18,19] The amygdala is a cerebral structure involved in emotional processes including facial perception and expression of emotional states such as anger or fear.[20] Hypomimia is one of the signs of PD that develops during the disease process, but is not usually a presenting symptom. It has been well documented that PD patients exhibit marked deficits in recognition of emotional expression of faces[21] and affective prosody.[22] Moreover, dopaminergic therapy is able to correct the abnormal pattern of cerebral activation observed by functional MRI (fMRI) during recognition of facial emotions in PD.[23]

We also observed hippocampal volumetric loss in demented and nondemented Parkinson's patients compared with that in controls. Hippocampal volumetric atrophy in PD has been reported on previously using MRI[6,7] and in postmortem studies.[2,3] Histopathological studies have described Lewy bodies and Alzheimer's-type changes in the hippocampus in demented PD patients, both of which probably contribute to cognitive loss.[24,25] Lewy bodies and Lewy neurites are observed mainly in the CA2 and CA3 fields and fibrillar tangles in the CA1 sector of the hippocampus.[4,17] Demented PD patients have increased neurofibrillary tangles in the CA1 sector of the hippocampus.[24]

Churchyard and Lees[4] stressed the impact of hippocampal degeneration on the process of dementia in PD. These authors suggest that the pathological process associated with Lewy neurite formation in CA2 disrupts the hippocampal function, and hence cognition, by interfering with inputs to the CA1 field. In that study, Lewy neurite density in the CA2 field of the hippocampus was related to the severity of dementia.

In a previous study using voxel-based morphometry (VBM) in the same sample of demented patients,[9] we also observed hippocampal atrophy in PDD compared with that in controls, but we did not obtain significant results for the amygdala. These discrepancies were also observed by Good and colleagues[26] in a study with Alzheimer's disease patients. In their study, the ROI analyses seemed more sensitive to volume loss in the amygdala whereas VBM seemed more sensitive to regional hippocampal volume loss.

Although MRI volumetric studies are presently of limited clinical utility for the individual diagnosis of dementia, they may help to increase our knowledge of the in vivo neuropathological bases of cognitive and emotional deficits associated with PD.

In summary, we found amygdalar and hippocampal volume reductions in PD patients with dementia. MRI is sensitive to the limbic involvement in PD, and limbic atrophy seems to present a continuum between demented and nondemented patients.

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ORIGINAL COMMUNICATION

Longitudinal evaluation of cerebral morphological changes in Parkinson's disease with and without dementia

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Abstract *Objective* To investigate the pattern of brain atrophy across time in a sample of Parkinson's disease (PD) patients with and without dementia using voxel-based morphometry (VBM) analysis. *Methods* The initial sample comprised thirteen non-demented PD patients and sixteen demented patients. Longitudinal cognitive assessment and structural MRI were performed. The mean follow-up period was 25 months (SD = 5.2). From this initial group, eight PD patients with dementia (5 men and 3 women) and eleven PD patients without dementia (7 men and 4 women) were reevaluated. MRI 3D structural images were acquired and analyzed by means of the optimized VBM procedure with Statistical Parametric Mapping (SPM2). *Results* VBM analysis showed a progressive grey matter volume decrease in patients with PD without dementia in limbic, paralimbic and neocortical associative temporo-occipital regions. In patients with dementia the loss mainly involved neocortical regions. *Conclusion* VBM revealed a significant loss of grey matter volume in PD patients with and without dementia with disease progression. The decrease in limbic and paralimbic regions is widespread in non-demented patients. Neocortical volume reduction is the most relevant finding in patients with dementia. This suggests that the neocortex is a substrate for dementia in Parkinson disease.

Key words Parkinson's disease · dementia · MRI · voxel-based morphometry · longitudinal study

Introduction

In the last few years cognitive impairment of variable degrees has been increasingly recognized in patients with Parkinson's disease (PD) [16, 22]. There have been several cross-sectional studies in which prevalence of dementia in PD was reported to range from 18–41 % [1, 35, 38], although a recent longitudinal study in a community-based population has suggested a cumulative incidence of about 80 % [2].

The pathological findings observed in post mortem studies of PD with dementia (PDD) are Lewy body-type degeneration in limbic and cerebral cortical areas and Alzheimer-type changes of variable degree. Studies using alpha-synuclein antibodies to identify Lewy pathology support the view that dementia is closely correlated with the presence and density of neocortical and limbic Lewy bodies and neurites [4, 10, 27, 37]. Other studies have also suggested that the coincident Alzheimer-type pathology is an important contributor to dementia in PD [8, 14].

Structural imaging studies using the technique of voxel-based morphometry (VBM) have shown differences in gray-matter volume between demented PD patients and controls in cortical and subcortical cerebral regions. Specifically, Burton et al. [9] reported reduced gray matter volume in PDD patients compared with controls in the temporal lobe bilaterally, including hippocampus and parahippocampal gyrus, in the occipital lobe, the frontal and parietal lobes, and some subcortical regions. We have previously reported gray matter loss in the basal ganglia, hippocampus bilaterally, and left parahippocampal region in PDD [43].

The technique of VBM has been shown to be useful in characterizing regional brain decreases across time in degenerative diseases such as Alzheimer's disease [36] and in patients with cognitive impairment without dementia [46]. To our knowledge, there are no published studies on the progression of regional volume loss in PD using VBM. One longitudinal study, in which a technique for the quantification of absolute brain changes was used showed that non-demented PD patients had significant reductions in whole brain volume compared with controls over a two-year follow-up period [26].The present study aimed to determine the pattern of brain atrophy across time in PD patients with and without dementia using the VBM technique.

Methods

Patients

Patients were recruited from an outpatient movement disorders clinic (Parkinson's Disease and Movement Disorders Unit, Department of Neurology, Hospital Clinic, Barcelona). All of them fulfilled the UK Brain Bank criteria for PD [12]. The patients were part of a previously-studied initial sample of 29 patients: 13 PD and 16 PD with dementia. They were invited by telephone for a follow-up assessment. The average follow-up period was 25 months (SD = 5.2), similar to that reported in the only previous longitudinal study in PD [26]. Written informed consent was obtained for all subjects. The ethics committee of our hospital approved the study.

From the original PD sample without dementia, one subject declined to participate and another was demented at follow-up. Concerning the original PD sample with dementia, four subjects died, while in another four patients it was impossible to perform magnetic resonance imaging owing to severe motor impairment. Thus, eleven patients with PD and eight patients with PD with dementia were included in the follow-up evaluation.

The follow-up assessment included a history provided by the patient and the caregiver, a neurological (Unified Parkinson's Disease Rating Scale (UPDRS) [18] and Hoehn and Yahr Rating Scale [28]) and neuropsychological examination, and MRI.

The diagnosis of dementia at follow-up was made by the neurologist based on an interview with the patient and a caregiver using the Diagnostic and Statistical Manual of Mental Disorders, Revised Fourth Edition (DSM IV-TR) [3] as a guide, along with administration of the Mini Mental State Examination (MMSE) [20]. Subjects needed a MMSE score of 23 or lower and DSM-IV-TR items to fulfill dementia criteria. Presence of hallucinations was assessed by a structured interview developed in our hospital. The scale comprised items covering the type (visual, auditory, tactile and olfactory) and temporal aspects of the hallucinations (time of day, frequency and duration). Depression was rated using the Hamilton scale [24].

Neuropsychological assessment

Subjects were tested individually in a well-lit, quiet room by a neuropsychologist experienced in testing neurologically impaired individuals. The neuropsychological assessment included test of memory, and of visuoconstructive and frontal lobe functions. The Rey Auditory Verbal Learning Test (RAVLT) assesses immediate memory span, new learning and delayed recall [34]. It consists of 15 words read aloud for five consecutive trials, each trial being followed by a free recall test. After a 20-min. delay period, each subject is again required to recall the words in the list. The Digit Span forward and backward subtest of the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) was used to assess attention and working memory. Here, subjects have to recall a series of digits in the same order and in reverse order. The modified version of the WAIS Block Design subtest was used to examine visuospatial and visuoconstructive abilities. We used the reduced version (four blocks) without registering the execution time. Letter fluency was used to test prefrontal functioning [34]. Individuals were given 1 minute to generate words starting with F, A, and S, excluding proper nouns and numbers.

Statistical analysis

Statistical analysis was carried out using SPSS 11.0. For clinical and demographic variables, we used the Mann-Whitney U-test for independent samples. The neuropsychological measures at both sessions were analyzed using the non-parametric Wilcoxon test for related samples.

MRI and Voxel-Based Morphometry

MRI acquisitions were performed using a 1.5 Tesla Signa Nvi/Cvi 8.4 General Electric (Milwaukee, USA). The imaging protocol included axial 3D IR Prep SPGR (Inversion Recovery Prepared Spoiled Gradient-echo) sequence of the entire brain and the following parameters: TR (Repetition time) = 17; TE (Echo time) = 5; TI (Inversion time) = 300; 1.5 mm thickness; FOV (Field of view) = 24x24; 256x256; 1 NEX (Number of excitations).

Images were analyzed with MATLAB 6.5 (MathWorks, Natick, MA) and SPM2 (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, London, UK). Original MR Images registered in DICOM format (one two-dimensional file per slice) were organized into three-dimensional files (volumes) by means of MRIcro software (University of Nottingham, UK) and saved in ANALYZE 7.5 format compatible with SPM2. Images were aligned along the anterior-posterior commissure (AC-PC) line.

Application of the optimized voxel-based morphometry (VBM) procedure [23], as well as details of our acquisition protocol and analyses are described elsewhere [43]. Paired *t*-tests using SPM2 were undertaken to compare base-line vs. follow-up gray matter volumes within each group. VBM analysis was thresholded at voxel level p uncorrected < 0.001. Only the significant clusters of more than 20 contiguous voxels were considered in the analysis. We only interpreted clusters with a p corrected < 0.05.

Results

Both groups were comparable in terms of age, sex and years of education. There were no differences in disease duration or stage of the illness, although the PDD group

did show a higher score on Part III of the Unified Parkinson's Disease Rating Scale. Both PD groups differed in the degree of mental impairment assessed by Mini Mental State Examination in both evaluations: baseline and follow-up (see Table 1).

Table 2 shows the clinical progression and the proportion of PD patients with hallucinations. We did not find any statistical significance regarding the progression of clinical severity evaluated by Hoehn and Yahr or by the UPDRS scale. None of the PD patients without dementia showed hallucinations, but this symptom occurred in all demented patients studied. Complex visual hallucinations (VH) were the most common type of hallucinatory phenomena. These were persistent in 6 of 8 cases. The presence of VH did not correlate with gray matter volume in the temporo-occipital region neither at baseline nor at the follow-up evaluation.

Results of the neuropsychological assessment are presented in Table 3. Across time the PD group showed a decreased performance on several tests, but only the scores in digit forward reached statistical significance. The raw scores of the group with dementia decreased on all tests, and the RAVLT learning score reached significance.

VBM results are described in Table 4 and illustrated in Figs. 1 and 2. When compared with baseline, the group without dementia showed significant clusters of reduced gray matter volume in the right anterior and posterior cingulate gyrus, bilateral temporo-occipital region, bilateral insula, right hypothalamus and nucleus accumbens, and left hippocampus. The PDD group showed a decrement in gray matter volume in the right fusiform gyrus, right parahippocampal gyrus and hippocampus, right temporo-occipital region, and right medial anterior temporal gyrus.

To investigate the relationship between cognitive decline and brain volume loss, we performed an analysis of covariance (ANCOVA) using the neuropsychological scores that achieved statistical significance or a trend towards it in the base-line vs. follow-up conditions. Specifically, for the PDD patients we included the RAVLT learning scores and for the PD patients the RAVLT learning and digit forward scores. When entered into the analyses the above mentioned covariates, the grey matter differences between pre and post MRI acquisitions lost significance. This suggested that cognitive decline is related to grey matter volume loss.

Table 1 Demographic and clinical characteristics of the sample at the follow-up

	PD	PDD	Test statistics	p-value
Age (years)	74.45 ± 4.6	70.25 ± 10.1	37.00[a]	0.559
Gender (men/women)	7/4	5/3	0.003[b]	0.960
Years of education	7.73 ± 4.03	7.63 ± 5.8	39.00[a]	0.671
Disease duration (years)	12.36 ± 6.6	13.50 ± 5.7	38.00[a]	0.619
Hoehn and Yahr stage	3.2 ± 0.9	3.9 ± 1.0	27.00[a]	0.145
UPDRS III	21.09 ± 6.3	42.38 ± 18.6	20.00[a]	0.047*
Hamilton score	4.27 ± 5.4	3.13 ± 2.6	43.50[a]	0.968
MMSE baseline	28.64 ± 1.03	20 ± 2.39	0.001[a]	< 0.0005*
MMSE follow-up	27.55 ± 1.4	15.50 ± 5.7	1.00[a]	< 0.0005*

Values are mean ± SD
PD Parkinson's disease; *PDD* Parkinson's disease with dementia; *UPDRS* Unified Parkinson's Disease Rating Scale; *MMSE* Mini Mental State Examination
[a] Indicates calculated using Mann-Whitney U-test
[b] Indicates calculated using the χ^2 test
* denotes significant ($p < 0.05$) differences between PD and PDD patients

Table 2 Clinical results at baseline (Time 1) and follow-up (Time 2) in PD samples

	Group	Time 1	Time 2	z-value Wilcoxon test (Time 1 vs. Time 2)	p-value
Hoehn and Yahr stage	PD	2.9 ± 0.8	3.2 ± 0.9	−1.32	0.187
	PDD	3.2 ± 0.9	3.9 ± 1.0	−1.76	0.078
UPDRS III	PD	22.27 ± 11.7	21.09 ± 6.3	−0.31	0.759
	PDD	32.0 ± 6.3	42.38 ± 18.6	−1.12	0.262
Presence of hallucinations	PD	–	–	–	–
	PDD	8/8	6/8		

Values are mean ± SD
PD Parkinson's disease; *PDD* Parkinson's disease with dementia; *UPDRS* Unified Parkinson's Disease Rating Scale

Table 3 Neuropsychological test scores

Task	Group	Time 1	Time 2	z-value Wilcoxon test (Time 1 vs. Time 2)	p-value
RAVLT Learning	PD	35.00±6.1	30.64±5.9	−1.94	0.052
	PDD	20.57±6.1	13.86±5.2	−2.37	0.018*
RAVLT Forgetting	PD	3.36±1.9	2.09±4.4	−1.24	0.215
	PDD	2.29±2.7	1.75±1.5	−0.43	0.670
Digit forward	PD	7.36±2.01	6.18±1.2	−2.01	0.045*
	PDD	5.57±1.0	5.38±1.4	−0.37	0.713
Digit backward	PD	3.91±1.8	3.73±1.0	−0.49	0.623
	PDD	2.29±1.4	1.63±1.3	−1.09	0.276
Block design	PD	16.73±5.6	14.64±5.5	−1.27	0.205
	PDD	5.14±7.2	3.43±4.8	−0.74	0.461
Letter fluency (FAS)	PD	8.48±4.0	7.50±3.6	−1.38	0.168
	PDD	4.29±3.9	3.19±2.5	−1.33	0.183

Values are mean ± SD
PD Parkinson's disease; *PDD* Parkinson's disease with dementia; *RAVLT* Rey Auditory-Verbal Learning Test; *RAVLT Learning* Sum of words correctly recalled of Trial 1 to 5; *RAVLT Forgetting* Number of words lost after the 20-minute delay; *FAS* Sum of all admissible words for the three letters divided by three
* denotes significant score decrease in the follow-up

Table 4 Results from the analysis of decreases in grey matter volume in PD groups*

Cerebral Region	Cluster		Voxel			
	Number of voxels	Corrected p	Z value	Talairach's coordinates		
				x	y	z
Decreases in gray matter volume in PD group in the follow-up						
Right anterior cingulate gyrus	8482	< 0.0005	4.72	1	31	19
Right temporo occipital region	6179	< 0.0005	4.41	44	−65	0
Left insula	3241	< 0.0005	4.29	−32	2	9
Right insula	1612	0.002	4.18	37	−6	0
Right posterior cingulate gyrus	1614	0.002	4.11	11	−49	30
Left temporo occipital region	982	0.021	1.01	−37	−62	12
Right hypothalamus/Nucleus accumbens	1314	0.006	3.98	1	−9	−5
Left hippocampus	921	0.026	3.44	−22	−19	−11
Decreases in gray matter volume in PD group with dementia in the follow-up						
Right fusiform gyrus/Right Hippocampus and parahippocampal gyrus	4773	< 0.0005	4.58	26	−56	−8
Right temporo occipital region	1059	0.018	4.04	40	−56	6
Right medial anterior temporal gyrus	781	0.050	3.93	42	−18	−6

* Each reported anatomical location exceeds a voxelwise statistical threshold of $p < 0.001$ uncorrected level. The cerebral regions are referred to the location of the cluster. The Tailarach coordinate refers to the location of the most statistically significant voxel in the cluster

Discussion

The present research provides the first *in vivo* documentation using VBM of progressive gray matter loss in PD with disease progression. Both patients with and without dementia showed volume reductions in neocortical and limbic structures. In PD patients without dementia the brain loss broadly involved the paralimbic regions (anterior and posterior cingulate and insular cortex) along with other limbic structure such as the hippocampus. Grey matter loss in the associative temporo-occipital neocortex also occurred. In demented patients limbic volume loss was only observed in the hippocampus and the neocortical decrement tissue involved regions in temporal and occipital lobes.

In the non demented PD group we observed a clear paralimbic and limbic involvement. This is consistent with post-mortem data showing neuronal loss and Lewy body pathology in insular cortex and cingulate gyrus in PD [5, 7]. Moreover, hypoperfusion of insular region in a group of non-demented advanced PD has been re-

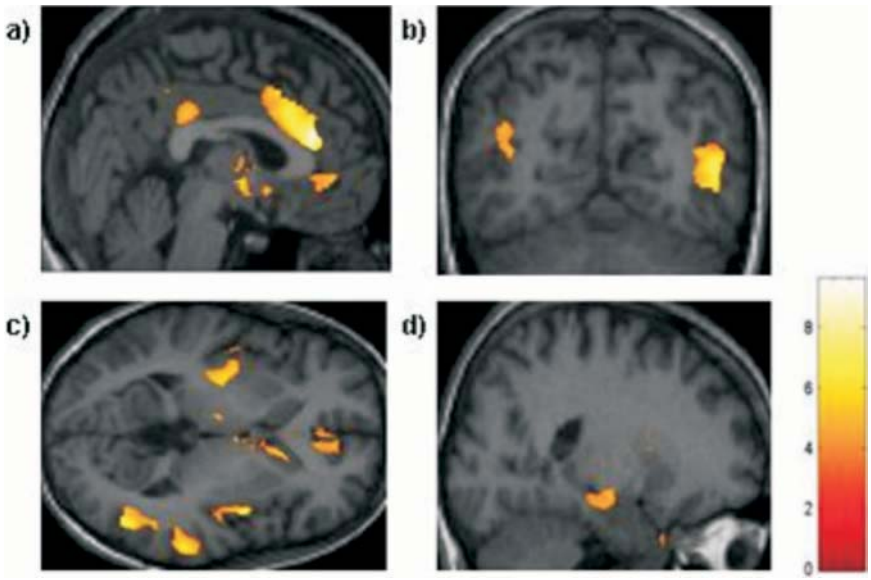

Fig. 1 Results of the comparison between initial and follow-up MRI in non-demented PD patients. Voxels reaching significance at the uncorrected $p < 0.001$ level are rendered on T1 image. Clusters of gray matter loss are seen in **a**) right anterior and posterior cingulate gyrus, right hypothalamus and nucleus accumbens (**b**) bilateral temporo occipital region (**c**) bilateral insula, right anterior cingulate, and right temporal region (**d**) left hippocampus

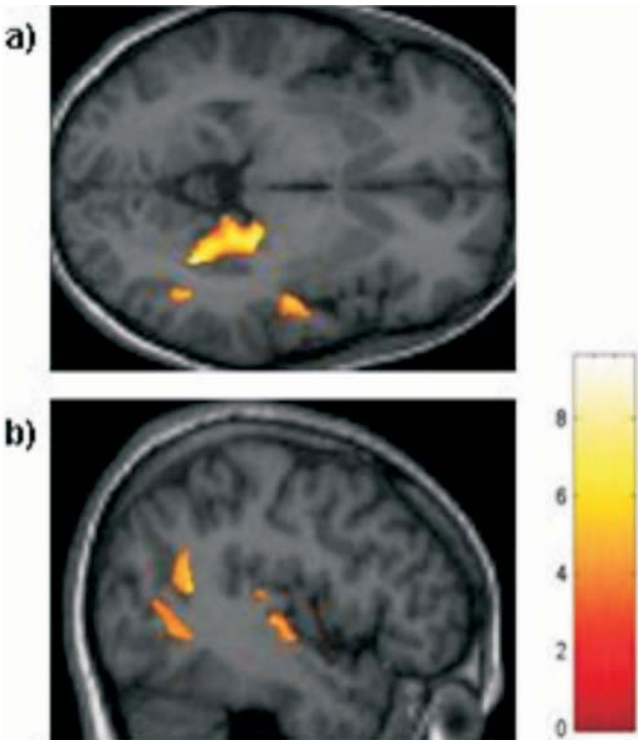

Fig. 2 Gray volume loss in demented PD patients. Voxels reaching significance at the uncorrected $p < 0.001$ level are rendered on T1 image. Clusters of volume difference are observed in (**a**) right fusiform gyrus, hippocampus and parahippocampal areas and (**b**) right temporo occipital region and right medial anterior temporal gyrus

ported previously [31]. We also observed a progressive volume loss of hippocampus. Using manual volumetric analysis comparing PD patients with and without dementia, Camicioli et al. [11] found a pattern in hippocampal reduction. Non demented patients showed hippocampal volume value between those of demented patients and controls suggesting progressive hippocampal loss in PD.

Old age, advanced stage of the disease, and impairment in verbal memory have been identified as risk factors to the development of dementia [32, 33]. Our PD sample is old, shows an advanced H & Y stage, a trend to memory decline, and a significant hippocampal reduction, but they have not developed dementia in two years of follow up. Longer longitudinal studies would be necessary to identify possible evolution to dementia. In this way, Aarsland et al. [2], found that more than three quarters of their PD cohort developed dementia in an 8-year study period.

In demented patients volume loss involved several neocortical areas. This is consistent with single-photon-emission CT studies in which marked perfusion deficits were described in posterior associative regions [30, 44] and with neuropathological studies which suggest a relationship between the presence of dementia and cortical pathology (LB-type degeneration or and Alzheimer-Type pathology) [4, 8, 10, 14, 27, 37]. Our results with VBM neuroimaging support the concept that the neocortex is a substrate for dementia in PD, in addition to limbic [6] and subcortical structures [13, 40, 47].

The cortical volume loss in the sample of patients with dementia included a marked decrease in volume in the fusiform gyrus with disease progression. The volume reduction of this cerebral region could be related with high densities of Lewy bodies in medial temporal regions in patients with dementia with Lewy bodies and demented PD patients with visual hallucinations [25]. The progressive tissue loss that we found might influence the persistence and progressive nature of halluci-

nations in PD [17, 21]. However, we found no correlation between grey matter volume and presence of visual hallucinations either in baseline or in the follow-up evaluation. So, although volume reduction of this cerebral region might be partially related with visual hallucinations, additional factors such as neurochemical deficits reported in these patients seem to be necessary for the presence of this symptom (see Diederich et al., for a review) [15].

Surprisingly, the progressive volume loss in PD patients without dementia was widespread and marked. These results could reflect the different regional involvement with disease progression in agreement with neuropathological staging reported by Braak et al. [7]. These authors described the topographic extent of PD-related brain lesion (Lewy neurites/bodies) in progressive stages. According to this study, limbic and paralimbic degeneration (Stage 4) precede neocortical degeneration (Stage 5 and 6). The demented patients are probably in a more advanced neuropathological stage in which degeneration of the limbic and paralimbic regions may be less active. Such interpretation could explain why patients without dementia showed a widespread gray matter loss. In fact neuropathological [19] and neuroradiological [29, 39, 42] studies suggest that a slower progression occurs in more advance stages of the disease.

The small sample size and the high number of decreased brain areas are points against carrying out a classical correlation analysis. However, when considering the cognitive scores of PD samples as covariates, the gray matter differences between pre and post MRI acquisitions lost significance. This suggests a relationship between cognitive status and gray matter loss across time.

One limitation of the study is the small sample tested in the follow-up. However, our sample is comparable in term of size to that reported by Hu et al. [26] and we studied well matched groups in terms of disease duration. Additionally, in the present report we used a quantitative and automatic approach which contributes a novel and complementary analysis not performed until now.

A methodological consideration to bear in mind is that we considered the statistic maps threshold at $p < 0.001$ uncorrected for multiple comparisons. A comparison without a priori hypothesis of the brain regions that may have been affected by the progression of the disease in both groups should have been addressed using a p corrected value for multiple comparisons (for instance at $p < 0.05$). However, owing to the preliminary nature of this investigation since no previous data using VBM in longitudinal studies are available, as well as the small size of our samples we decided to use a less stringent cut-off.

Another limitation is the absence of a control group. Previous evidence from MRI studies showed an age-related loss of brain tissue. Good et al. [23], using VBM found that normal ageing is associated with a linear decline in grey matter with an accelerated loss in parietal and frontal areas and with a relative preservation of medial temporal lobe structures. Prominent tissue loss in frontal and parietal areas as compared to temporal and occipital areas have also been found in a longitudinal study performed using semi-automated techniques for a quantitative analysis of MR volumes of normal cognitive older adults [41]. In this way the temporal and occipital loss found in PD samples could be more related to the neurodegenerative process than to the age effect, given that these structures have a relative sparing with ageing. However, in a recent study using VBM, Tisserand et al. [45] reported decreases in gray matter density in various frontal regions but also in the temporal lobes in elderly subjects without cognitive decline. Brain volume changes in our PD groups could partially be explained by the age effect but the time between the first and the second assessment was the same for both groups examined, therefore the pattern of cerebral changes due to ageing should be similar.

In summary, this is the first study using VBM which found that both demented and non demented PD patients showed progressive grey matter loss in several cerebral regions. The neocortical grey matter decrease in demented patients suggests that cortical involvement plays an important role in dementia in Parkinson's disease. In the future, it will be essential to perform prospective longitudinal studies involving longer follow-up with a larger number of subjects and including healthy elderly people.

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Neuropsychological deficits in Parkinson's disease patients with visual hallucinations

(*Mov Disord*, 2006 in press)

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ABSTRACT

Recent neuropathological and neuroimaging studies suggest the involvement of several temporal regions in Parkinson's disease (PD) patients with visual hallucinations (VH). We examined 24 non-demented PD patients with VH, 21 PD patients without VH, and 21 healthy controls using a battery of tests assessing different aspects of temporal lobe function. PD patients with VH showed poorer performance in language, verbal learning, semantic fluency and visuoperceptive functions compared to controls and PD patients without VH. Differences in verbal learning and visuoperceptive functions were independent of general cognitive status, disease severity and depression. We suggest that a wide range of neuropsychological deficits can contribute to the emergence of VH in PD.

Keywords: Parkinson's disease, visual hallucinations, language, memory, visuoperceptive.

INTRODUCTION

Visual hallucinations (VH) belong to the most frequent neuropsychiatric symptoms of Parkinson's disease (PD), affecting 22 to 50% of patients.[1,2] Although they have been associated with the presence of cognitive impairment or frank dementia,[1,2] only few studies have addressed specific neuropsychological deficits in non-demented PD patients with VH. Barnes et al.[3,4] found that hallucinating PD patients showed deficits in object perception and visual recognition memory in comparison with both non-hallucinating PD patients and healthy controls. Cognitive deficits related to executive functions have also been reported in hallucinating PD patients.[5] In terms of the underlying brain mechanisms, neuroimaging and neuropathological studies found an association between temporal and frontal cerebral abnormalities and VH in PD patients.[6,7,8] Our study investigates the potential relationship between VH in PD and deficits in different neuropsychological domains, with a particular emphasis on test of temporal lobe function.

METHODS

Subjects

Participants were recruited from the Parkinson Disease and Movement Disorders Unit, Hospital Clinic Universitari, Barcelona, Spain. The sample comprised 24 PD patients who had experienced VH in the previous year, 21 PD patients who never suffered from VH, and 21 healthy elderly controls. The controls comprised spouses of PD patients and community volunteers without any history of psychiatric or neurological disorders who were matched with patients for age and education. All subjects gave informed consent to participate in this study, which was approved by the local Ethics Committee.

Diagnostic criteria and clinical evaluation

The details of the diagnostic criteria and clinical assessment are described elsewhere.[9] Patients who fulfilled DSM-IV-R criteria for dementia or presented clinical depression (Hamilton score ≥ 15) were excluded. All patients passed a visual acuity test consisting of reading from a distance of approximately 40 cm.

Age, gender distribution, years of education and visual acuity did not differ among the groups. PD patients with VH obtained a lower MMSE ($P < 0.0005$) and a higher Hamilton scores ($P < 0.05$) than both non-VH PD patients and healthy controls. Concerning clinical differences between both PD groups, hallucinating PD patients presented similar motor severity as assessed by the UPDRS motor subscale ($P = 0.21$) but a more advanced Hoehn and Yahr stage ($P = 0.015$). No differences in levodopa daily dose were found between the two PD groups ($P = 0.071$).

The VH in our PD sample consisted of well-formed images of people, faces or animals. Insight into the hallucinatory nature of the phenomenon was maintained in 63% of the patients. Associated delusions were present in 33% of the patients. These were primarily paranoid in type and involved elementary misbelieves concerning infidelity of theft. All hallucinating PD patients but one were on dopaminergic treatment at the time of evaluation. A modification of the antiparkinsonian treatment preceding the onset of VH was recorded in 33% of the patients. The VH disappeared after dopaminergic drug dosage reduction in eleven cases (45.8%), while five patients (20.8%) needed antipsychotic medication and five (20.8%) required both interventions. In the remaining patients medication was not modified because the hallucinations were well tolerated.

Neuropsychological assessment

General intellectual ability was assessed by the Information and Similarities subtests from WAIS-III. Language was evaluated by a verbal comprehension test (Token Test) and a picture naming test (Boston Naming Test), frontal functions by phonological and semantic fluency tests. A modified version of the Rey Auditory-Verbal learning test (RAVLT) was used to assess verbal learning, delayed recall, and recognition. To assess visuoperceptive functions, we used the Benton Facial Recognition Test and the standard drawing and multiple-choice versions of the Benton Visual Form Discrimination Test[10]. Finally, we evaluated visual memory functions using the subtest Memory for Faces from Warrington's Recognition Memory Test. All tests were administered and scored according to conventional procedures.[11]

Data analysis

Statistical analysis was carried out using SPSS 11.0. Gender distribution was compared with $\chi 2$ tests. For normally distributed quantitative variables with homogeneity of variance, we used an analysis of variance (ANOVA test) and the post-hoc Bonferroni test. For non-normally distributed variables, and/or in the case of no equality of variance between the groups, we used the non-parametric Mann-Whitney U test. Finally we performed an analysis of covariance (ANCOVA) using MMSE, Hoehn and Yahr stage and Hamilton scores to determine whether differences between the two PD groups on cognitive tests persisted after controlling for these variables.

RESULTS

The results of the neuropsychological assessment are shown in Table 1. The groups did not differ in general intellectual ability as evaluated with the Similarities (P = 0.343) and Information (P = 0.777) subtests from WAIS-III. However, the analysis of variance showed group differences in the other domains assessed: language, memory, frontal

and visuoperceptive functions. The post hoc test revealed poorer performance in PD patients with VH than in healthy controls in all neuropsychological measures except RAVLT- recognition. Patients with VH were more impaired than those without VH on language assessed by Token and Boston Naming tests (P = 0.034 and P = 0.032 respectively), verbal learning (P < 0.0005), semantic fluency (P = 0.022) and visuoperceptive functions evaluated by Benton Facial Recognition (P < 0.0005) and Visual Form Discrimination (P = 0.042). The only significant difference between PD patients without VH and healthy controls was observed in visual memory (P = 0.001).

PD samples with and without VH differed in MMSE, Hoehn and Yahr, and Hamilton's scores. Given that the specific neuropsychological deficits may be related to the global cognitive performance (MMSE score) and to the differences in illness stage and mood score, we performed an ANCOVA analysis between the two PD groups using these clinical variables as covariates. After removing the effect of these variables, verbal learning ($p<0.0005$), and scores of Benton Facial Recognition Test ($p=0.013$) remained significant.

DISCUSSION

PD patients with VH showed several cognitive deficits affecting not only visuoperceptive performance, as previously reported, but also language and verbal memory domains. This suggests that cerebral dysfunction in PD with VH extends beyond the subcortical-frontal circuits typically described in PD.

On test of verbal memory PD patients with VH demonstrate the classical PD pattern consisting of deficits in free recall but normal recognition.[12] However, in addition, our patients with VH showed deficits in long term retention (RAVLT-Memory loss) and presence of false intrusions. These findings could reflect an involvement of limbic and

temporal cortex ,as suggested by neuropathological studies,[7] in addition to a disruption of nigro-striato-thalamo-cortical circuitry.

The differences on Benton's Facial recognition test in the hallucinating patients are in keeping with the neuropsychological[4] as well as neuroimaging findings suggesting involvement of visual associative areas in patients with VH.[6,8] These differences are not likely to be caused by a lower visual acuity, although we can not exclude an influence of other primary visual deficits such as those of colour or contrast discrimination.[13] In contrast, the perfomance on Visual Form Discrimination Test which requires, apart from visuoperceptive skills, formation of strategy analysis, seems to depend to in a higher degree on the general cognitive status as reflected by MMSE score.

In addition to complex visual dysfunction, we observed deficits on language comprehension. The poor performance on Token Test could be related to an impairment in sentence processing[14] which has been associated with a reduced activation of anteromedial prefrontal cortex and posterolateral temporal regions.[15] Additionally, the reduced performance on Token Test could also be related to a visual attention impairment, as alterations of parieto-frontal connections associated primarily with the attentional modulation of visual perception have been implicated in the pathophysiology of VH.[8]

The recruitment of inferior frontal and ventral temporal regions have been observed during confrontation naming and semantic fluency tasks in healthy subjects.[16,17] The deficits found in these cognitive domains in our hallucinating sample could, therefore, reflect dysfunction in these brain areas. From the clinical point of view, naming impairment has been related to the level of general cognitive dysfunction in PD[12] and

prospective studies have identified deficits in verbal fluency as predictors of the development of dementia.[18] This is consistent with our finding that the differences between the PD groups in naming and category fluency lost significance once the effects of general cognitive status were removed from the analysis. The reduced efficiency in language and semantic fluency in our PD patients with VH could reflect the starting point of the more general cognitive decline which might later lead to dementia.

In conclusion, hallucinating PD patients were characterised by a wide range of impairments affecting several cognitive domains. The presence of so extensive deficits may escape the compensatory processes and thus favour the perception of VH. Given the well-documented relationship between dementia and hallucinations, it remains to be shown in longitudinal studies whether visuoperceptive and memory impairments found in our hallucinating PD sample are the earliest symptoms of a progressive cognitive decline.

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TABLE 1. *Neuropsychological test scores*

	PD with VH (n= 24)	PD without VH (n= 21)	Controls (n=21)	*P* Value[a]
General intellectual ability				
Similarities (WAIS-III)	11.7 ± 4.8	12.7 ± 6.0	14.0 ± 5.1	ns
Information (WAIS-III)	11.5 ± 6.9	12.4 ± 6.1	12.9 ± 7.3	ns
Language				
Token Test	27.8 ± 4.4	30.6 ± 2.8	31.9 ± 3.0	<0.05**
Boston Naming Test	47.3 ± 7.0	51.8 ± 4.3	52.5 ± 5.4	<0.05**
Verbal Memory				
RAVLT- Learning	24.8 ± 7.2	38.8 ± 7.0	41.9 ± 7.2	<0.0005**
RAVLT- Memory loss	8.4 ± 10.8	3.7 ± 4.4	3.0 ± 2.7	0.043*
RAVLT- Correct recognition	12.5 ± 2.1	12.8 ± 2.1	13.7± 1.4	ns
RAVLT- False recognition	2.4 ± 2.3	1.3 ± 1.3	0.9 ± 0.8	0.007*
Executive Functions				
Phonological fluency (P)	7.4 ± 4.5	9.7 ± 3.7	12.7 ± 6.1	0.002*
Semantic fluency (animals)	9.4 ± 4.5	13.3 ± 4.7	17.1 ± 5.1	<0.05**
Visuoperceptive Functions				
Benton Facial Recognition Test	43.7 ± 4.5	49.0 ± 4.3	49.4 ± 2.9	<0.0005**
Visual Form Discrimination Test	26.4 ± 3.8	28.8 ± 3.1	30.4 ± 2.0	<0.05**
Visual Memory				
Warrington's Recognition Test	31.1 ± 5.6	33.5 ± 6.5	40.4 ± 5.6	<0.005*

[a] Analysis of variance.

* Significant difference between PD patients with VH and controls.

** Significant difference between PD patients with VH and controls and between PD patients with VH and PD patients without VH.

PD, Parkinson's disease; *VH*, Visual hallucinations; *WAIS-III*, Wechsler Adult Intelligence Scale; *RAVLT- Learning,* Sum of words correctly recalled from Trial 1 to 5; *RAVLT- Memory loss,* Percentage of memory loss: percentage of words loss after 20 min of interference; *RAVLT- Correct recognition*, Number of words correctly recognized from the original list; *RAVLT- False recognition*, Number of words falsely recognized from the original list.